UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE
GRIGORE T. POPA IAȘI

HABILITATION THESIS

NAVIGATING THROUGH THE REALITIES AND CHALLENGES OF PEDIATRIC CHRONIC KIDNEY DISEASE: A COMPLEX APPROACH

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ABBREVIATIONS

(D-) HUS	Hemolytic Uremic Syndrome Diarrhea-Negative
(D+) HUS	Hemolytic Uremic Syndrome Diarrhea-Positive
AAP	American Academy of Pediatrics
AB	Acid-base
ACE	Angiotensin-converting enzyme
ACR	American College of Rheumatology
ACT	Activated clotting time
ADTKD	Autosomal Dominant Tubulointerstitial Kidney Disease
aHUS	Atypical Hemolytic And Uremic Syndrome
AI	Activity index
AK	Angiokeratoma
AKI	Acute kidney failure or Acute kidney injury
AKIN	Acute kidney injury network
AMV	Amur virus
ANA	Anti-nuclear antibody
ANDV	Andes Orthohantavirus
anti-ds-DNA	Antibodies against double-stranded DNA
AP	Anatomopathological
APGAR	Appearance, pulse, grimace, activity, respiration
APTT	Activated partial thromboplastin clotting time
ARB	Angiotensin II receptor blocker
ARPKD	Autosomal recessive polycystic kidney disease
AT	Antithrombin
AUC	Area under the curve
AWAKEN	Incidence and outcomes of neonatal acute kidney injury
BBD	Bladder-bowel dysfunction
BCM	Body composition monitoring
BMI	Body mass index
bNGAL	Blood neutrophil gelatinase-associated lipocalin
BP	Blood preasure
BUN	Blood urea nitrogen
C3G	C3 glomerulopathy
CA-AKI	Community-acquired AKI
CAKUT	Congenital kidney and urinary tract malformations
CAP	Continuous antibiotic prophylaxis
CAPD	Continuous ambulatory peritoneal dialysis
CBC	Complete blood count
CDA	Celiac Disease autoimmunity
CEVUS	Contrast-enhanced voiding urosonography
CFB	Complement factor B
CFU	Colony-forming unit
CI	Chronicity index

CK	Creatine kinase
CKD	Chronic Kidney Disease
CKD-MBD	Chronic Kidney Disease - Related Bone and Mineral Disorders
CKiD	Chronic Kidney Disease in Children
Cl	Chloride
CPK	Creatine Phosphokinase
CrCl	Creatinine clearance
CRP	C-reactive protein
CsA	Cyclosporine A
CT	Computer tomography
CUA	Calcific uremic arteriolopathy
CVC	Central venous catheter
ddcf-DNA	Donor-derived cell-free DNA
DGF	Delayed graft function
DGKE	Diacylglycerol kinase-epsilon
DKD	Diabetic kidney disease
DM	Diabetes mellitus
DMSA	Mtc-dimercaptosuccinate
DNA	Dezoxiribonucleic acid
DOACs	Direct-acting oral anticoagulants
DOBV	Dobrava virus
DPPD	Department for Pedagogic and Didactic Preparation
dsDNA	Anti-double-stranded deoxyribonucleic acid
DTPA	Diethylene triamine pentaacetic acid
DVT	Deep vein thrombosis
EC	Enterochromaffin
eCCl	Estimated Creatinine Clearance
eGFR	Estimated glomerular filtration rate
ELBW	Extremely low birth weight
ELISA	Enzyme-linked immunosorbent assay
EPO	Erythropoietin
ERKReg	The European Rare Kidney Disease Registry
ERT	Enzyme-replacement therapy
ESA	Erythropoiesis-stimulating agent
ESBLs	Extended-spectrum beta-lactamases
ESRD	End-stage renal disease
EULAR	European League of Associations for Rheumatology
F	Female
FABP	Liver-type fatty-acid-binding protein
FD	Fabry disease
FH	H factor
FI	I factor
FSGS	Focal segmental glomerulosclerosis
Gb3	Globotriaosylceramide
GBM	Glomerular basement membrane

GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transpeptidase
GH	Growth hormone
GI	Gastrointestinal
GL3	Globotriaosylceramide
GLA	Galactosidase alpha gene
HA-AKI	Hospital-acquired AKI
HAVCR1	Hepatitis A virus cellular receptor 1
Hb	Hemoglobin
HbA1c	Glycated hemoglobin
HCM	Hypertrophic cardiomyopathy
HD	Hemodialysis
HE	Hidroelectrolyte balance
HF	Heart failure
HFRS	Hemorrhagic fever with renal syndrome
HHV6	Human herpesvirus 6
HHV8	Human herpesvirus 8
HIV	Human immunodeficiency virus
HIV	Human immunodeficiency virus
HPS	Hantavirus pulmonary syndrome
HR	Hazard rate (risk ratio)
HTA	Arterial hypertension
HTLV1	Human T-lymphotropic virus 1
HTN	Hypertension
HTN virus	Hantaan virus
HUS	Hemolytic Uremic Syndrome
IAA	Indole-3-acetic acid
IBS	Irritable bowel syndrome
IC-MPGN	Immune complex-mediated membranoproliferative glomerulonephritis
IDMS	isotope dilution mass spectrometry
IFN-γ	Alpha interferon
IGM	Infant gut microbiota
IgMN	IgM nephropathy
IJV	Internal jugular vein
IL	Interleukine
IMD	Index of microbial dysbiosis
IS	Indoxyl sulfate
JC virus	John Cunningham virus
K	Potassium
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney disease results quality initiative
KIM 1	Kidney injury molecule-1
KRT	Renal replacement therapy
KT	Kidney transplantation

LBW	Low birth weight
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
L-FABP	Liver-type fatty acid-binding protein
LK	Left kidney
LPS	Lipopolysaccharides
LVS	Left ventricular hypertrophy
lysoGb3	Globotriaosylsphingosine
M	Male
MAHA	Microangiopathic hemolytic anemia
MBD	Mineral and bone disease
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCKD2	Medullary cystic kidney disease-2
MCNS	Minimal glomerular lesions
MCP	Membrane cofactor protein
MCV	Mean corpuscular volume
MezPGN	Mesangial proliferation
MFM	Mycophenolate mofetil
Mg	Magnesium
MGN	Membranous glomerulonephritis
MHC	Major histocompatibility complex
MMACHC	Metabolism of cobalamin associated c
MPGN	Membranoproliferative glomerulonephritis
MRI	Magnetic resonance imaging
N	Normal
Na	Sodium
NAPRTCS	North American Pediatric Renal Trials and Collaborative Studies
NF-κB	Nuclear factor kappa B
NHBD	Non-heart-beating donors
NICU	Neonatal intensive care units
NP	Not performed
nRIFLE	Neonatal RIFLE
NS	Nephrotic syndrome
NYHA	New york heart association
OR	Odd ratio
PAGln	Phenylacetylglutamine
PAS	Periodic acid–Schiff
PBS	Prune-belly syndrome
PCR	Polymerase chain reaction
p-CS	P-cresyl sulfate
PD	Peritoneal dialysis
PE	Pulmonary embolis
PERC	Pulmonary embolism rule-out criteria
PF4	Platelet factor

PICU	Paediatric intensive care unit
PI-IBS	Post-infectious irritable bowel syndrome
pmarp	Per million of the age-related population
PML	Progressive multiple leukoencephalopathy
pNGAL	Plasma neutrophil gelatinase-associated lipocalin
PRES	Posterior reversible encephalopathy syndrome
pRIFLE	Pediatric RIFLE
PTE	Pulmonary thromboembolism
PTH	Parathyroid hormone
PUUV	Puumala virus
PUV	Posterior urethral valve
QoL	Quality of life
RAAS	Renin-angiotensin-aldosterone system
RAI	Renal angina index
RBUS	Ultrasound of the kidneys and bladder
rhGH	Recombinant human growth hormone
RIFLE	Risk, injury, failure, loss and end- stage renal disease classification
RK	Right kidney
RNA	Ribonucleic acid
ROC	Receiver operating characteristic
ROTEM	Rotational thromboelastography
r-TEG	Rapid thromboelastography
RvT	Recurrent venous thrombosis
SaO2	Oxygen saturation of arterial blood
SCFA	Short- chain fatty acids
SD	Standard deviations
SEOV	Seoul virus
sIL-2r	Soluble interleukin-2 receptor
SLE	Systemic Lupus Erythematosus
SLICC	Systemic lupus collaborating clinics
SLs	Sphingolipids
SRNS	Steroid resistant nephrotic syndrome
SSNS	Steroid sensitive nephrotic syndrome
STEC-HUS	HUS related to Shiga-toxin producing E. Coli
T1DM	Type 1 Diabetes mellitus
T2DM	Type 2 Diabetes mellitus
TDCA	Taurodeoxycholic acid
TEE	Thromboembolic events
TEG	Thromboelastography
TFF	Trefoil family factors
TGF-β	Transforming growth factor beta
TGO	Glutamic-oxaloacetic transaminase
TGP	Glutamic pyruvic transaminase
THBD	Thrombomodulin
THP	Tamm–Horsfall protein

TIM1	T-cell immunoglobulin mucin receptor 1
TLR4	Toll-like receptor 4
TMA	Thrombotic microangiopathy
TMAO	Trimethylamine N-oxide
TNF-α	Tumor necrosis factor alfa
TTP	Thrombotic thrombocytopenic purpura
TULV	Tula virus
UACR	Urine microalbumin to creatinine ratio
UMOD	Uromodulin
uNGAL	Urinary neutrophil gelatinase-associated lipocalin
UOP	Urine output
UPCR	Urine protein/creatinine ratio
UPJ	Ureteropelvic junction obstruction
UTI	Urinary tract infections
UVJ	Ureterovesical junction
VCUG	Voiding cystourethrogram
VLBW	Very low birth weight
VLBW	Very low birth weight
VTE	Venos Thromboembolism
VUCG	Voiding urethrocistography
VUR	Vesicoureteral reflux
VUS	Variant of Uncertain Significance
vWF	Von Willebrand factor
WBC	White blood cells
α-Gal A	Alpha-galactosidase A
β2MG	Beta 2 microglobulin

ABSTRACT

The habilitation thesis **"Navigating through the realities and challenges of pediatric chronic kidney disease: a complex approach"** presents the most important achievements in my academic, professional and scientific career that I have accomplished after finishing my doctoral studies in July, 2011. This thesis is also underlining future prospects on three main development directions of a mentor in the medical field: academia, clinical practice and research activity. This thesis's structure complies both to National Attesting Council for Titles, Degrees and Academic Certificates indications and to the specific methodology of University of Medicine and Pharmacy "Grigore T. Popa" Iași.

The habilitation thesis is organised in two distinct sections.

First section, titled "**Section A - Background of professional, academic and scientific achievements"** focuses on presenting my professional, academic and scientific evolution after obtaining my PhD title.

In a short introduction I present my achievements in the medical field, namely the specializations that I took in Pediatrics and Pediatric Nephrology. In the same section, I concentrated the most significant results of my post-doctoral research activity, with an accent on notable studies that have been published in specialty journals with a high impact factor. These results are presented in 4 chapters:

Chapter I – **Chronic kidney disease in children, from genetic to immunology** – is organized in 5 subchapters, according to distinct research domains: glomerular pathology, thrombotic pathology related to chronic kidney disease (CKD), genetic diseases with evolution towards chronic kidney disease, acute pathology (acute kidney injury of different etiologies, in different age-groups) as well as evolving modalities and complications of chronic kidney disease related. Etiologically, CKD is caused by glomerular or non-glomerular diseases, and in the pediatric population, it is frequently associated with congenital kidney and urinary tract malformations (CAKUT) or hereditary nephropathies. The incidence of end-stage renal disease (ESRD) in pediatric patients (0–18 years old) has doubled in the last two decades, according to recent data. In this context, this chapter is very important, and my research has tried to bring together the most important manifestations and their consequences on the child's health.

Chapter II – **Urinary tract infections and urinary tract malformations** – two distinct yet related conditions of urinary system – represents the research topic that continues my doctoral studies, focusing on a frequent pathology in Pediatric Nephrology, that of urinary tract malformations and their infectious complications.

Chapter III – **New insights into the human microbiome and its clinical implications in pediatric pathology** – presents a subject that raises a great interest nowadays. Trough studies that have been published in high-impact journals, I have contributed in underlining the distinct role of microbiota in pediatric pathology, with an accent on chronic diseases, including chronic kidney disease.

Chapter IV – **Ethical and social practices in Pediatric Nephrology** – is a chapter I consider that should always have its place in a presentation of scientific activity. Here, I present a summary of my research activity related to transplantation ethics and psychological aspects of caring for pediatric chronic patients, with an accent on the relation established between doctors and their patients.

The second section, titled ”**Section B - Perspectives in the professional, academic and scientific field”** presents the priority domains that I want to develop as well as my objectives related to them.

Implementing professional standards in the career of a university lecturer is essential because it implies continuous improvement in the quality of the educational system. The privilege of practicing a profession that encompasses three exceptional domains—education, healthcare, and research—offers both a unique opportunity and a challenge. Each of these domains, separately, brings multiple professional satisfactions but, at the same time, requires ongoing training and a desire for improvement to meet the ever-increasing demands for quality and competition in each of them.

In addition to my work in the healthcare sector, which itself involves maintaining certain standards of professional and human quality, the university environment brings a multitude of opportunities and responsibilities.

In this last setion of my thesis, I present the developing plan of my academic career, considering that my role as a mentor for the younger generations is of the essence, contributing in forming valuable specialists.

I also present the future directions related to my clinical activity and my interest in developing the Pediatric Nephrology specialty by implementing innovative techniques of investigation and accessing new means of treatments.

Directions in scientific development are also briefly discussed in this former part, insisting in raising both personal and my academic community’s national and international visibility.

The thesis ends with the reference list, comprising over 600 titles, that have been collected form research papers briefly discussed in this work.

REZUMATUL TEZEI

Teza de abilitare cu titlul **“Navigating through the realities and challenges of pediatric chronic kidney disease: a complex approach”** expune principalele mele realizări în domeniul academic, profesional și științific, desfășurate după finalizarea programului doctoral și susținerea tezei din iulie 2011. De asemenea, sunt evidențiate în această lucrare și perspectivele viitoare pe cele trei direcții de dezvoltare ale unui cadru didactic din învățământul universitar medical, respectiv, domeniul academic, cel clinic și cel de cercetare. Structurarea acestei teze respectă indicațiile oferite de Consiliul Național de Atestare a Titlurilor, Diplomelor și Certificatelor Universitare (CNATDCU), precum și metodologia Școlii Doctorale a Universității de Medicină și Farmacie "Grigore T. Popa" din Iași.

Teza de abilitare este împărțită în două secțiuni distincte.

Prima secțiune, denumită "**Section A - Background of professional, academic and scientific achievements"**, se axează pe prezentarea evoluției mele profesionale, academice și științifice ulterioare obținerii doctoratului. Într-o scurtă introducere am prezentat achizițiile mele în domeniul medical, specializările obținute în domeniul Pediatriei și Nefrologiei pediatrice. Tot în această secțiune am concentrat rezultatele semnificative ale activității mele de cercetare postdoctorală, aducând în prim-plan realizările notabile obținute prin publicații în reviste specializate, cu factor mare de impact, rezultate dezvoltate în 4 capitole:

Capitolul I - Chronic kidney disease in children, from genetic to immunology – organizată în 5 subcapitole, pe domenii distincte de cercetare: patologia glomerulară, patologia trombotică legată de boala renală cronică (BRC), boli genetice cu evoluție spre boală renală cronică, patologia acută (insuficiența renală acută de diverse etiologii, la diverse vârste pediatrice), modalități evolutive și complicații ale bolii renale cronice. Din punct de vedere etiologic, BRC este cauzată de boli glomerulare sau neglomerulare, iar în populația pediatrică, se asociază frecvent cu malformații congenitale ale rinichilor și tractului urinar (CAKUT), sau nefropatii ereditare. Incidența bolii renale în stadiu terminal la copii și adolescenți (0-18 ani) s-a dublat în ultimele două decenii, potrivit datelor recente. În acest context, acest capitol este foarte important, iar cercetările mele au încercat să reunească cele mai importante manifestări ale bolii renale cronice și consecințele acestora asupra sănătății copilului.

Capitolul II - Urinary tract infections and urinary tract malformations - two distinct yet related conditions of urinary system – este practic capitolul de cercetare care continuă studiile doctorale, axându-se pe o patologie extrem de frecventă în practica de Nefrologie pediatrică, aceea a malformațiilor de tract urinar și complicațiilor infecțioase ale acestora.

Capitolul III - New insights into the human microbiome and its clinical implications in pediatric pathology - este un capitol de actualitate, în care am evidențiat prin studii publicate în reviste cu factor mare de impact, rolul microbiotei în patologia actuală pediatrică, cu emfază pe bolile cronice, inclusiv boala renală cronică.

Capitolul IV - Ethical and social practices in Pediatric Nephrology – un capitol fără de care nu se poate încheia o prezentare a activității științifice. În acest capitol am redat pe scurt preocupările în domeniul eticii donării de organ, dar și în domeniul psihologiei pacientului cronic pediatric, insistând pe relația medic-pacient.

A doua secțiune, numită **"Section B - Perspectives in the professional, academic and scientific field"** schițează domeniile prioritare de dezvoltare, precum și obiectivele pe care mi le-am propus în acest sens.

Implementarea standardelor profesionale în cariera unui lector universitar este esențială deoarece presupune îmbunătățirea continuă a calității sistemului educațional. Privilegiul de a practica o profesie care cuprinde trei domenii excepționale - educație, asistență medicală și cercetare - oferă atât o oportunitate unică, cât și o provocare. Fiecare dintre aceste domenii, separat, aduce multiple satisfacții profesionale, dar, în același timp, necesită o pregătire continuă și o dorință de îmbunătățire pentru a răspunde cerințelor tot mai mari de calitate și concurență în fiecare dintre ele.

Pe lângă munca mea în sectorul sănătății, care implică în sine menținerea unor standarde de calitate profesională și umană, mediul universitar aduce o multitudine de oportunități și responsabilități.

În această ultimă parte a tezei mele am insistat pe dezvoltarea carierei didactice, rolul meu de formator al tinerelor generații de pediatrii și mai ales, nefrologi pediatrii, fiind esențial în obținerea unor specialiști de valoare. Am punctat și direcțiile de dezvoltare ale activității clinice, dezvoltarea specialității prin asumarea unor noi metode și tehnici de investigare, accesarea unor noi terapii.

Dezvoltarea cercetării științifice este și ea redată succint în aceasta ultimă parte, insistând pe creștererea vizibilității naționale și internaționale a mea, în calitate conferențiar universitar, de specialist nefrolog, de coordonator de rezidențiat de Nefrologie pediatrică, dar și a comunității academic din care fac parte.

Teza se încheie cu lista referințelor, peste 600, adunate din lucrările de cercetare discutate succint în teză.

"Medical education is a journey you travel with patients, becoming a student of their lives."

Sydney Kimmel

SECTION A - BACKGROUND OF PROFESSIONAL, ACADEMIC AND SCIENTIFIC ACHIEVEMENTS

With the dynamic changes that mark the entire Romanian society, higher education is undergoing a period of profound transformation. "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, one of the oldest and most respected medical institutions in the country, is aligning itself with the evolution towards modernity and European integration. Achieving this overall goal requires the collective efforts of the entire university.

Both Romanian legislative changes and field-specific European standards have an impact on the current regulatory environment, which affects the future growth of our university. Regarding the former, the Bologna Declaration of 1999 and the Berlin Declaration of September 2003 both highlight the European Higher Education Area and the European Research Area as the two main cornerstones of an evidence-based society.

It is evident that university lecturers must strive to align their personal growth with the ongoing transformations occurring in the higher education sector, as we are currently experiencing a period of substantial macro and micro modernization.

Given the described legislative and scientific context, I believe that the development of a modern academic career must build upon the steps taken in previous years in this field. For the future, it should focus on maximizing the existing positive elements, improving current deficiencies, and adapting continuously to the new and modern.

Implementing professional standards in the career of a university lecturer is essential because it implies continuous improvement in the quality of the educational system. The privilege of practicing a profession that encompasses three exceptional domains—education, healthcare, and research—offers both a unique opportunity and a challenge. Each of these domains, separately, brings multiple professional satisfactions but, at the same time, requires ongoing training and a desire for improvement to meet the ever-increasing demands for quality and competition in each of them.

In addition to my work in the healthcare sector, which itself involves maintaining certain standards of professional and human quality, the university environment brings a multitude of opportunities and responsibilities.

I have had and continue to have the chance to develop professionally in a multicultural and multifunctional setting. In this context, I aim to achieve both short-term and medium- to long-term objectives—general objectives as well as specific ones related to each stage of my evolution. Doctors, and particularly university professors in the medical field, are constantly held to a high standard of professionalism. To establish the limits of medical practice and the requirements for medical education, Epstein and Hundert's definition of professionalism is very helpful. This definition serves as an introduction to the topic and illustrates the elevated objectives of teaching medical students and residents professionalism. Our profession is the foundation of our professionalism. A profession that necessitates the accumulation and ongoing application of knowledge and practical abilities. Students enter medical school with a commitment to becoming excellent physicians, caring for patients, and achieving professional success. However, if they are not properly guided in their actions, they can quickly lose their idealism. In this regard, my objective is also to support and direct the development of future generations of physicians and medical auxiliaries. To broaden their horizons, prevent them from losing interest and idealism, and enable them to practice their profession anywhere in the world to the highest standards

The ultimate goal is the continuous professional development and enhancement of the quality of medical, educational, and research practices.

PROFESSIONAL ACHIEVEMENTS

Professional development is the cumulative, objective, and appreciative result of an individual's life experiences. Achieving high performance and academic recognition represents the triumph of success following the efforts made up to that point. I must admit that my decision to pursue a career in medicine was mostly impromptu, stemming from an early determination that emerged during my primary school years. A profound desire to pursue a career in medicine with the goal of treating my fellow classmates who were suffering from various illnesses served as the driving force behind this resolution.

I quickly realized that individuals aspiring to proficiently pursue this occupation must be prepared to allocate significant amounts of time, energy, financial resources, and emotional investment towards acquiring and demonstrating essential qualities and knowledge that serve as the foundation for their medical practice.

In 1992, I graduated from the National College "Mihail Sadoveanu", Iasi.

In 1998, I graduated from the "Grigore T. Popa" Faculty of Medicine and Pharmacy with a focus in General Medicine. During my years of study, I met people who (being a student and then a resident) aroused in my feelings of admiration and respect, especially those who proved an innate vocation as teachers and who managed to smooth out the roughness of some sterile subjects, absolutely theoretical, making it much easier for us to penetrate the sometimes extremely deep secrets of medical science. I felt that those people loved their job and did it with love, talent, and dedication. The meeting with them was defining in my evolution as a person and a professional, planting in my soul the desire to follow in their footsteps and try to design a future teaching career.

My fellowship in Family Medicine began in March 2000 at the Clinical Rehabilitation Hospital in Iasi and afterwards at St. Spiridon Emergency Hospital in Iasi. During that period, I discovered a strong empathy for pediatric patients while completing a rotation at the IVth Pediatric Clinic of St. Maria Emergency Children's Hospital in Iasi.

My interest in pediatrics crystallized during this time, thanks to the exceptional mentors who influenced my career: Prof. Dr. Ingrith Miron in Pediatric Hemato-Oncology, Prof. Dr. Ovidiu Brumariu, and Lecturer Dr. Mihaela Munteanu in Pediatric Nephrology, both of whom were integral parts of the clinic where I was assigned as a young resident. I began my residency in Pediatrics in 2002, motivated by a desire to help children.

These mentors inspired me to begin my teaching career on October 1, 2002, in the Discipline of Childcare at Iasi's "Grigore T. Popa" University of Medicine and Pharmacy. There, I advanced my teaching career with Prof. Dr. Cristiana Dragomir and Lecturer Dr. Laura Florescu, as well as in the specialty of Neonatology (preterm children) with Prof. Dr. Maria Stamatin.

Here are the main advantages of my previous training for occupying this university position:

- From October 1, 2002, to February 25, 2008, I held the position of teaching assistant at the Infant Care Discipline, Faculty of Medicine, "Grigore T. Popa" University of Medicine and Pharmacy in Iasi, through competition.
- From February 25, 2008, to February 18, 2019, I occupied the position of assistant at the Pediatrics Discipline, Faculty of Medicine, "Grigore T. Popa" University of Medicine and Pharmacy in Iasi, obtained through competition.
- From February 18, 2019, until June 27, 2023, I have held the position of Lecturer at the Pediatrics Discipline, Faculty of Medicine, "Grigore T. Popa" University of Medicine and Pharmacy in Iasi, obtained through competition.

- From June 27, 2023, until now, I have held the position of Associate Professor at the Pediatrics Discipline, Faculty of Medicine, "Grigore T. Popa" University of Medicine and Pharmacy in Iasi, obtained through competition.

The completion of my doctoral studies was the next step in the consolidation of my career. This was organized by the Faculty of Medicine at the University of Medicine in Iasi, and directed by Prof. Ovidiu Brumariu, MD, PhD, in 2011. I hold a Doctor of Medicine diploma obtained through my doctoral thesis titled "Urinary Tract Infection in Children: Diagnostic and Treatment Issues".

An individual's advancement within a particular domain, typically characterized by desirability, can be defined as a university career. The acquisition of professional status is typically formalized through the attainment of diplomas, attestations, certifications, and recognition.

And, ultimately, it is achieved through the consistent and dedicated performance of activities related to one's chosen occupation. For this reason, I have also acquired several important qualifications and certifications:

- I became a specialist in Family Medicine by contest in March 2003.
- I became a specialist in Pediatrics by contest in March 2006.
- I became a specialist in Pediatric Nephrology by contest in January 2019.
- I became a specialist in Nephrology by contest in May 2022.
- I have obtained various medical certifications for specialization in Pediatric Endocrinology, Clinical Homeopathy, Medical Ethics, General Ultrasound, and Medical Services Management.

I am a member of national and international scientific societies in the medical field, and I have contributed to various scientific publications, book chapters, and specialized books. In addition to my academic and research endeavors, I have been actively involved in administrative activities within the university, the Faculty of Medicine, and the hospital where I work.

I have been a part of various committees such as:

- Member of the Commission for the implementation of standards for hospital accreditation
- Member of the Transfusion and Haemovigilance of the Emergency Clinical Hospital for Children "Sfanta Maria", Iasi
- Member of the Commission for the implementation and analysis of the results of use protocols and practice guides of the Emergency Clinical Hospital for Children "Sfanta Maria", Iasi
- Member of the Medicines Commission of the Emergency Clinical Hospital for Children "Sfanta Maria", Iasi
- Member of the Medical Council of the Emergency Clinical Hospital for Children "Sfanta Maria", Iasi
- President of the Ethics Council of the Emergency Clinical Hospital for Children "Sfanta Maria", Iasi (2018 - 2022)
- Chairman of the Board of Directors Maternity Cuza Vodă, Iași (since 2021)

Since January 2019, I have been the head of the Pediatric Nephrology department, have been coordinating the Pediatric Nephrology residency program and I have been titular member in the Ministerial Commission of Pediatric Nephrology.

Since March 2022, I have been the Coordinator of the „National Treatment Program for Rare Diseases: Atypical Hemolytic Uremic Syndrome". Currently, I hold the titles of senior specialist in pediatrics, which I obtained in 2012, senior specialist in Pediatric Nehrology, obtained in 2023, and specialist in Nephrology since 2022.

Throughout my professional journey, I have actively participated in numerous specialized courses focusing on pediatric nephrology and related disciplines.

My personal skills include being a good organizer and coordinator, being suitable for teamwork, and having leadership qualities. Over the course of 24 years of clinical activity, I have witnessed radical changes driven not only by the evolution of the possibilities of patient monitoring but also by the emergence of new concepts, guidelines, and protocols of treatment.

In clinical disciplines, the professional prestige, which is sometimes difficult to objectively asses, is important for both professional and teaching development, increasing the interest and addressability of residents in that specific specialty.

Why did I choose Pediatrics? Because this is a complex specialty, a distinct kind of medicine, which seems to include everything I am fond of: pathologies that are characteristic for specific age group, the severity and difficulty of certain cases and the possibility of applying individualized therapies, the joy in the eyes of children at certain times.

Working as a physician at the Clinic of Neonatology initially, then in the IV-th Pediatric Clinic (the departments of General Pediatry, Nephrology, Hemodialysis, Hemato-Oncology, and Palliative Care) gave me the opportunity to accumulate a wide range of experience in the diagnosis and therapy of patients with acute conditions as well as in the monitoring of chronic patients. After this accumulation, I decided to develop my career in Pediatric Nephrology, which specializes in the management of children with a variety of acute and chronic kidney diseases.

The objectives of the treatment of chronic kidney disease are grouped in two main directions: reducing morbidity and improving the quality of life of the sick, because when a chronic disease cannot be cured, maximizing quality of life becomes an essential goal of medical care.

The Department of Nephrology was established as an independent structure in the the hospital in 2013, but there has been a department within the IV Pediatric Clinic since 1995. Currently, the medical staff consists of five doctors. The Hemodialysis Station, an integral part of the Nephrology Section of the Clinical Emergency Hospital for Children "Sf. Maria", Iaşi, has five hemodialysis stations and a sector dedicated to carrying out peritoneal dialysis exchanges. It was established in 1995 and is now one of the four national centers for extra-renal cleansing in children.

For me and my team, this means over 35,000 chronic dialysis sessions for more than 240 children addressed to the department. Continuing concern for the qualification of staff: 40% of nurses have higher education degrees, completed at UMF Iaşi, with a license in Pediatric Nephrology. I held the first specialized exam in Pediatric Nephrology in the country.

I have a constant concern for training young doctors in the specialty I am managing: stimulating the publication of first-author articles, book chapters, works at national and international conferences, access to skills.

Professionalism is an essential component of the contract between medicine and society. Jordan Cohen stated in his farewell address as president of the Association of American Medical Colleges, "The medical professional is defined not only by what he or she must know and do, but most importantly by a profound sense of what a doctor ought to be." Then, I must be a professional, and that is what I strive to become through all of my experiences.

My expertise in health policies, healthcare, and management has enabled me to actively contribute to the improvement plans of both my department and the hospital where I am working.

ACADEMIC ACHIEVEMENTS

Academic achievement, also referred to as educational attainment, pertains to the level of success attained by a student, teacher, or educational institution in meeting their intended educational objectives, whether they are immediate or long-term in nature. The attainment of educational milestones, such as speciality's degrees and bachelor's degrees, signifies significant academic accomplishments. In this equation, medical education under the supervision of a professional teacher is mandatory to access the higher professional post.

Through my undergraduate and graduate studies, I had the chance to have excellent mentors who trained me in the spirit of a valuable medical school so that, becoming a doctor, I ended up being appreciated and promoted not only for my professional skills but also for my ability to properly serve those who needed my help: patients, students, trained doctors, and colleagues. The academic career integrates complex requirements, especially in the medical and research fields. In my 24 years of academic activity, I have accumulated vast experience in managing student groups, working with residents, and clinical practice. Throughout my academic career, I have been captivated by the prospects of research.

I began my academic career as a teaching assistant at the "Grigore T. Popa" University of Medicine and Pharmacy in the Infant Care Department.

As a young university assistant, I was co-opted into the research team of four partnership projects won through competition.

1. Partnership Project, contract 81050/2007 - Composite Textile Structures for Electromagnetic Radiation Protection Systems, acronym SIR, coordinated by "Gh. Asachi" Technical University in partnership with "Gr. T. Popa" University of Medicine and Pharmacy, project duration 2007 - 2010, completed, project leader Prof. Dr. O. Baltag, team member.
2. Partnership Project, contract 71046/2007 - New High-Resolution Biomagnetometric Methods and Techniques for Biomedical Investigation and Diagnosis, acronym BIOMAG, coordinated by "Gr. T. Popa" University of Medicine and Pharmacy, project duration 2007 - 2010, completed, project director Prof. Dr. O. Baltag, team member.
3. Partnership Project, contract 41089/2007 - New Non-Invasive Biomedical Investigation, Diagnosis, and Monitoring Methods with Non-Ionizing Electromagnetic Radiations, acronym BIOELECTRA, coordinated by "Gr. T. Popa" University of Medicine and Pharmacy, project duration 2007 - 2010, completed, funded by the National Center for Program Management, project director Prof. Dr. O. Baltag, team member.
4. CEEX Project, contract 136/2006 - Magnetometric Methods and Techniques for Cardiac Activity Investigation, acronym CARDIOMAG, coordinated by "Gr. T. Popa" University of Medicine and Pharmacy, project duration 2006 - 2008, completed, funded by the National Center for Program Management, project director Prof. Dr. O. Baltag, team member.

Over time, I advanced to the position of assistant in the same hospital's Pediatric Clinic IV. To enhance my teaching career, I attended the DPPD (Department for Pedagogic and Didactic Preparation) courses, achieving a perfect score of 10. The disciplines I studied there, such as educational psychology, pedagogy, non-formal education management, counseling, and guidance, as well as educational sociology, have been of great help in my interactions with students and residents during the teaching process.

One particular area of focus was the study of "intercultural education" in the psychopedagogic module, considering my current role in teaching foreign students both

English and French. I have also achieved the B2 European level in English and French after attending language courses and passing the final tests.

Since 2018, I have been involved in the Internal Grant of UMF Grigore T. Popa, Contract 27497/2018, directed by Prof. Gavrilovici Cristina, MD, PhD, intitled "Managing primary vesicoureteral reflux in children: towards an individualized approach" as a team member.

Since 2019, I have advanced to the position of Lecturer at the same Pediatrics Department at the "Grigore T. Popa" University of Medicine and Pharmacy.

Currently, I am honored to hold the position of Associate Professor, a title I earned through a comprehensive evaluation of my entire professional journey. Teaching has consistently been a passion of mine, as it grants me the opportunity to impart the wealth of experience I have garnered to my students and residents, thereby enriching their future knowledge and expertise. It is my way of giving back to the previous generations who have supported and guided me throughout my career.

Teaching my students and residents, conducting lectures and seminars, and overseeing the practical aspects of pediatrics in English, French, and Romanian for General Medicine and Dental Medicine students, as well as Nursing students, is a great honor for me. I have cultivated a practice of employing interactive methods to communicate information, drawing not only from my personal experiences but also from the literature I have contributed to as an author.

Furthermore, I strongly advocate for the implementation of clinical examinations as the cornerstone of professional growth. I firmly believe that the practical skills acquired during university studies are fundamental for shaping future generations of medical professionals. As the renowned William Osler aptly put it, "He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all." This quote underscores the crucial importance of hands-on experience in the medical field, complementing theoretical knowledge.

Being one of the few senior specialists in Pediatric Nephrology in our country and serving as the coordinator of the residency program at our university, I bear a significant responsibility in preparing my residents for the demands of a dynamic and growing specialty.

This involves the seamless integration of various disciplines, including intensive care, neurology, cardiology, gastroenterology, genetics, and oncology. Ensuring our residents are well-equipped to face these challenges is at the core of my mission, as it contributes to the advancement and excellence of our field.

The correct and complete implementation of the clinical examination of the patient, the "cornerstone" of medical thinking, remains one of my priority objectives, which I try to impose on each generation of students or residents with whom I work. In this spirit, I organize weekly for and with my students and my residents case presentations and debate sessions based on the latest scientific articles and guidelines in our specialty field. Additionally, I have supervised Romanian and foreign students in their undergraduate theses, with a total of over 100 papers focused on pediatric care and nephrology.

With the aim of professional improvement, I have actively participated in numerous activities to enhance personal skills, obtaining four medical specializations (Family Medicine, Pediatrics, Pediatric Nephrology, and Nephrology), along with four supplementary certificates (Pediatric Nephrology, homeopathy, medical ethics, pediatric endocrinology, and general ultrasonography), as well as the Certificate in Health Management.

SCIENTIFIC ACHIEVEMENTS

An extremely important dimension of the teaching career is the professionalization especially in the initial stages of training, which ensures a real, well-oriented, motivated and open development for those who choose this direction. I believe that my professional career is defined by 3 major stages namely: the acquisition stage, the application stage and the improvement stage. If the first two areas of academic development (clinical and teaching) are significant, then research is essential for the advancement of teaching careers. I believe that the role of a university teaching framework should be to serve as a liaison between research groups and to develop new themes that encourage young people to conduct research.

I have consistently recognized the fundamental significance of scientific research in the realm of medical practice. As a strategy in the development of scientific writing skills I proposed to go through three consecutive steps, informing, engaging and concrete in valuable results.

I started my scientific achievements by completing my doctoral studies, which I completed in 2011. I hold a Doctor of Medicine diploma obtained through my doctoral thesis titled "Urinary Tract Infection in Children: Diagnostic and Treatment Issues", under the guidance of Prof. Univ. Dr. O. Brumariu (H/0006663, pursuant to Order of the Minister of Education and Research 6468, of 7.12.2011).

My scientific research activity carried out during the 24 years results in the publication of 46 scientific articles as the main author published in ISI-rated journals with a high impact factor: International Journal of Molecular Sciences (IF = 5,6), Diagnostic (IF = 3.706), Cells (IF = 6), Children (IF = 2,4), Genes (IF = 3,5), Nutrients (IF = 4,171), Medicine (IF = 1,6), World Journal of Diabetes (IF = 4,1), Frontiers (IF = 2,6). I have published 22 main-author articles and 13 co-author articles in BDI-indexed journals. I achieved a Hirsch index of 7 and a cumulative impact factor of 168. I am a reviewer in international journals, for which I conducted a total of 58 peer reviews in the last year (17 for Medicine® and 41 for MDPI-various journals).

My scientific research activity has been recognized with various national prizes, and also with an international too, in 2021 - International Award - GRAND PRIZE EUROINVENT Book Salon, www.euroinvent.org, European Exhibition of Creativity and Innovation, under the auspices of the Ministry of Research, Innovation and Digitization and the Romanian Academy of Scientists. The award-winning work was “Treatment of acute child poisoning”, Constantin Iordache and Alina-Costina Luca (M. Stârcea - author of chapter in the treaty). I was co-opted into the research team of five partnership projects won through competition.

I wrote 18 book chapters and I coordinated with prof Miron Ingrith one monography in our expertise domain, “Concepte actuale în practica pediatrică”, editura Grigore T. Popa, 2023. I am an active member of the academic community, participating in multiple licensing committees and acting on the National Central Resident Commission of Targu Mures. Constantly, I provide on admissions examination committees or evaluation examinations for academic or medical network positions, both in the specialty of Pediatrics, the specialty of Pediatric Nephrology (where I am also the coordinator), and the specialty of Family Medicine. As a member of the doctoral admission and guidance committees, I gained the necessary experience to become a doctoral coordinator.

CHAPTER I. CHRONIC KIDNEY DISEASE IN CHILDREN FROM GENETIC TO IMMUNOLOGY

State of art in chronic kidney disease in children

Chronic kidney disease (CKD) is a pathological entity with multiple complications and a wide range of clinical and paraclinical manifestations. The definition of CKD includes the presence of structural or functional kidney impairment that persists for at least three months. Etiologically, CKD is caused by glomerular or non-glomerular diseases, and in the pediatric population, it is frequently associated with congenital kidney and urinary tract malformations (CAKUT) or hereditary nephropathies.

Worldwide, CKD is recognized as a top public health priority. It is estimated that the disease affects 10% of the world's population, or more than 800 million adults, of whom approximately 4 million require renal replacement therapy (KRT), (Harambat 2023, Jager 2019). In contrast to the prevalence of CKD in the adult population, which has been systematically evaluated worldwide, the epidemiology of CKD in children is less known. The majority of children's epidemiological knowledge is derived from KRT registries such as the ESPN/ERA Registry in Europe, the USRDS in the United States, and other registries (Harambat 2023, Harada 2022, Ploos van Amstel 2018).

The incidence of end-stage renal disease (ESRD) in pediatric patients (0–18 years old) has doubled in the last two decades, according to recent data. Similarly, prevalence has tripled over the same time period (Harambat 2023, Chand, 2009). The prevalence of CKD ranges from 56 to 74.7 cases per million of the age-related population (pmarp).

Unfortunately, there is no optimal method for estimating glomerular filtration rate (GFR) accurately in infants. GFR varies with age, sex, race, ethnicity, and height, which complicates the development of exact estimated GFR (eGFR) equations in children, particularly in the early phases of kidney damage and in children under 3 years old. But widespread standardization of creatinine measurements has led to better eGFR equations, such as the revised Schwartz formulas (CKiD), which are used in clinical practice and research all over the world (Schwartz 2009, Pierce 2021).

Hemodialysis remains the most common form of KRT. The number of children undergoing hemodialysis exceeds the number of children undergoing kidney transplants and peritoneal dialysis combined (Chand, 2009). Vascular access is considered to be the method's backbone. This poses a distinct challenge for the medical staff and dialysis service provider in children due to the small blood vessel diameter and vascular hyperreactivity.

A persistent decrease in the estimated GFR, a steady increase in the amount of protein in the urine, or both can indicate functional damage. Based on this definition, the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines (KDIGO 2012 Clinical Practice Guideline) gives criteria for diagnosing and staging pediatric CKD.

The KDIGO diagnosis of pediatric CKD is contingent on the presence of one of the following clinical criteria (KDIGO 2012 Clinical Practice Guideline):

- GFR of less than 60 mL/min per 1.73 m2 for more than three months
- GFR greater than 60 mL/min per 1.73 m2, accompanied by structural damage or other markers of functional kidney abnormalities, such as proteinuria, albuminuria, renal tubular disorders, or pathologic abnormalities detected by histology or inferred from imaging.

Also included in this category are patients with functioning kidney transplants. The KDIGO CKD staging system for children older than two years stratifies the risk for progression of CKD and its complications based on GFR and is used to guide treatment (table 1.1) (Levey, 2020).

Table 1.1 *KDIGO CKD staging relative to children more than 2 years (adapted after Levey, 2020)*

GFR category	GFR (ml/min/1,73m^2)	Terms
G1	≥ 90	Normal to high
G2	60 to 89	Mildly decreased
G3a	45 to 59	Mildly to moderately decreased
G3b	30 to 44	Moderately to severely decreased
G4	15 to 29	Severely decreased
G5	< 15	Kidney failure

KDIGO: Kidney Disease: Improving Global Outcomes; CKD: Chronic Kidney Disease; GFR: Glomerular Filtration Rate

Our practice adheres to the KDIGO recommendations in the Clinical Practice Guide (Harambat 2023, KDIGO 2012 Clinical Practice Guideline, Levey 2020).

- **Stages G1 and G2**: Children are typically asymptomatic and require close monitoring for kidney function decline. There was an opportunity for these children to treat any reversible cause of kidney dysfunction and to prevent or delay the progression of CKD. Educational development is earlier initiated so that the child and family understand and implement care to avoid risk factors that can accelerate the progression of CKD (e.g., nephrotoxic medications, recurrent infections, dehydration, obesity, and smoking in adolescents) and include measures (e.g., strict blood pressure control and/or proteinuria reduction) that can slow the progression of the disease.
- **Stages G3a and G3b**: Children may experience complications associated with CKD. Hydro-electrolyte disorders, secondary erythropoietin deficiency anemia, hypertension (HTN), dyslipidemia, endocrine abnormalities, impaired growth, mineral and bone disease (MBD), and decreased clearance of substances ordinarily excreted by the kidneys (uremia) are among these conditions. The management of these patients focuses on preventing and treating complications. In addition, the aforementioned risk factors should be avoided in order to delay the progression of ESRD.
- **Stages G4 and G5**: Patients with progressive disease should be identified well in advance of the time when KRT is required in order for them to receive the appropriate training and education. It is directed both at the patient and his or her family. Preparation for KRT typically begins in stage G4 CKD, when the GFR falls below 30 mL/min/1,73m2.

The aforementioned classification system does not apply to children under two years of age because of the physiologically lower GFR, even when corrected for body surface area (VanSickle 2022, Colantonio 2012). To detect renal failure in these patients, abnormal kidney function based on serum creatinine can be compared with age-appropriate normative values (table 1.2). The KDIGO guidelines suggest that a serum creatinine level that is greater than one standard deviation above the mean should be a cause for concern and further surveillance is required on an ongoing basis.

***Table 1.2**. KDIGO recommendation relative to children under 2 years (adapted after VanSickle 2022, Colantonio 2012). Creatinine pediatric reference values measured by two different laboratory assays: enzymatic reaction by isotope dilution mass spectrometry (IDMS) and the Jaffe reaction. Creatinine values are based on age and sex.*

Enzymatic creatinine			**Jaffe creatinine**		
Age group	mg/dL	micromol/L	Age group	mg/dL	micromol/L
0 to 14 days	0.32 to 0.92	28 to 81	0 to 14 days	0.42 to 1.05	37 to 93
15 days to <2 years	0.10 to 0.36	9 to 32	15 days to <1 year	0.31 to 0.53	27 to 47
2 to <5 years	0.20 to 0.43	18 to 38	1 to <4 years	0.39 to 0.55	34 to 49
5 to <12 years	0.31 to 0.61	27 to 54	4 to <7 years	0.44 to 0.65	39 to 57
12 to <15 years	0.45 to 0.81	40 to 72	7 to <12 years	0.52 to 0.69	46 to 61
15 to 19 years (male)	0.62 to 1.08	55 to 95	12 to 15 years	0.57 to 0.80	50 to 71
15 to <19 years (female)	0.49 to 0.84	43.3 to 74	15 to <17 years (male)	0.65 to 1.04	57 to 92
			15 to <17 years (female)	0.59 to 0.86	52 to 76
			17 to <19 years (male)	0.69 to 1.10	61 to 97
			17 to <19 years (female)	0.60 to 0.88	53 to 78

As CKD progresses, appetite and nutritional intake decrease in adolescents (Ayestaran 2016, Chen 2017, Harambat 2023). Due to decreased appetite, intestinal absorption of nutrients, metabolic acidosis that affects physical growth, and alterations in the gut microbiome, malnutrition is common in children with CKD (Sgambat 2019). When GFR falls to 35 mL/min per 1.73 m2, weight loss occurs, and this weight loss is associated with an increased risk of rapid progression to ESRD (Ku 2019). Evaluation and monitoring of growth and nutrition are based on the 2008 Clinical Practice Guide of the Kidney Disease Results Quality Initiative (KDOQI) for Child Nutrition with Chronic Kidney Illness and the Working Group on Pediatric Kidney Nutrition (KDOQI Work Group 2009, Shaw 2020, Rees 2021, McAlister 2020, Nelms 2021). Based on the severity of kidney function and age, these recommendations provide a schedule for health and nutrition monitoring in children with CKD. Ideally, a dietitian with expertise in pediatrics and renal nutrition should coordinate individualized nutritional therapy based on developmental parameters for each child with

CKD. Nutritional management should take into account the caloric, protein, vitamin, mineral, and electrolyte requirements of each individual patient.
Complications due to CKD become more apparent as the disease progresses from stages G3 to G5, and include:

Fluid and electrolyte abnormalities:
- **Salt loss and hypovolemia**: children with obstructive uropathy and/or dysplastic kidneys frequently exhibit salt loss and decreased urinary concentrating ability. These children are at risk for clinically significant hypovolemia because they are unable to adequately respond to the acute intravascular volume depletion that can result from episodes of vomiting and diarrhea.
- **Salt and fluid overload**: when kidney function is severely compromised (GFR 15 ml/min/1.73 m^2), sodium and water retention can result in chronic intravascular volume overload. In children with CKD and volume excess, dietary sodium restriction and diuretic therapy are advised (Grade 2C). In our practice, daily sodium consumption is limited to 1.5 to 2.4 grams. In the early phases of CKD, thiazide diuretics (e.g., hydrochlorothiazide) are favored over furosemide or other loop diuretics.
- **Hyperkalemia**: For the prevention of hyperkalemia in children with moderate to severe CKD, a low-potassium diet is recommended (1C). Other treatments include the administration of loop diuretics (e.g., furosemide) and the correction of metabolic acidosis.
- **Metabolic acidosis**: recommendation is to administrate of enteral sodium bicarbonate to infants with CKD and metabolic acidosis in order to maintain a serum bicarbonate level of 22 mEq/L (Grade 2C). Because citrate preparations increase aluminum absorption, they should be avoided (Groothoff 2018).

Hyperuricemia, caused by decreased urinary excretion, seems to contribute to the progression of CKD. The mechanism involved decreases renal perfusion by stimulating the proliferation of afferent arteriolar vascular smooth muscle cells. An observational study of children with CKD found that a serum uric acid level greater than 7.5 mg/dL was a risk factor for accelerated CKD progression in children and adolescents (Rodenbach 2015).

CKD-Related Bone and Mineral Disorders (CKD-MBD) management involves continuous monitoring of bone metabolism (measurements of serum calcium, phosphorus, parathyroid hormone, and alkaline phosphatase levels) and appropriate therapeutic interventions such as diet phosphate restriction, phosphate binders, active vitamin D analogues and calcimimetic drugs.

Anemia: At least once a year, hemoglobin (Hb) testing should be done in children with CKD. Anemia is defined as a Hb level below the 2.5th percentile for age and sex. Anemia caused by CKD is treated with iron supplements and erythropoietin therapy. The recommendation is an erythropoiesis-stimulating agent (ESA) when the Hb level is less than 10 g/dL unless there is evidence of iron deficiency or another cause of anemia (Grade 2C). It recommends keeping Hb between 11 and 12 g/dL (Grade 2C) in children with CKD using ESAs.

HTN: In children with CKD and HTN, it recommends the use of an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) rather than other classes of antihypertensive agents to maintain target goals of blood pressure below 90^{th} percentiles for height and sex (Grade 2C) (Wilson 2020).

Cardiovascular disease (CVD) risk is the primary factor contributing to mortality among children with CKD (Wilson 2020). Cardiac arrest is the prevailing etiology, followed by arrhythmia, cardiomyopathy, and cerebrovascular illness. Consequently, CKD in pediatric patients is recognized as a important condition linked to a heightened susceptibility to accelerated atherosclerosis and uremic calcific arteriopathy. The elevated occurrence of early CVD might be attributed to the substantial prevalence of many risk factors, including HTN, left ventricular hypertrophy (LVH), obesity, dyslipidemia, disorders in glucose metabolism, and CKD-MBD (Lalan 2018).

Dyslipidemia - The annual screening for in children with CKD involves the acquisition of fasting lipid profiles. It is advisable to first suggest nonpharmacological interventions, such as dietary modifications and regular physical activity (grade 2C). Statin medication should be taken into account for children more than 10 years old who exhibit consistently high levels of low-density lipoprotein cholesterol (LDL-C), even after adhering to adequate dietary interventions for a minimum of three months (Grade 2C) (Baek 2020).

Malnutrition and failure to thrive are prevalent problems in children diagnosed CKD. Growth failure in these children is the result of a number of factors, including metabolic acidosis, reduced caloric intake, CKD-MBD, as well as growth hormone (GH), somatomedin, and insulin-like disorder. It is advisable to implement a meticulous treatment of the nutritional status of children diagnosed with CKD to maximize their growth potential. Recombinant human growth hormone (rhGH) can be considered a therapeutic intervention for children experiencing persistent growth problems with the goal of improving linear growth, but in absence of metabolic acidosis (Drube 2019).

Neurodevelopmental impairment is a potential concern for children diagnosed with CKD, as they experience increased susceptibility to neurocognitive dysfunction, particularly in the domains of executive functioning and attention. Ongoing and timely neurodevelopmental assessment is necessary to ascertain the need for early psychological or psychiatric intervention or educational assistance (Ruebner 2019, Johnson 2020).

Uremia is a clinical condition that occurs as CKD progresses. Uremia manifestation arises from the deterioration of renal function, and is distinguished by the presence of abnormalities in fluid, electrolyte, hormone, and metabolic levels. The literal meaning of uremia is "urine in the blood", which most usually develops in chronic and end-stage kidney disease. This syndrome include anorexia, nausea, vomiting, growth retardation, peripheral neuropathy, central nervous system abnormalities, an increased tendency to bleed due to platelet dysfunction (called uremic bleeding), as well as thrombosis and pericarditis.

In children with CKD, KRT is necessary when the GFR declines below 15 ml/min per 1.73 m2 and, in certain cases, before this. Consequently, once the estimated GFR falls to 30 ml/min per 1.73 m2 (G4 stage), it is time to begin preparing the infant and family for KRT. The patient and his or her family should be informed about the schedule and selection of KRT (preventive kidney transplant, peritoneal dialysis, and hemodialysis) (Harambat 2023, KDIGO 2012 Clinical Practice Guideline, Levey 2020).

I.1 Glomerular diseases in children

Diagnosis and treatment of glomerular diseases with an onset in infancy present special challenges. The description of a significant number of genetic risk alleles for childhood-onset glomerular disease was the most recent contribution to genetics. Nearly all causes of glomerulonephritis in adults, nephrotic syndrome, and thrombotic microangiopathy have been described in children, though the prevalence of specific causes varies. Post-infectious glomerulonephritis, Henoch-Schonlein purpura nephritis, and minimal change disease continue to be the most prevalent causes of glomerular disease in children. Although renal biopsy remains the gold standard for diagnosing glomerular pathology, the aforementioned diseases can be diagnosed clinically without the need for a biopsy. Although research has improved our understanding of how to classify and manage glomerular diseases in children, the need for biomarkers of disease-specific activity and chronicity remains a challenge. The immune system's vigor and the growth and maturation that occur during adolescence are distinctive and necessitate age-specific disease management strategies (Wenderfer, 2017).

My relevant papers and research on Glomerular diseases in children are listed below.

Articles ISI - principal author

Starcea IM, Bogos RA, Scurtu G, Munteanu M, Russu R, Lupu VV, Lupu A, Trandafir L, Miron IC, Mocanu MA. Pathological and Evolutive Correlations in Steroid Resistant Nephrotic Syndrome in Children. International journal of general medicine, 2022, 15, 4187–4193, IF=2.3/2022, Q3, https://www.dovepress.com/pathological-and-evolutive-correlations-in-steroid-resistant-nephrotic-peer-reviewed-fulltext-article-IJGM

Stârcea M, Gavrilovici C, Munteanu M, Miron I. Focal segmental glomerulosclerosis in children complicated by posterior reversible encephalopathy syndrome. J Internat Med Research 2018, 46 (1) 8 jan 2018, IF= 1.351/2018, Q3, https://journals.sagepub.com/doi/10.1177/0300060517746559

Gavrilovici C, Miron I, Voroneanu L, Bădărău S, **Stârcea M**. Posterior reversible encephalopathy syndrome in children with kidney disease. Int Urol Nephrol 2017; 49: 1793 -1800, IF= 1.692/2017, Q3, https://link-springer-com.dbproxy.umfiasi.ro/article/10.1007/s11255-017-1684-x

Article BDI coauthor

Teslariu O., Mititelu-Tartau L., **Stârcea M**., Miron I.C., Nechifor M., Magnesium in pediatric nephrotic syndrome, Rev. Med. Chir. Soc. Med. Nat., Iaşi – 2016 – vol. 120, no. 4, pag. 818-823, (Coautor), https://www.revmedchir.ro/index.php/revmedchir/article/view/169

Book chapters

Stârcea M., Iliescu Haliţchi C., Munteanu M., Russu R., GLOMERULONEFRITA ACUTĂ, în Pediatrie, tratat, Editura Gr.T.Popa, Iași 2016 (ISBN 978-606-544-429-4), capitolul VI, pag. 238 – 241;

I.1.1. Nephrotic syndrome in children – diagnosis and complications

I.1.1.1 Introduction

Nephrotic syndrome (NS) is one of the most frequently encountered glomerulopathy in children, being characterized by altered permeability of the glomerular capillaries and the inability to control urinary protein loss, leading to hypoproteinemia, hyperlipidemia and edema (Stoycheff 2009). The term NS is used for the association of edema and massive proteinuria.

According to the last KDIGO guidelines (KDIGO Glomerular Diseases Work Group 2021) the steroid sensitive nephrotic syndrome (SSNS) is the NS with the complete remission after 4 weeks of therapy with prednisone or prednisolone at standard dose. Steroid resistant nephrotic syndrome (SRNS) is defined as a lack of complete remission at 4 weeks of therapy with prednisone orprednisolone at standard dose (Rovin 2021).

From a therapeutic point of view, it is important to distinguish between primitive and secondary kidney damage. Most children (90%) develop primitive NSs, characterized histologically by minimal glomerular lesions (MCNS), mesangial proliferation (MezPGN), or focal segmental glomerulosclerosis (FSGS). 10% of children have NSs secondary to systemic diseases (infections, vasculitis, neoplasms, etc.), hereditary diseases (Alport syndrome), or treatments with various drugs (gold salts, D-penicillamine, mercury, nonsteroidal anti-inflammatory drugs, conversion enzyme inhibitors, etc.). FSGS has been reported in patients with mitochondrial cytopathy, in Galloway-Mowat syndrome (microcephaly, hiatal hernia and NS) and in Schimke syndrome (spondyloepiphyseal dysplasia, immunodeficiency and NS). The clinical evolution, the prognosis and the therapeutic response to NS in children are directly determined by the anatomopathological aspect.

In NS, impaired glomerular function causes tubulointerstitial alterations through different mechanisms: glomerular hemodynamic and selectivity disturbances, immunologic mechanisms, inflammatory mediators, leukocyte migration. All these lead to destruction of the glomeruli and renal tubules, and finally to tubulointerstitial lesions (Nath 2006). About one third of steroid-resistant cases evolve towards end stage renal disease within 5 years of disease onset. Histopathology with minimal glomerular damage and mild mesangioproliferative glomerulonephritis has a benign clinical and pathological course without major tubulointerstitial lesions. Instead, FSGS and diffuse mesangioproliferative glomerulonephritis associate significant tubulointerstitial alterations and an increased risk of developing CKD (Bagga 2011).

FSGS is a form of glomerulonephritis that develops in different kidney injuries, evolvingwith nephrotic-range proteinuria. Fixed and persistent proteinuria over several months may indicate underlying FSGS (Gibson 2007, Hogg 2007). Because most children with NS do not routinely have a renal biopsy performed, rigorous estimation of the incidence of FSGS in children is hindered. Determining minimal change NS is usually based on steroid responsiveness. Most frequently, the diagnosis of FSGS is underestimated because 15%–20% of these patients havean initial good response to

steroids (Hogg 2007). In 2003, studies from North America and the United Kingdom reported an incidence of NS of 2–4 new cases/100,000 children per year and biopsy-confirmed FSGS encompassed 15%–20% of the total (Filler 2003).

Children with renal disease, hypertensive encephalopathies, or those receiving immunosuppressive treatment are at particular risk of developing posterior reversible encephalopathy syndrome (PRES). "Reversible posterior leukoencephalopathy syndrome" was the original term used for this clinico-radiological entity, as described in patients with renal insufficiency, HTN, or under immunosuppressive therapy. This terminology intended to emphasize the reversible nature and the limited distribution of the brain lesions. However, this term is inaccurate, because morphological abnormalities of PRES are not strictly confined to the white matter, and they are not always reversible (Stott 2005, Prasad 2003). Several other terms have been subsequently advocated, such as "PRES" (Casey 2000), "immunosuppressive-associated leukoencephalopathy" (Singh 2000), "hyperperfusion encephalopathies" (Schwartz 2002), "reversible posterior cerebral edema syndrome" (Dillon 1998), or "reversible occipito-parietal encephalopathy" (Pavlakis 1999). Although there is still some debate about its accuracy, PRES is currently the most widely accepted (Ishikura 2012). PRES is a neurological condition that is characterised by seizures, altered mental status, head- aches, and visual impairment (Hinchey 1996). PRES has a reported incidence of 4%–9% of children with renal conditions (Onder 2006, Ishikura 2012). However, this incidence might be underestimated because some patients may develop PRES without seizures (Ishikura 2006, Gavrilovici 2017).

I.1.1.2 Aim

Early recognition of the histopathologic type and of the degree of the tubulointerstitial damage could be useful in establishing a targeted and effective therapy. We analyze the anatomo-pathological aspects and their correlations with evolution in 68 cases of SRNS hospitalized in the Pediatric Nephrology Department in Iaşi, Romania. We aimed also to evaluate serum Mg concentration in children with NS and highlight the relationship between Mg concentration and acute nephropathy. PRES should be suspected in all children with kidney disease HTN and/or immunosuppressive treatment (such as cyclosporine), who develop sudden neurological symptoms, even if imaging abnormalities are not restricted to the subcortical white matter of the occipital lobe. Severe neurological complications may develop if left untreated. Therefore, early recognition of PRES and optimal therapy are important to prevent serious neurological sequelae in these patients. We made a review on this topic and also report a rare case of FSGS in a child who was complicated by seizures, altered conscious level, and impaired vision and was treated with cyclosporine A (CsA).

I.1.1.3 Material and methods

Between 2010 and 2019, 187 children with the initial diagnosis of primitive NS were hospitalized in the Pediatric Nephrology Department in Iaşi. 121 cases were SSNS and 68 steroid-resistant SRNS cases. We excluded children under 6 months of age (for exclusion of congenital NS), the cases with a follow-up of less than 6 months, cases of non-nephrotic proteinuria, NS secondary to metabolic, infectious, vascular, malignant and cardiac diseases, as well as cases sent late, or cases already treated (to avoid biases of referral and selection). The following were analyzed: age at the onset of NS, distribution of cases according to the

anatomopathological aspect identified by percutaneous renal biopsy and assessment of prognostic factors by calculating the activity and chronicity index, the response to treatment evaluated by obtaining total clinical remission or absence of remission, correlations between the anatomopathological aspects identified in the studied patients and the response to treatment. In all the cases biopsied, we performed light microscopy and immunofluorescence, with minimum 15 glomeruli by each bioptic sample.

We conducted also a retrospective study of 27 patients, aged 2 to 17 years, admitted to the Nephrology clinic of the Iasi "Sf. Maria" Children′s Hospital between 2011- 2015 with the diagnosis of idiopathic NS, first episode or relapse. Of the 27 patients, 12 had acute NS, 6 SSNS and 6 SRNS. The remaining 15 patients were in the remission phase of NS, 7 SSNS, and 8 being steroid-resistant. Inclusion criteria were: age 0 - 18 years; diagnosis of idiopathic nephrotic syndrome. Exclusion criteria were: diagnosis of congenital NS or secondary NS; simultaneous presence of other diseases such as systemic lupus erythematosus (SLE), Henoch-Schonlein purpura, conditions that could cause mag- nesium loss (gastrointestinal illnesses, burns), administration of nephrotoxic sub- stances (loop diuretics, gentamicin, contrast agents).

We used a control group of 14 children, aged 2-17 years, with normal renal function, hospitalized in the General Pediatrics Clinic with functional abdominal pain syndrome, in which we followed-up the serum Mg levels for comparing them with the levels reported in the study group.

All these studies were conducted with the approval of the Ethics Committee of the institution for the use of medical data and informed consent was obtained from all patients.

We report a rare case of FSGS in a child who was complicated by seizures, altered conscious level, and impaired vision and was treated with CsA after we made an extensive review of the literature related to PRES.

I.1.1.4 Results

Of the total cases of NS hospitalized in our clinic, 68 developed corticosteroid resistance, representing 36%. Of the 68 children with SRNS, 65 children (95.5%) were primary SRNS, after 4 weeks of standard therapy with prednisone and 3 children with secondary SRNS, after first relapse of NS. The distribution by sex is approximately equal (B: F = 36:32). The mean age at the onset of patients with SRNS was 9.18 years, with limits between 1 year and 7 months and 16 years. Renal biopsy was performed in 55 children with SRNS (80.88%). The distribution of cases according to age and AP lesions is shown in Table 1.3.

Renal biopsy allowed the evaluation of the activity index (AI) and chronicity index (CI) in the analyzed cases. AI is calculated by summing the scores given for mesangial proliferation (0, 1, 2 or 3), the number of glomeruli with segmental necrosis (0 for 0% affected glomeruli, 1 for 1–20% affected glomeruli, 2 for 21–50% affected glomeruli and 3 for more than 50% affected glomeruli) and for interstitial edema and infiltrate with mononuclear (0, 1, 2 or 3). AI is maximum 9.

Among the patients studied, AI varied between 1 and 8. There are significant correlations between AI and the anatomopathological aspects ($p = 0.05$), as it seems that patients with MezPGN are more likely than other histological types to have lower levels of activity (Fig. 1.1).

Table 1.3. *Distribution of Cases According to Age and Anatomopathological Lesions*

Anatomopathological Aspect	Age < 7 Years	Age > 7 Years
MCNS (minimal glomerular lesions)	6	3
MezPGN (mesangioproliferative glomerulonephritis)	7	19
MGN (membranous glomerulonephritis)	2	7
MPGN (membranoproliferative glomerulonephritis)	1	4
FSGS (focal segmental glomerulosclerosis)	1	5
Absence of biopsy	9	4
Total	**26**	**42**

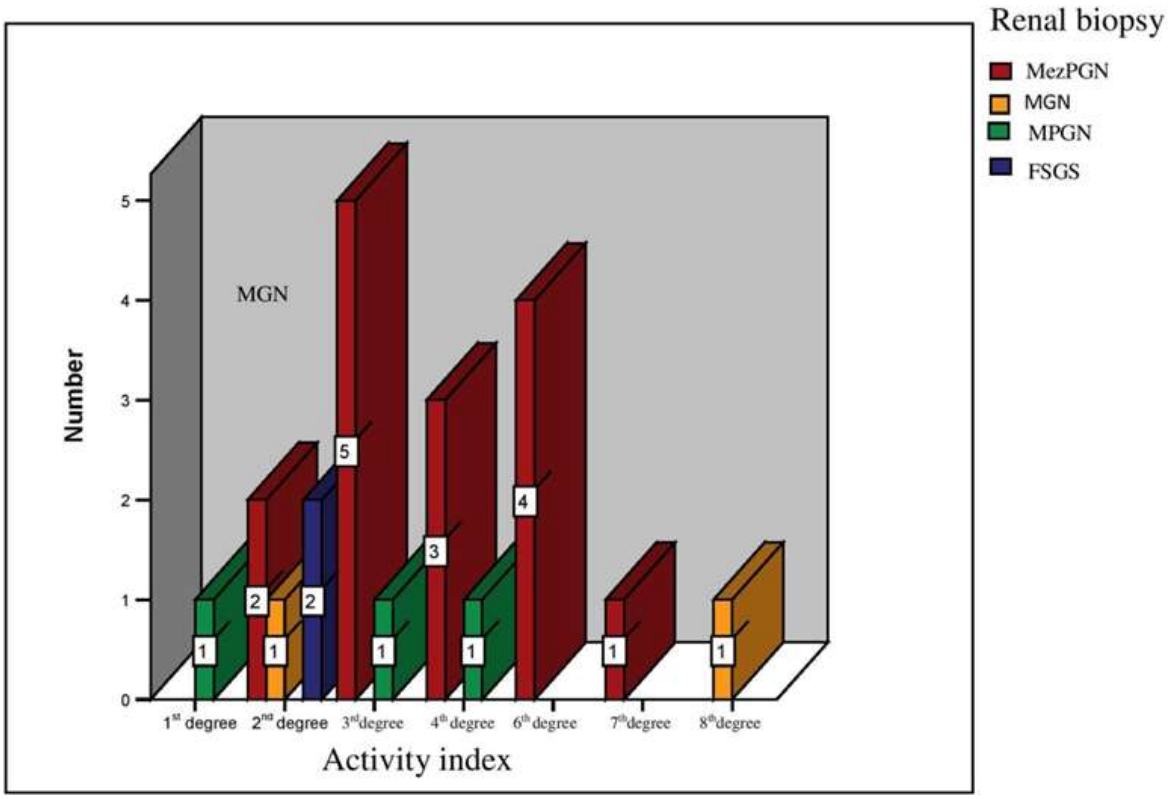

Fig. 1.1*. Renal biopsy – evaluation of the activity index. MezPGN – mesangioproliferative glomerulonephritis; MGN – membranous glomerulonephritis; MPGN – memranoproliferative glomerulonephritis, FSGS – focal segmental glomerulosclerosis*

CI is calculated by summing the scores given for glomeruli with fibrous crescents or synechiae, hyalinosis, segmental sclerosis or global sclerosis (0, 1, 2 or 3) and for tubular atrophy and interstitial fibrosis or the presence of inflammatory cells (0, 1, 2 or 3). The CI is maximum 6. In the patients in the analyzed group the IC varied between 0 and 5. There are significant correlations between CI and the anatomopathological aspects (p = 0.048).

The analysis of the evolution of SRNS cases was performed only in 48 children (70.58%), at which the follow-up exceeded 12 months. Patients were treated with various treatment regimens, using in the second line of treatment Methylprednisolone in pulses,

1g/sqm, Cyclophosphamide 0.5g/sqm, CsA 3–5mg/kg, Mycophenolate mofetil (MFM) 800–1200mg/sqm, Enalapril and plasmapheresis. Total duration of treatment was minimum 6 months, but in general, we gave in medium 18 months of therapy at each patient. Total remission was obtained in 30 children from the studied group (44.11%), clinical remission in 19 children and absence of remission in 19 children (27.94%). So, 72.05% of cases went into remission. The correlation of the anatomopathological aspects with the evolution is presented in Fig. 1.2.

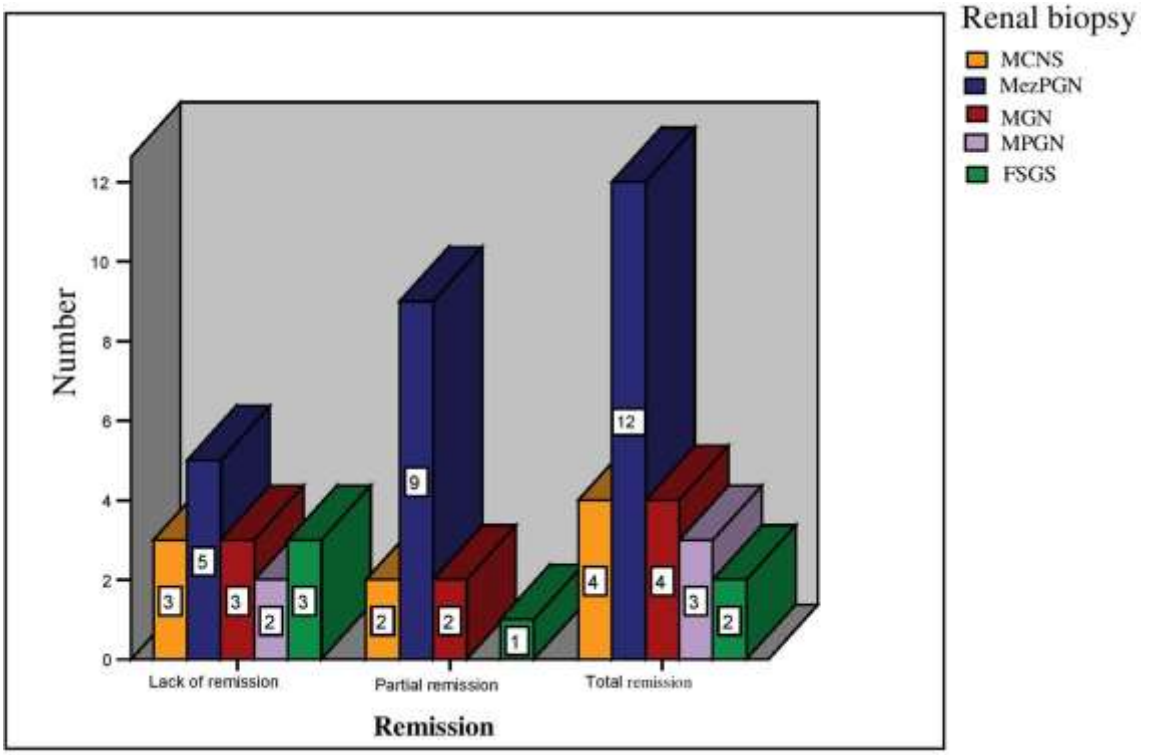

***Fig. 1.2**. Evaluation of the evolution of SRNS cases. MCNS - minimal glomerular lesions; MezPGN – mesangioproliferative glomerulonephritis; MGN – membranous glomerulonephritis; MPGN – memranoproliferative glomerulonephritis, FSGS – focal segmental glomerulosclerosis*

The second study was conducted on a sample of 27 patients (16 males and 11 females), aged 2 to 17 years, diagnosed with idiopathic NS, which had at least one hospitalization in the Nephrology Clinic in the interval 2011-2015.

The diagnosis of NS was based on the presence of the following biological changes: hypoproteinemia, hypercholesterolemia, proteinuria. For NS in remission phase, the values of these parameters were within normal ranges. In the study group, 12 patients had acute NS and 15 patients NS in remission phase. Depending on the response to treatment, steroid resistance was detected in 6 patients with active SN and 8 patients in remission (Fig. 1.3 and table 1.4). The mean age was 6.58 ± 4.14 years for active NS group, and 9.66 ± 4.65 years for remission NS group.

***Fig. 1.3**. Distribution of nephrotic syndrome in the study group. NS – nephrotic syndrome.*

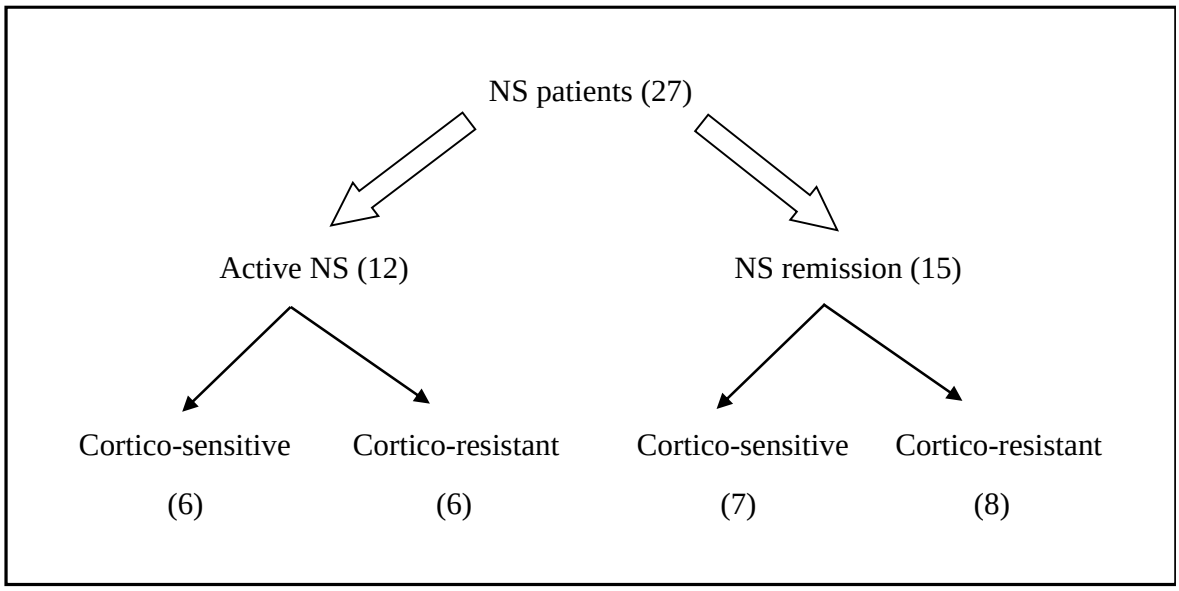

***Table 1.4.** Biochemical parameters in study patients*

Parameter	**Active NS (n=12)**	**NS remission (n=15)**
total serum proteins (g/l)	44.62 ± 7.18*	68.21 ± 5.40
total cholesterol (mg/dl)	381.16 ± 134*	169.06 ± 31.49
urinary proteins (mg/dl)	300 ± 0*	0
urea (mg/dl)	32.91 ± 11.62	27.33 ± 6.14
creatinine (mg/dl)	0.71 ± 0.58	0.59 ± 0.12
creatinine clearance (ml/min/1,73m2)	82.23 ± 31.38	96.90 ± 23.63
Serum Mg (mg/dl)	1.96 ± 0.30*	2.31 ± 0.77

NS - nephrotic syndrome; mg – milligrams; dl – deciliters; g – grams; l – liters
* $p<0.0001$

Renal histopathological analysis of steroid-resistant patients in the 2 groups revealed the following pathological aspects: active NS group: optically normal glomeruli (1 case), minimal mesangial changes (2 cases), IgM nephropathy (IgMN) (3 cases); remission NS group: minimal mesangial changes (3 cases), mesangioproliferative glomerulonephritis (4 cases), IgMN (1 cases).

The most common histological aspect was minimal mesangial changes (36%), followed by the mesangioproliferative aspects (29%) and IgM deposits (28%). The results showed decreased serum magnesium (Mg) levels in active NS group (1.96 ± 0.30 mg/dl) compared to control group (2.23 ±0.10 mg/dl), the difference being statistically significant ($p<0.05$) (Table 1.5).

However, although serum Mg was significantly lower in patients with acute nephropathy compared to controls ($p<0.05$), divalent cation concentration showed no significant variation between active and remission groups.

***Table 1.5**. Serum Mg (mg/dl) in the groups active NS, remission NS and control. Statistical significance – unpaired t test*

Group	n	Mean	Standard Deviation	Standard Error	Min	Max	p
Active NS	12	1.96	0.30	0.08	1.53	2.30	<0.05*
Remission NS	15	2.31	0.77	0.19	1.61	4.81	0,71
Control	14	2.23	0.10	0.02	2.10	2.43	

NS – nephrotic syndrome, *vs. control

We present also the case of a 10-year-old girl who was initially admitted for generalized oedema, malignant HTN and nephrotic-range proteinuria. Complement fractions, antinuclear antibodies anti-double-stranded dezoxiribonucleic acid (DNA), and liver enzymes were within normal limits. She had from the beginning SRNS. Under quadruple association of clonidine 5 mcg/kg, enalapril 0.5 mg/kg, telmisartan 1 mg/kg, and spironolactone 2 mg/kg, we managed to control the blood pressure.

The kidney biopsy showed FSGS. The patient was started on methylprednisolone pulse therapy in association with CsA 5 mg/kg/day, according to current guidelines (KDIGO 2012 Clinical Practice Guideline).

After just 1 week of therapy, the child was admitted to the pediatric intensive care unit (PICU) because of generalized seizures, and respiratory distress. Serum CsA levels were normal (125 ng/mL).

The patient's symptoms progressively worsened, with development of loss of consciousness, focal seizures, intermittent bilateral amaurosis, drooling, and severe respiratory insufficiency requiring mechanical ventilation.

Acute toxicity of CsA was considered, and thus immunosuppressive therapy was stopped. Furthermore, she continued to develop right-sided focal tonico-clonic seizures.

A blood culture and uroculture showed negative results. The cerebrospinal fluid was normal as follows: osmolarity at 37◦C was 281 mOsm/L, pH was 7.30, protein level was 0.11g/L, Cl level was 6.41 mgNaCl/L, glucose level was 50 mg/dL, cellularity was 1 cell/mm2, and culture was negative.

A brain computed tomography scan was normal. Brain magnetic resonance imaging (MRI) showed degeneration of white matter with diffuse demyelination in the parietal and

posterior occipital lobes (Fig. 1.4 and 1.5). The rapid progressive course of the disease and MRI features suggested posterior encephalopathy.

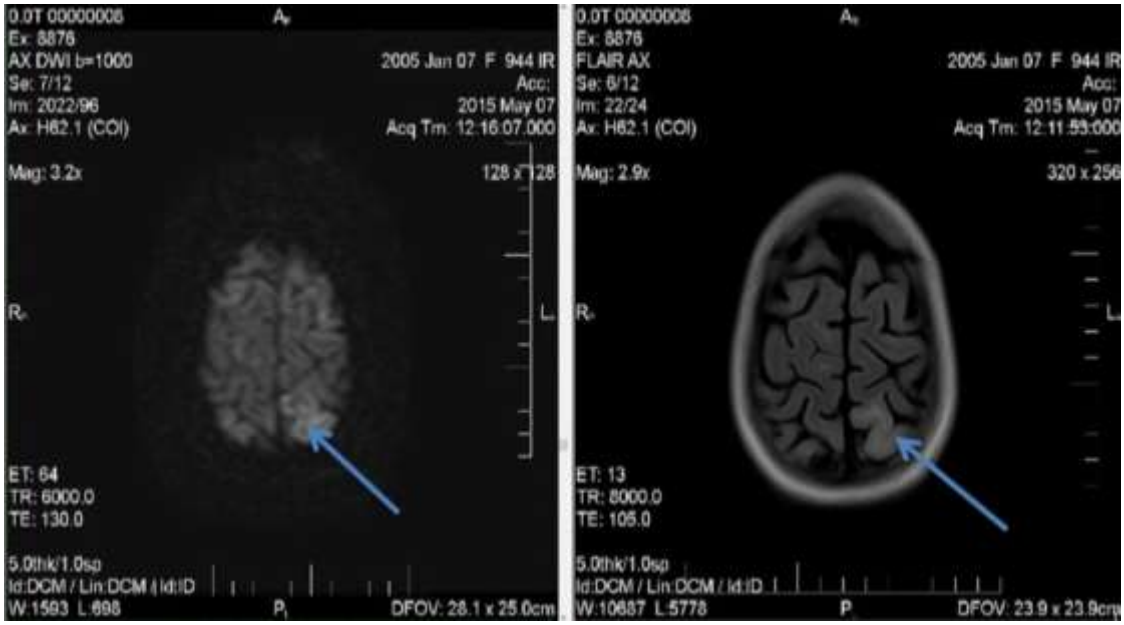

Fig. 1.4. *MRI diffusion and FLAIR: cortical hyperintensity in the parietal posterior lobe - white matter*

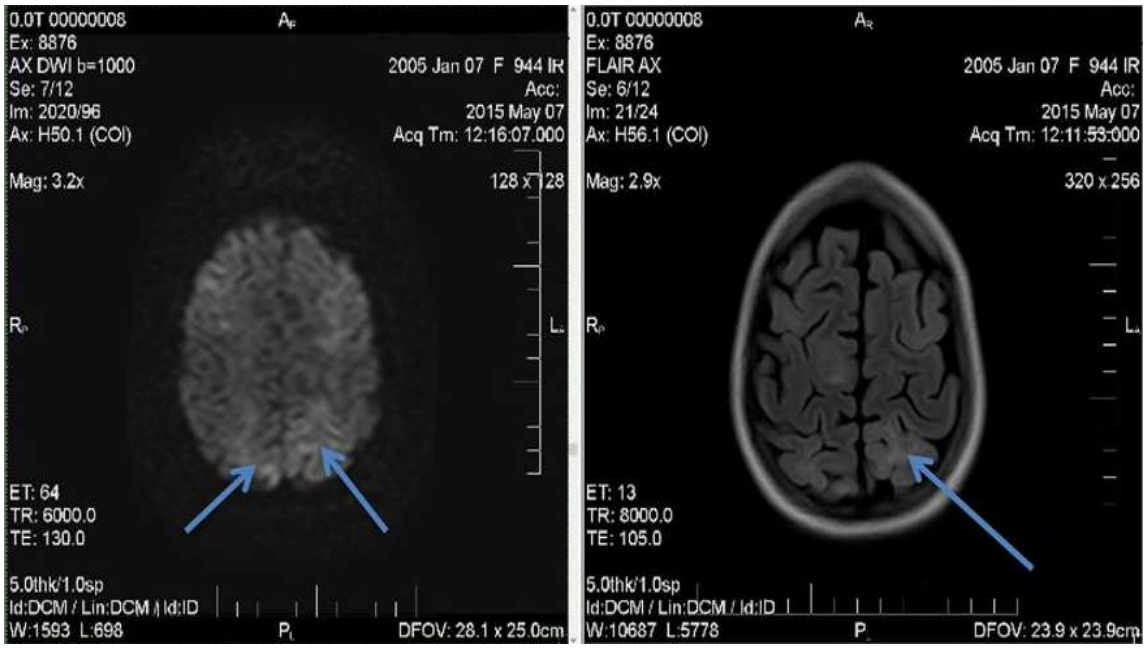

Fig. 1.5. *MRI diffusion and FLAIR: cortical hyperintensity in the parietal superior gyrus - white matter injury*

We concomitantly observed continuous deterioration of kidney function, which required continuous veno-venous hemofiltration. Intravenous immunoglobulins (0.5 g/kg/day) were administered for 5 days in association with continuous veno-venous hemofiltration and antihypertensive therapy.

She had no neurologic sequelae at 6 months of follow-up. During these 6 months, we continued FSGS treatment with monthly intravenous pulses of methylprednisolone.

Our patient stopped receiving medical care for the following 18 months when she was in ESRD and a chronic hemodialysis program was implemented. She is currently transplanted and in good general condition.

I.1.1.5 Discussion

The analysis of our group shows an increased incidence of corticosteroid resistance (36%), compared to KDIGO studies in which the percentage of corticosteroid resistance is 10–20% (KDIGO 2012 Clinical Practice Guideline).

The criteria for performing a kidney biopsy in a child with idiopathic NS have been restricted over time, in order to avoid unnecessary biopsies in the NS with minimal changes. However, there is still a diversity of views on biopsy criteria (Gulati 2000).

The various histopathological aspects represent different stages of evolution of the NS (Pal 2016). MCNS and FSGS do not differ in clinical presentation, but the prognosis is different; FSGS is completed by the onset of chronic renal failure, while MCNS rarely reaches this stage. Juxtaglomerular located glomeruli are preferentially affected by sclerosis in primary FSGS; therefore, it must be analyzed whether the biopsy was performed in the cortical depth, especially in cases apparently without lesions in light microscopy. It should also be noted that any area of tubular atrophy is significant in renal biopsy, raising the suspicion of segmental and focal sclerotic lesions, therefore serial sections should be examined (Agarwal 2013).

The variety of anatomopathological and evolutionary aspects, in relation to a variety of therapeutic means, raises the question: are there different pathogenic factors that act on the same target or is there a single trigger that causes different responses?

The structure of the glomerular filtration barrier includes an inner layer of endothelial cells along the capillary loops, the glomerular basement membrane (GBM) and the outer podocytes. The exact structure of the filter slit is still incompletely known (Jalanko 2009). In our statistics, it is observed that 25 of the cases of SRNS (36.8%) started under 7 years old, which contradicts the idea that young age is a favorable prognostic factor. It is discussed whether the report of FSGS frequency increase reflects the real increase in the prevalence of this histological type, or is only the consequence of changing biopsy indications or increasing access to renal biopsy (Agarwal 2013).

Most published studies draw attention to the predominance of MCNS at an early age (under 7 years), while FSGS has been reported at older ages. In the analyzed group, the relationship between the age of onset and the histological subtypes is consistent with the data reported in the literature, in terms of the age of onset of cases with minimal lesions and cases of FSGS. Renal biopsy allowed the evaluation of the AI and CI in the analyzed cases, in accordance with the studies in the literature (Vanikar 2013).

Immunofluorescence may alter the histological classification of NS. In MCNS, immunofluorescence is usually negative. However, some biopsies have shown deposits of IgM and C1q in the mesangium, requiring a description of the entity of IgMN, the prognosis of which is controversial. IgMN is an important but rather neglected pathology responsible for renal morbidity in children and adults. According to some authors, this anatomopathological form does not respond to cortisone treatment and therefore has a reserved prognosis, (Mubarak 2014) while other authors claim that there is no clinical significance (Connor 2017). About one-third of patients are steroid-responsive, and the other two-thirds are resistant or addicted to steroids (Tullus 2018).

Literature data (Futrakul 1999, Deekajorndech 2005) have suggested a link between serum and urinary Mg and tubulointerstitial function, given that both reabsorption of filtered Mg and retention of serum Mg occur in renal tubules. Any structural or functional alteration of the renal epithelium interferes with the tubular loss and reabsorption of Mg, leading to increased Mg urinary excretion. The results of our study show that serum Mg levels were significantly lower in patients with active nephropathy compared to those in remission ($p<0.5$). Since Mg is a divalent cation and its homeostasis depends on kidney filtration, low Mg levels in children with active NS reflect an alteration of renal excretion and reabsorption of Mg (Futrakul 1999, Deekajorndech 2007). In the literature, there are few studies regarding the homeostasis of Mg in NS (Futrakul 1999, Deekajorndech 2005), showed the existence of increased Mg urinary excretion, in focal and segmental glomerulosclerosis and mesangioproliferative glomerulonephritis.

The diagnosis of FSGS is exclusively bioptic because there are no distinctive clinical features that differentiate it from other types of chronic glomerulopathy. FSGS in children is often coupled with steroid resistance and HTN, and there is also a risk of progression towards end-stage renal disease.16,17 According to North American Pediatric Renal Transplant Cooperative Study data, nearly 60% of such children with a diagnosis of FSGS progress to dialysis or transplantation within 24 months of entry into the registry (patients with FSGS account for 14.2% of dialysis patients and for 11.5% of transplant patients) (NAPRTCS 2014).

Treating the underlying condition is the main trigger of management of secondary forms of FSGS. Treatment of primary FSGS includes conservative and immunosuppression regimens aimed at controlling proteinuria and preserving kidney function.

Renal survival has been directly associated with proteinuria control in long-term cohort studies in patients with primary FSGS (Gibson 2007). The current treatment strategies of primary FSGS involve one or more of the following: steroid therapy, cyclophosphamide treatment (rare cases), calcineurin inhibitors (CsA and tacrolimus), MFM, mizobirine, renin–angiotensin system blockade, galactose, rituximab, a synthetic adrenocorticotropin analogue, abatacept (cytotoxic T-lymphocyte-associated antigen 4–immunoglobulin fusion protein), adalimumab, and fresolimumab (Han 2016, Kemper 2014).

NS is a condition that may predispose to the development of PRES. Patients with NS are at risk of PRES because they often receive calcineurin inhibitors and steroids and they often have HTN and/or renal insufficiency. However, even mild HTN may be detrimental in NS patients treated with cyclosporine.

Furthermore, in NS vasogenic edema could be induced by decreased intravascular oncotic pressure, increased permeability of intracerebral capillaries, and fluid overload (Ishikura, 2008). T cell activation and inflammatory cytokine production have been suggested as additional predisposing factors for PRES in children with NS, particularly during relapses (Ishikura 2012, Zhang 2008, Ikeda 2001, Nakahara 2005).

Other kidney diseases in children that may predispose to the development of PRES include acute glomerulonephritis (Soylu 2001, Becquet 2010), hemolytic uremic syndrome (Gomez-Lado 2007), lupus nephritis (Punaro 2007, Zhang 2008), Wegener's granulomatosis (Ohta 2004), Henoch–Schönlein purpura nephritis (Ozcakar 2004), renal insufficiency or ESRD (Ikeda 2001, Ishikura 2008), renal artery stenosis (Benoist 2013), and grade IV vesico-ureteric reflux (Sharma 2014, Nakahara 2005). In the setting of ESRD, both the rise in blood preasure (BP) and uremia itself may serve as triggers for PRES (Sakai 2010, Girişgen 2010).

The use of immunosuppressive therapy may result in development of PRES. This situation has been frequently reported in haemato-oncological diseases, Henoch–Schonlein purpura, SLE, Guillain–Barre syndrome, and preeclampsia (Endo 2012, Arzanian 2014).

Our systematic search of all PubMed case reports of PRES in children showed that our case was the fifth reported case of FSGS in children who were treated with CsA and complicated by seizures, altered conscious level, and impaired vision. The other case reports were by Saeed (Saeed 2008), Gera (Gera 2014), Tenta (Tenta 2015), and Sakai (Sakai 2010).

The diagnostic of PRES is mainly based on MRI, which is currently considered the gold standard in this regard (Ishikura 2012, Ishikura 2008). The clinical manifestations and neuroradiological findings are typical for PRES, regardless of its etiology (Ishikura 2012). The differential diagnosis must mainly rule out cerebral infarction and venous thrombosis. Progressive multiple leukoencephalopathy (PML) is an opportunistic infection of the brain caused by the JC virus, with variable clinical presentation and lethal outcome. To exclude PML, a search for JC virus DNA in the cerebro-spinal fluid is required.

Other differential diagnoses of PRES include acute disseminated encephalomyelitis, infectious encephalitis, and meningitis. Particularly, herpes simplex encephalitis should be considered and, when suspected, rapid treatment with intravenous acyclovir and antibiotics may be lifesaving, while the diagnostic workup is still being pursued (Ishikura 2012, Hobson 2012).

I.1.1.6 Conclusion

Our results showed that histopathological lesions indicating the presence of a glomerulonephritis with minimal changes manifestation, with steroid resistance in proportions ranging from 25% to 45.5%.

The onset of NS under 7 years is not a guarantee of favorable evolution, with patients in this age group representing 36.8% of cases of SRNS.

MezPGN represents the dominant anatomopathological aspect in children with SRNS, but remission was obtained in 44% of cases of SRNS, without being able to establish a statistically significant correlation with the anatomopathological subtypes. It is well known that mesangial proliferation is at an early stage or may accompany FSGS, which can explain the evolution of steroids resistance in children under the age of 7 years who associate this with histological aspect.

Predicting the response to long-term treatment in SRNS is difficult using only renal biopsy; it is necessary to introduce genetic molecular analyses to establish a judicious therapeutic attitude.

PRES should be suspected in all children with kidney disease, HTN, and/or immunosuppressive treatment (such as cyclosporine) who develop sudden neurological symptoms, even if imaging abnormalities are not restricted to the subcortical white matter of the occipital lobe. Severe neurological complications may develop if left untreated. Therefore, early recognition of PRES and optimal therapy are important to prevent serious neurological sequelae in these patients.

Rigorous control of HTN and blood concentrations of calcineurin inhibitors are important strategies in managing children with kidney disease in order to prevent the development of PRES. Further advances with MRI, are required to improve diagnostic accuracy and the ability to predict outcomes in patients with early-stage PRES, as well as to better understand the complex pathophysiology of this disorder. Further research is needed to set up guidelines for PRES diagnosis and treatment.

I.2 Thrombotic pathology related to CKD in children

A wide range of clinical and paraclinical manifestations accompany CKD, which is a pathological entity with numerous complications. Venous thromboembolism (VTE), one of the complications of this complex pathology, is a major cause of death and illness, with multiple etiopathogenic mechanisms at play in its development. The prompt diagnosis and treatment of VTE require a high index of suspicion corroborated with specific blood analyses and imaging investigations.
The most relevant contributions in this topic are presented below.

Articles ISI – principal author

Lazaruc TI, Bodescu AIL, Lupu VV, Muntean C, Bogos RA, Ivanov A, Scurtu G, **Starcea IM**, Miron IC, Mocanu MA. Thrombosis in Chronic Kidney Disease in Children. Diagnostics, 2022, 12, 2931, IF= 3.6/2022, Q2, (Autor corespondent), https://www.mdpi.com/2075-4418/12/12/2931

Mocanu A, Bogos RA, Lazaruc TI, Cianga AL, Lupu VV, Ioniuc I, Alecsa M, Lupu A, Ivanov AV, Miron IC, **Starcea IM**. Pitfalls of Thrombotic Microangiopathies in Children: Two Case Reports and Literature Review. Diagnostics. 2023; 13(7):1228, IF= 3.6/2022, Q2, https://doi.org/10.3390/diagnostics13071228

Article BDI – principal author

Dusa CP, **Starcea IM**, Mocanu A, Munteanu M, Russu R, Mihaila D, Buhus G, Ivanov A, Gavrilovici C, Miron I. Thrombotic complications in central venous catheterization with long-life catheters in pediatric chronic hemodialysis. Jurnalul Pediatrului – Year XXI, Vol. XXI, Nr. 83-84, july-december 2018, pag. 8-12, (Autor corespondent), http://www.jurnalulpediatrului.ro/magazines/83-84.pdf

Book chapter

Iliescu D., Russu R., **Stârcea M**., Tromboembolismul la copil, în Tromboembolismul pulmonar în situații clinice speciale, Editura PIM, 2017 (ISBN 978-606-13-3734-7), cap. III, pag. 23 – 29;

I.2.1 Thrombosis in CKD in Children

I.2.1.1 Introduction

Children with CKD present an increased risk of VTE, and special attention must be directed to possible recurrences. Children, especially those with dialysis, require special management before and after imaging investigations such as CT angiography.

Children with CKD and suspected VTE require special diagnostic strategies, such as anesthesia, scheduling the hemodialysis session, adjusting the doses of radiotracers, anticoagulants, or other specific therapies. In adult patients with suspected VTE, several prediction scores (Wells PE, Wells DVT, revised Geneva score, PERC score) were designed.

The scores offer good sensitivity and specificity but cannot rule out the VTE diagnosis; instead, they are important to determine the high or low probability of VTE. (Wells 200, Le Gal 2006).

For children with suspected VTE, there are no validated scores or other types of tools. Several studies extrapolated these scores, Wells and PERC, to pediatric patients, but no predictive scores were validated (Hennelly 2016, Biss 2009). The thromboelastogram and thrombin generation test are global hemostasis tests that provide information on both bleeding and clotting tendencies. The thromboelastogram has been used in the management of extracorporeal circuits in ESRD. Measurement of antithrombin (AT), protein C, and protein S levels, as well as the identification of factor V Leiden or prothrombin gene mutations, only provide information about a specific component of the hemostatic system, but they do not allow quantification of the general thrombotic tendency resulting from the interaction between inherited and acquired factors.

The AT level can be influenced by heparin therapy, while the activity of protein C and protein S can be falsely decreased during vitamin K antagonist therapy (Radulescu 2015). Low levels are also found during the evolution of the NS, explaining the tendency to hypercoagulability in these patients. APTT is used to evaluate the effect of therapy with unfractionated heparin. To assess the anticoagulant effect of fractionated heparin or some of the newer direct-acting oral anticoagulants (DOACs), the anti-Xa assay or activated clotting time (ACT) is routinely used to assess bleeding and thrombosis risks. (Le Gal 2006).

The level of D-dimers is a measure of fibrin production and degradation. Normal pediatric ranges of D-dimers are age-dependent (Radulescu 2015). However, global coagulation tests do not assess the significant role played by platelets and endothelial cells. Platelet function can be assessed by identifying markers of platelet activation and reactivity in plasma and/or on circulating platelets, such as platelet factor 4 and thromboglobulin in platelet-poor plasma. This is usually performed by blood flow cytometry, which is used to measure activated platelets as well as platelet turnover (Nair 2021). Consequently, newer assays that directly measure thrombin generation in plasma, as well as those that assess the stages of hemostasis, including clot initiation, propagation, and fibrinolysis in whole blood by viscoelastic methods, are what may allow a global measurement of the hemostatic system. Currently available methods for viscoelastic testing include thromboelastography (TEG) and the related rapid thromboelastography (r-TEG), as well as rotational thromboelastography (ROTEM) (Nair 2021).

The treatment with the new DOACs in children is not yet considered a standard of care, especially in children with renal impairment because of the increased risk of bleeding complications. Several studies in the field, such as the DIVERSITY and EINSTEIN-Jr. studies, ruled out children with various degrees of renal failure. DOACs have many advantages, and, in general, the patients require normal renal function. Although the renal excretion of every type of DOAC is different, their administration in patients with CKD is limited (Halton 2021, Male 2020).

I.2.1.2 Aim

The first article is a state-of-the-art overview, where we have reviewed the physiologic and pathologic mechanisms underlying pediatric thrombosis and updated current diagnostic and treatment options, emphasizing personal experience as well.

I.2.1.3 Materials and Methods

This paper reviews the clinical presentation, pathophysiology, differential diagnosis, treatment and evolution of thrombotic pathology related of CKD, from our clinical experience.

This is a retrospective study, approved by the IRB, with patients hospitalized in Pediatric Nephrology and Pediatric Onco-Hematology Clinics of "Sfanta Maria" Emergency Children Hospital, Iasi, Romania. The research adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee (6878/26.02.2022) of our hospital.

While in the general pediatric population, the incidence of VTE is only 0.07–0.49 cases/ 10,000 children, in children hospitalized for any cause, it reaches 4.9–21.9 cases/10,000 children (Kerlin 2012). This reveals the importance of VTE in the course and prognosis of patients during hospitalization and indicates that in the pediatric patient, the susceptibility for the development of VTE is closely related to the presence and progression of underlying pathologies. The mortality risk of deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) as constituent entities of VTE is 2–6 times higher than in the general pediatric population (Kerlin 2012), and these patients also associate a 5–10% prevalence of post-thrombotic syndrome (disabling venous insufficiency) with the development of recurrent VTE in 10% of cases (Kerlin 2012). However, it is necessary to take into account that the increase in the incidence of VTE at this age is linked to the progression of chronic renal pathologies. Biological manifestations lead to the emergence of the specific pathophysiological context of VTE occurrence, which is conceptualized in the form of Virchow's triad (Fig. 1.6). CKD favors the onset of this triad (consisting of venous stasis, endothelial injury and hypercoagulable status) by various mechanisms, which is why, compared to other pediatric chronic conditions, CKD has the highest rate of hospital-associated VTE (Setty2012). However, this association differs according to the etiology of the CKD, and the distribution and determinants of VTE (including VTE secondary to graft failure and VTE in AVF) have not yet been established for these children.

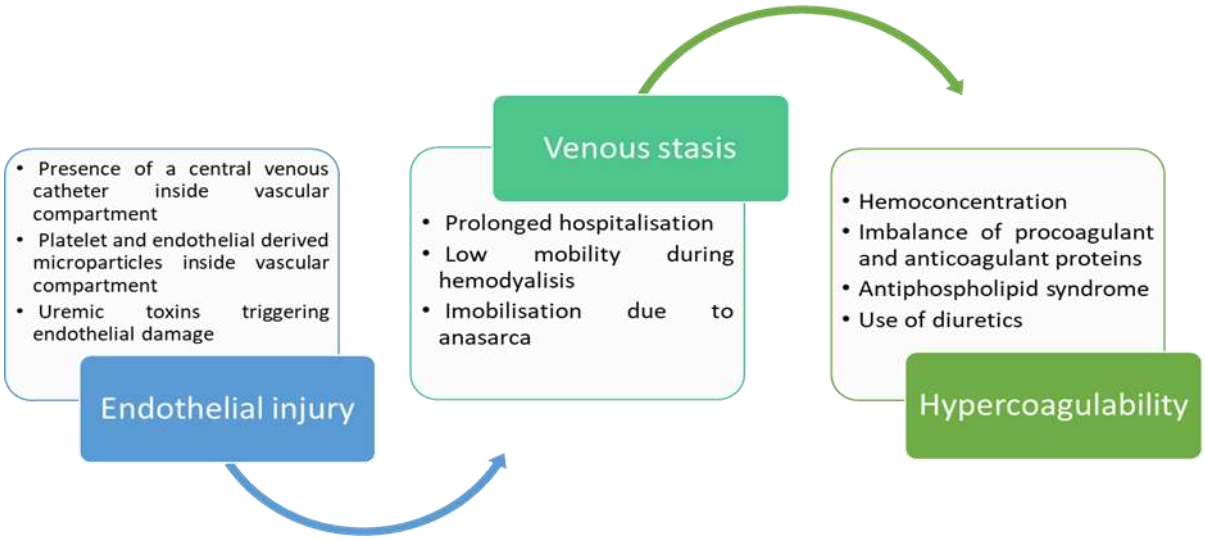

Fig. 1.6. *Renal involvement in Virchow's triad.*

A search was conducted on the PubMed database to retrieve all the published literature on pediatric atypical hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. The Medical Subject Headings (MESH) terms we used were (((atypical hemolytic uremic syndrome (Mesh Terms)) OR (aHUS (Mesh Terms))) AND (thrombotic thrombocy- topenic purpura (Mesh Terms))) OR (immune thrombocytopenic purpura (Mesh Terms)) AND

(pediatric (Mesh Terms)) OR (paediatric (Mesh Terms))) AND (((COVID-19 (Mesh Terms)) OR (SARS-CoV-2 infection (Mesh Terms))). The search did not have any limitations on the type of article or publication date. After removing duplicate articles and those without access to full-text reports, 9 case reports were identified, regardless of language, which included pediatric patients diagnosed with atypical hemolytic and uremic syndrome (aHUS) and thrombotic thrombocytopenic purpura (TTP) in relation to COVID-19 infection.

I.2.1.4 Results

VTE associated NS - in the Nephrology Division, "Sfânta Maria" Emergency Children Hospital, Iași, we have been confronted with thrombotic pathology in patients with NS. Of particular relevance is the case of a male patient, diagnosed with cortico-resistant nephrotic syndrome, in whom renal biopsy detected MCNS and IgM deposits. In evolution, he presented multiple relapses marked by massive oedema, requiring correction with albumin and diuretic therapy. In this context, he developed thrombosis of the inferior vena cava, as shown by Computer tomography (CT) imaging, with extension to the right renal vein and to the junction of the internal and external iliac veins (Fig. 1.7). In evolution, he developed three more episodes of thrombotic recurrence, under the same conditions of severe hypoproteinemia, and required 2 years of anticoagulant therapy.

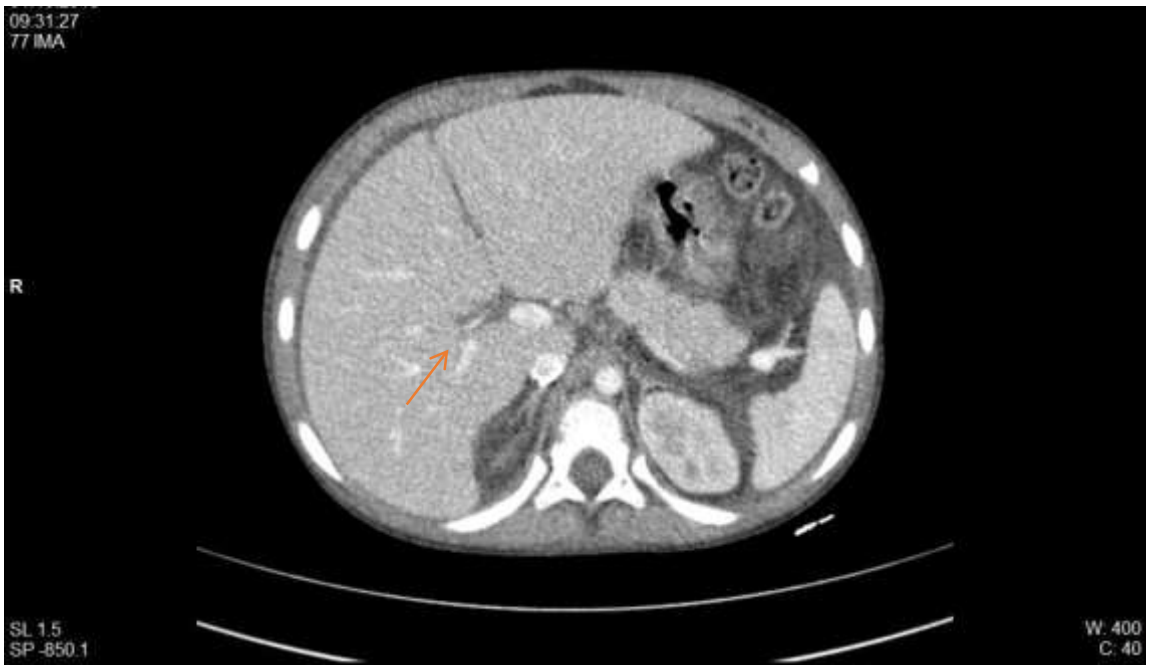

Fig. 1.7*. CT scan: thrombosis of the inferior vena cava with extension to the right renal vein (red arrow) (personal collection Nephrology Department).*

VTE associated SLE - a female patient diagnosed with SLE and class IV lupus nephritis, who was initially treated with pulse therapy with methylprednisolone and i.v. cyclophosphamide. After 4 months of evolution, she presented with fever and acute respiratory failure phenomena for which we excluded an infectious pathology (tuberculosis, viral, fungal or bacterial pneumonia). Biologically, the antiphospholipid syndrome was detected with high anticardiolipin antibodies titer (73.96 pg/mL), and the presence of lupus anticoagulant. CT imaging examination (Fig. 1.8) revealed the appearance of right

pulmonary artery segmental branch thrombosis, pulmonary embolism and right secondary pleurisy. Anticoagulant treatment with Enoxaparin was instituted for 6 months, at the end of which respiratory function tests revealed severe restriction and medium obstruction (CV = 47.6%, FEV 1 = 54.8%). Oral anticoagulant therapy was maintained under INR control for 2 years.

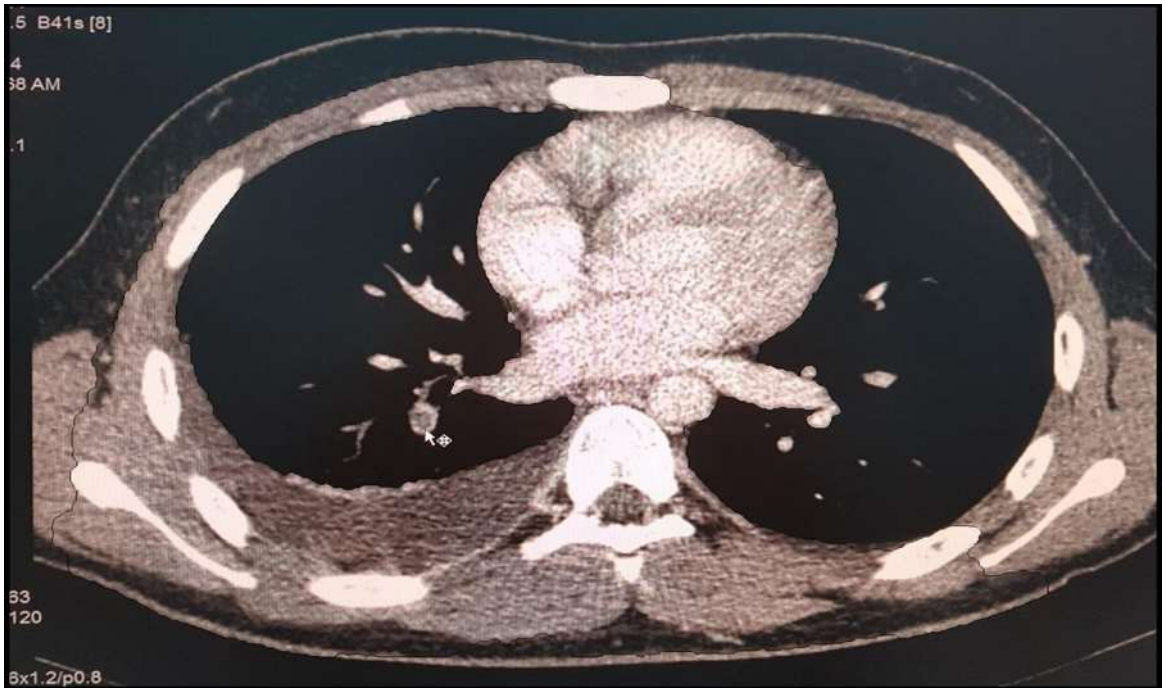

Fig. 1.8. *CT scan, appearance of right pulmonary artery segmental branch thrombosis, pulmonary embolism and right secondary pleurisy (personal collection Nephrology Department).*

VTE associated ESRD by posterior ureteral valve (PUV) - we illustrate the incidence of VTE with the case of a male patient diagnosed with recurrent urinary tract infections due to a late detected posterior urethral valve, which is associated with secondary vesicoureteral reflux.

He required initiation of dialysis on long-life central catheter in January 2016. In evolution, he presented two episodes of catheter disfunction through thrombosis, for which we initiated local therapy with Taurolok/Urokinase. Subsequently, he required catheter replacement because of septic complications. A new thrombotic episode was observed in the evolution, which was biologically supported by increased serum D-dimer level (2314 ng/mL) and confirmed by CT examination (Fig. 1.9), with localization in the right internal jugular vein (IJV).

In this context, thrombolytic treatment with tissue plasminogen activator factor was initiated, and further hemodialysis sessions required the placement of a temporary central venous catheter (CVC) on the right femoral vein. To prevent further thrombosis, anticoagulation was continued with enoxaparin in a dose adapted to the creatinine clearance.

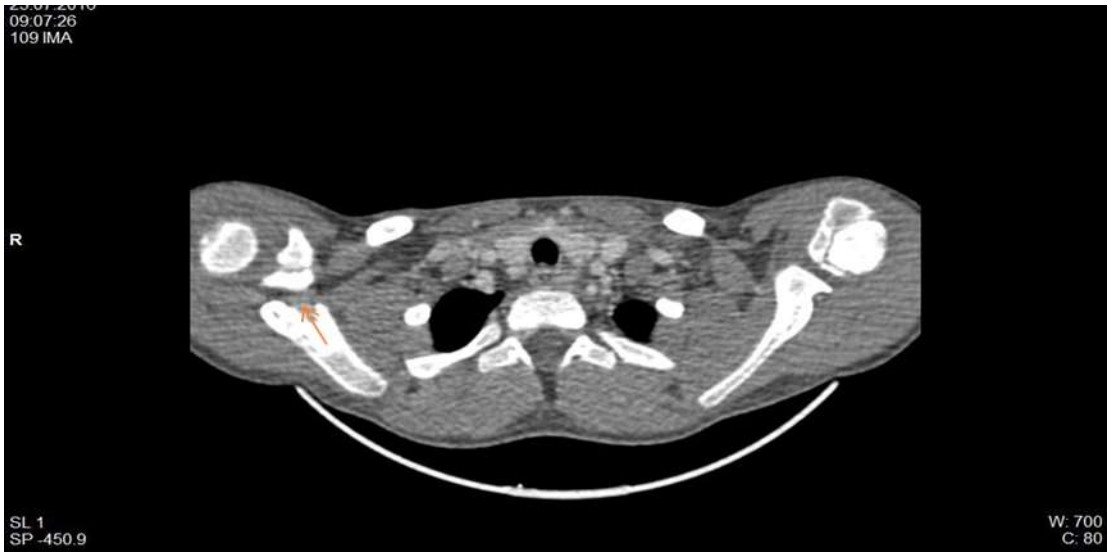

***Fig. 1.9**. CT scan, right IJV thrombosis (red arrow) (personal collection Nephrology Department).*

VTE associated ESRD by NS - another case in our clinic's collection was a female patient diagnosed with impure NS with unfavorable progression to end-stage CKD. She underwent KRT by continuous ambulatory peritoneal dialysis for 13 years but required conversion to chronic hemodialysis in the context of sclerosing peritonitis (Fig. 1.10). One year after conversion, she presented with an episode of catheter dysfunction, with CT scanning revealing right IJV thrombosis (Fig. 1.11) as well as tracheal calcifications in the context of calciphylaxis. Subsequently, hemodialysis proceeded with difficulty, with the patient evolving numerous thrombotic recurrences on the newly placed catheter.

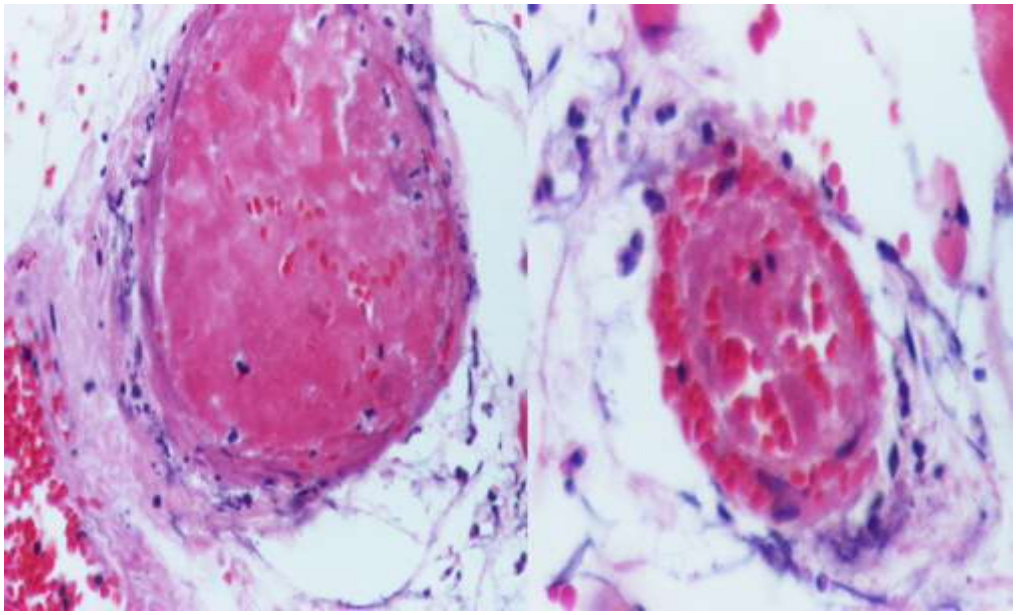

***Fig. 1.9**. Peritoneal biopsy - perivascular calcifications and thrombosis of the small peritoneal vessels.*

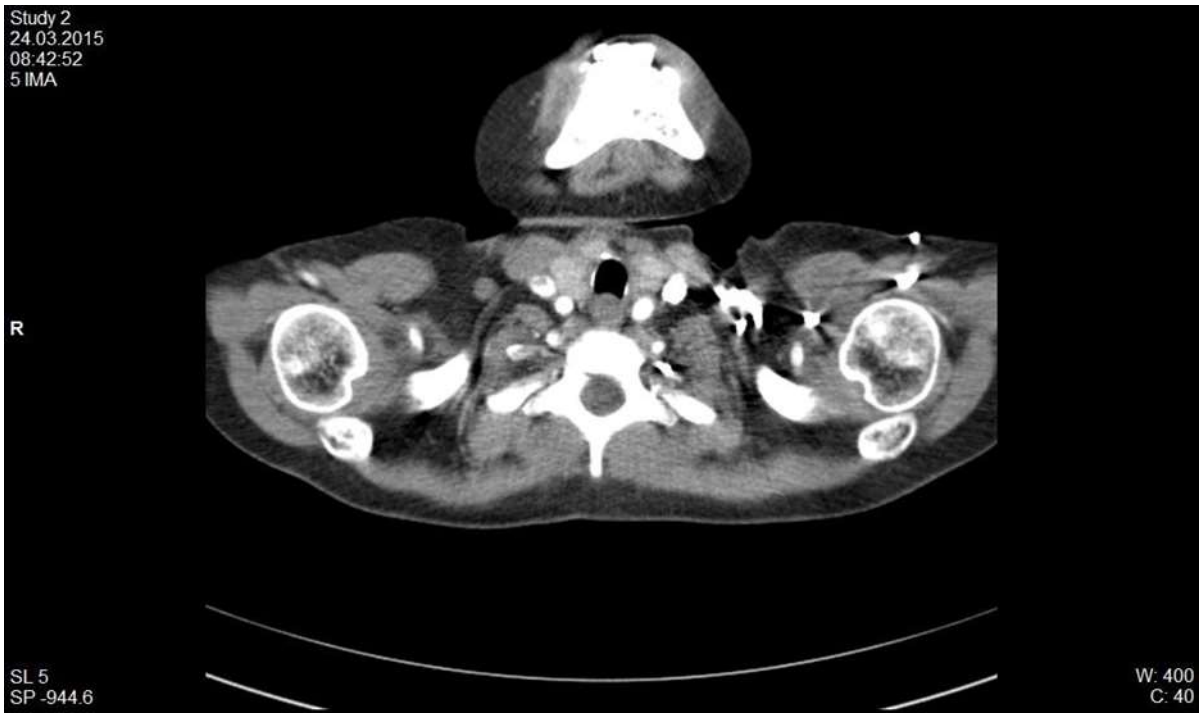

***Fig. 1.10**. CT scan, right IJV thrombosis, calcifications in the trachea in the context of calciphylaxis.*

VTE associated ESRD and thrombophilia - The last case presented with VTE, from our statistic is a girl who has reached the end stage of kidney disease due to a reflux nephropathy. In evolution, she presented multiple episodes of peritonitis, with secondary sclerosing of peritoneum, necessitating conversion to hemodialysis on CVC.

In the context of a heterozygous profile for thrombophilia, the girl developed numerous episodes of CVC thrombosis, which is a dysfunction that prejudiced the dialysis sessions. In the context in which she developed extensive thrombosis of the bilateral jugular vein and brachycephalic trunk (Fig. 1.12), the girl required an unusual vascular approach, with access to the iliac vein, through the Seldinger technique on the epigastric vein (Fig. 1.13).

The literature confirms that factor V Leiden and prothrombin G20210A are considered to be predominant genetic risk factors for VTE in Caucasian populations, and heterozygotes have a 20-fold increased risk of VTE, while individuals with the prothrombin G20210A allele had an increased about four times risk of thrombosis (Wu 2022).

Numerous studies have investigated the function of genes linked to thromboembolism in dialysis. Grupp (Grupp, 2019) evaluated several thrombophilic risk factors, such as mutations in factor V, MTHFR, and prothrombin, in hemodialysis patients, and the results indicated that thrombophilic risk factors were substantially associated with an increased shunt thrombosis risk.

The inherited thrombophilic mutations of the factor V gene (FVG1691A Leiden-FVL) may act as a risk factor for CKD, but the presence of thrombophilic mutations did not affect the overall survival of patients with CKD-5 (Liapi, 2021).

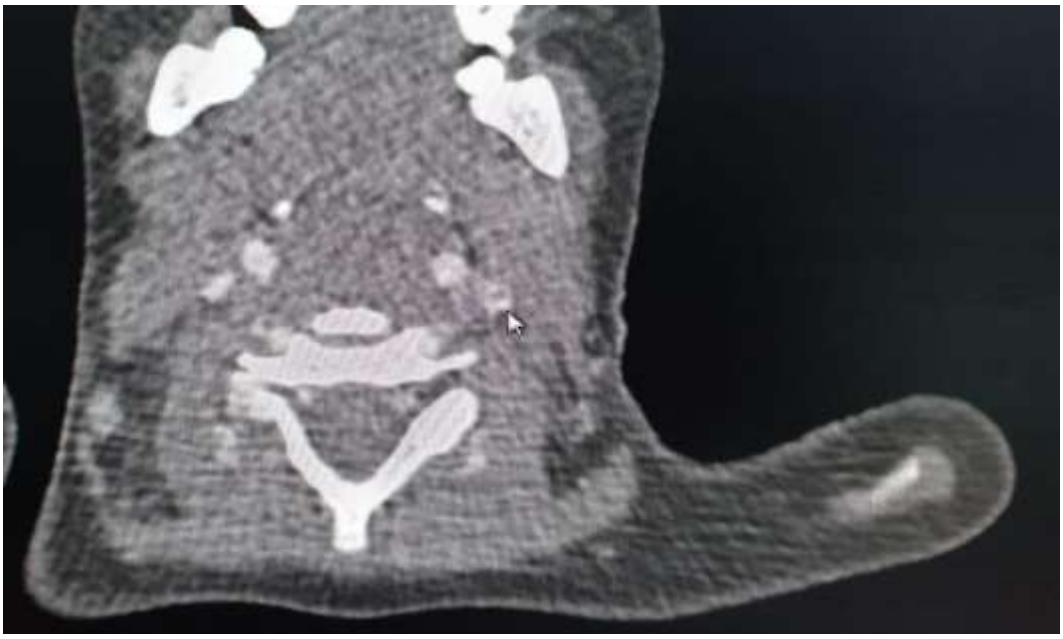

Fig. 1.11. *CT scan, left IJV thrombosis. (white arrow).*

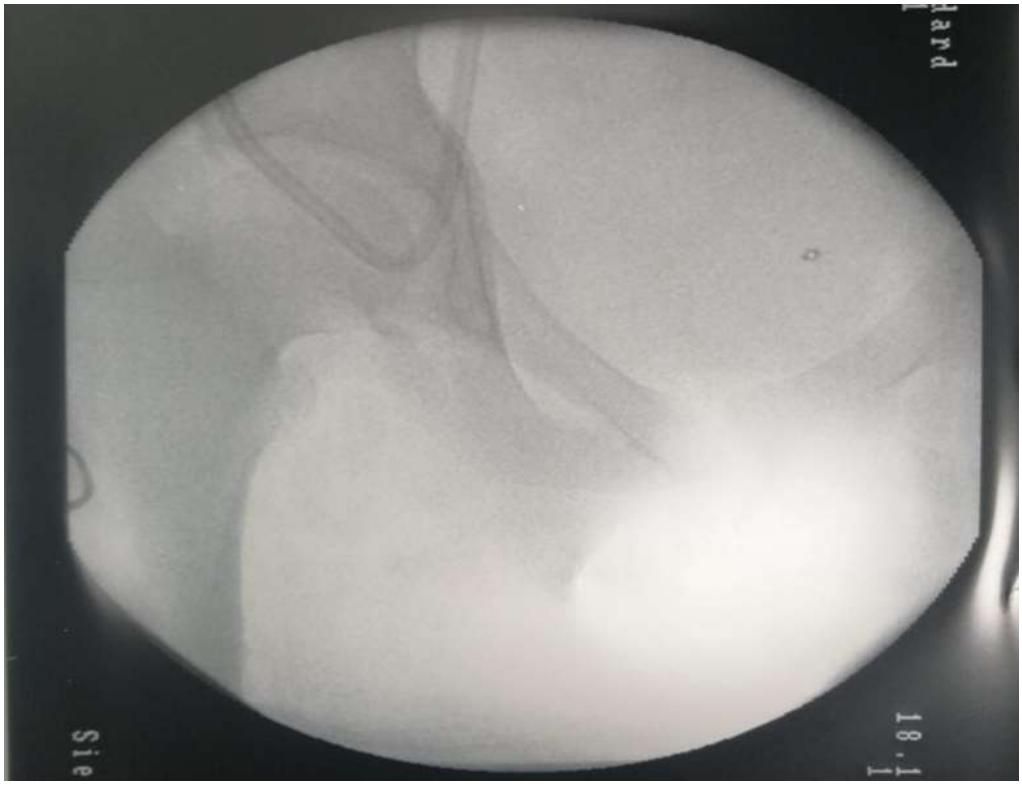

Fig. 1.12. *C arm X-ray - Unusual placement of central venous catheter in the epigastric vein for chronic hemodialysis.*

I.2.1.5 Discussion

VTE - is a severe complication in CKD of various etiologies, which is driven by complex and different mechanisms involving numerous risk factors. The main studies investigating this pathology in children are systematized below in Table 1.6.

Table 1.6 *Relevant studies depicting the children risk for VTE*

Authors	Study type	Sample Size and Age	Aims	Main results
Hennelly, 2016	Single-center retrospective study	561 children < 22 years of age	To evaluate the children risk for PE, using adult Wells criteria and Pulmonary Embolism Rule-out Criteria (PERC)	The risk of pulmonary VTE is low among children not receiving estrogen therapy and without tachycardia and hypoxia. Application of the PERC rule and Wells criteria should be used cautiously in the pediatric population.
Biss, 2009	Retrospective cohort study	50 children with PE	To evaluate D-dimer value and Wells probability score for PE in children	The Wells clinical probability score and D-dimer estimation may lack utility in the determination of pre-test probability of PE in children.
Van Ommen, 2001	Prospective 2-year registry of VTE in children	99 children ≤ 18 years old	To study the incidence, diagnostic, and complications of pediatric VTE	VTE is mostly diagnosed in hospitalized children, especially sick newborns with central venous catheters and older children with a combination of risk factors.
Setty, 2012	The Kids' Inpatient Database 2006	4500 children ≤18 years old	To evaluate the incidence of VTE in tertiary care settings	Pediatric VTE is most commonly seen in tertiary care. Adolescents are at greatest risk to develop in-hospital VTE.
Suri, 2013	Retrospective study	34 children	To evaluate the incidence of venous and arterial thrombosis in children with nephrotic syndrome	Venous and arterial thrombosis occur in children with nephrotic syndrome, with subtle clinical features. Neuroimaging and angiographic techniques confirm diagnosis, and early aggressive heparin therapy is necessary for a favorable outcome.
Zhang, 2014	Prospective study	512 patients in the study cohort, 80 children	To determine the prevalence PE and renal vein thrombosis in patients with NS	PE pulmonary embolism and RVT renal vein thrombosis are common in patients with NS, occurring in 19% of children and

				38% of adults. PE pulmonary embolism is more common than RVT renal vein thrombosis
Kerlin, 2009	Comprehensive chart review	326 children	To identify the risk factors of VTE in children with NS	Children with NS have risk for VTE, particularly those who are age 12 years or older, have severe proteinuria, or have a previous history of VTE.
Hoyer, 1986	Prospective study	16 children	To evaluate the incidence of VTE in children with steroid responsive minimal change nephrotic syndrome	The incidence of thromboembolic complications in children with severe nephrotic syndrome is as high as reported for adults.
Singh, 1997	The Report of the North American Pediatric Renal Transplant Cooperative Study database	4394 transplanted children	To identify the risk factors for VTE in transplanted children	Living donor transplant with a history of prior transplantation had a significantly higher rate of thrombosis as compared with those who received a primary transplant. Cold ischemia time greater than 24 h in the patient who received cadaver donor kidney increased the risk for thrombosis. The use of antibody induction therapy, donors greater than 5 years of age, and increasing recipient age were factors that decreased the risk for thrombosis.
Smith, 2006	The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) database	8990 transplanted children	To identify the risk factors for VTE in transplanted children	The use of IL-2 receptor antibodies as induction therapy is associated with a significantly decreased risk of graft failure due to thrombosis.

VTE – venous thromboembolism; PE – pulmonary embolism; RVT – recurrent venous thrombembolism

VTE and NS

NS is associated with a hypercoagulable state caused by thrombocytosis and numerous hemostatic abnormalities: on the one hand, low levels of AT III, free protein S and plasminogen in the context of urinary leakage, and on the other hand, increased levels of procoagulant proteins (fibrinogen and factors V and VIII) with consequent increased platelet activation.

Pathophysiologic factors involved in the increased risk of thromboembolic complications in children with NS also include hemoconcentration (Hb greater than 14 g/dl), dehydration, immobilization (especially in patients with anasarca), infection, venous or arterial puncture (CVC), diuretic consumption, corticosteroids (i.v.), thrombocytosis (over 450,000/mm3), proteinuria, hypoalbuminemia (below 20 g/dl), hyperfibrinogenemia as well as a possible underlying genetic thrombophilic tendency. The reported incidence of thromboembolic complications in children with NS is between 1.8 and 4.4% (Suri 2014), in patients with congenital NS, the incidence of VTE can be as high as 10–13% (Zhang 2014). This is consistent with the results of a retrospective study including 326 children with NS of different etiologies, conducted between 1999 and 2006, in which the incidence of thromboembolic events (TEE) was reported to be 9%, with a mean time to TEE of approximately 71 days after diagnosis of NS and with DVT as the most common entity seen in these children, which is closely correlated with CVC use (Kerlin 2009). Multivariate analysis demonstrated that the risk of TEE was higher in children over 12 years of age and increased with increasing urinary protein excretion use (Hennelly 2009). A recent study of 512 patients, 80 of whom were children, with NS either in remission or with minimal symptoms detected PE recurrent venous thrombosis (RvT) in 35% of cases (predominantly PE—85%), 19% of the pediatric group associated PE RvT (Kerlin 2009).

All these aspects suggest that subclinical VTE associated with NS may be much more common than commonly appreciated. The category of secondary NS includes SLE and IgA vasculitis, which associate antiphospholipid antibody production as well as a generalized inflammatory status that may biologically mediate the increased risk of VTE in these patients. Regarding the location of thromboembolism in patients with NS, both arterial and venous thrombosis have been reported, with the latter predominating and occurring most frequently in the cerebral and pulmonary veins. The cerebral symptoms may lend themselves to a differential diagnosis with PRES, especially in the case of patients treated with immunosuppressive drugs such as calcineurin inhibitors (Starcea 2018).

VTE and ESRD

Children with ESRD frequently show imbalances in hemostasis with the risk of consecutive bleeding or pathological thrombosis. Factors that increase the risk of VTE in ESRD are correlated, on the one hand, with the underlying pathology that caused the progression of CKD and, on the other hand, with ESRD-specific uremia. In this regard, uremic toxins derived from tryptophan catabolism stimulate thrombotic processes mainly by increasing platelet activation (in the context of increased fibrinogen receptor levels and decreased nitric oxide levels) and by the constitution of a "prothrombotic" endothelium (predominantly in the context of homocysteine-mediated endothelial cell injury, the formation of an intravascular reservoir of platelet- and endothelium-derived microparticles and the consequent increase in tissue factor concentration).

When a chronic dialysis catheter is used for a long time, complications like fibrin coating, mural thrombosis, venous thrombosis, and intraluminal clot formation are likely to happen (Whenzheng 2017, Kerlin 2015, Deepa 2012). After placing the central venous catheter, fibrin coating of the catheter may occur. Fibrin sheath development has been reported in 47% of CVC-placed patients. This, in itself, facilitates infection and mural

thrombosis (Whenzheng 2017). Mural thrombosis is usually found near the entrance of the catheter in the vessel or at the great vein junction. There are many risk factors for thrombosis, such as CVC biocompatibility, the positioning of the tip of the catheter or its insertion, the insertion point, thrombofilia, and CVC-related infections (Whenzheng 2017).

VTE and Kidney Transplantation

For pediatric ESRD patients undergoing renal transplantation, a common cause of graft rejection is renal artery or vein thrombosis. According to the 1995 North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) annual report (Warady 1997), vascular thrombosis accounts for 12.2% of causes of graft loss, and in the case of second transplantation, vascular thrombosis is blamed for 19.2% of graft loss, replacing acute rejection as the second most common cause of graft failure. Subsequently, the same working group conducted a study of 4394 transplanted children, 138 of whom experienced vascular thrombosis resulting in graft loss (Singh 1997). Vascular thrombosis is usually seen within the first few days to three weeks after transplantation. In this specific setting, VTE may occur secondary to technical complications such as torsion or vascular endothelial injury due to excessive manipulation. Risk factors for VTE in this category of patients are age under 2 years of the recipient, age under 6 years of the donor, long cold ischemia time (>24 h), hypoperfusion in young children receiving an adult graft, venous malformation in the recipient, pre-transplant peritoneal dialysis, a hypotensive episode during or after surgery, the presence of multiple arteries as well as previous cyclosporine therapy.

I.2.1.6 Conclusion

VTE is a serious complication of CKD and requires increased attention both for the management of acute episodes and for prophylactic measures when necessary. Of the CKD etiologies, NS is associated with the highest risk of thromboembolic events, and risk factors for VTE in children with NS are age over 12 years, history of VTE prior to diagnosis of NS, secondary nephrotic NS (SLE, IgA vasculitis) but also membranous nephropathy. Further research is needed to assess the impact of childhood NS and on vascular endothelial cell biology, which is suspected to play a major role in VTE progression. Observational cohort studies are needed to validate VTE risk groups that may benefit most from thromboprophylaxis and disease-specific treatment algorithms for SN-associated VTE await evidence from multicenter collaborative group studies.

Pediatric ESRD patients represent 1–2% of the general ESRD population. In them, uremia has a thrombogenic effect that overlaps with risk factors for VTE associated with the underlying pathology. In addition, performing hemodialysis on CVC is the most commonly used method of renal supplementation in these patients, and the presence of CVC in the vascular lumen increases the risk of TEE, with CVC occlusion or thrombosis being the main cause of CVC dysfunction.

In kidney transplant patients, vascular thrombosis is the third leading cause of rejection and is most commonly seen in the first few days after transplantation. Despite all the issues described, extensive and validated studies are needed in children with CKD to quantify and identify thromboembolic risk factors. Subsequently, susceptible patients should benefit from non-pharmacological TEE prevention measures or should be enrolled in clinical trials to verify the impact of initiating thrombo-prophylactic therapies.

I.2.2 Pitfalls of Thrombotic Microangiopathies in Children

I.2.2.1 Introduction

Atypical hemolytic and uremic syndrome (aHUS) is a type of thrombotic microangiopathy (TMA) that is caused by dysregulation of complement activation, either genetic or acquired (Kaufeld 2021). aHUS is a main part of Microangiopathic hemolytic anemia (MAHA), together with thrombotic thrombocytopenic purpura (TTP). TTP is a disorder characterized by the formation of platelet-rich thrombi within the vasculature, resulting from a severe deficiency of the von Willebrand factor (vWF)-cleaving metalloproteinase, ADAMTS13 (Chiasakul 2018). TTP represents a rare and severe medical condition, especially in the pediatric population. Complement system is the primary focus in pathophysiology of aHUS, as opposed to TTP. In aHUS, alternative pathway dysregulation seems to be implicated in more than 60% of cases (23–25) with possible findings in complement pathways exploration being decreased in Factor H or Factor I—main regulators of complement system—decreased C3 with normal or moderately decreased C4, anti-Factor H antibodies or no identifiable biochemical modifications in complement system exploration (Loirat 2016).

I.2.2.2 Aim

In this article, we discuss thrombotic microangiopathies, with emphasis on aHUS and TTP, which are rare diseases in children.

I.2.2.3 Material and Methods

aHUS case

A two-year-old boy has been referred to our clinic for severe diarrhea (10 stools per day) starting 4 days before presentation, with tonic–clonic seizures, oligo-anuria and melenic stools installing in evolution. Clinical examination showed profound general distress, severe dehydration, tachycardia, blood pressure 104/55 mmHg, systolic heart murmur, normal lung auscultation and no justification indicated for an acute surgical intervention for abdomen, while maintaining melenic diarrheal stools and anuria. CBC count revealed normochromic normocytic anemia (Hb 9.3 g/dL) and thrombocytopenia (39,000/mmc) while renal function assessment confirmed a severe acute kidney failure (AKI) (creatinine 3.9 mg/dL, blood urea nitrogen = 185 mg/dL) corresponding to class III pRIFLE AKI. A clinical suspicion of a **thrombotic microangiopathic anemia** was confirmed trough peripheral blood smear showing 8% schistocytes and increased LDH in context of hemolysis. Stool cultures were negative for Shiga-toxin producing E. coli serotypes. A decrease in Hb, thrombocytes number and renal function followed, with consistent anuria, hypervolemia, HTN and unilateral lower limb myoclonic seizures, accompanied by signs of mild cerebral edema, bilateral ethmoiditis, left lung infiltration and bilateral pleurisy on computed tomography. Hemodiafiltration, antihypertensive treatment (calcium-blocking agents, central alfa-dilators) and blood transfusions were started. Facing a TMA in a two-year-old boy with no prior disease history, aHUS was suspected and plasma exchange therapy was initiated. Serology for hepatic viruses B and C, immunodeficiency virus, Epstein–Barr virus, cytomegalovirus, Toxoplasma and COVID-19 PCR were negative. Serology for COVID-19 was also performed, showing moderately increased titers of anti-Spike protein IgG subunit S1 (340 UI/L) and S2 (399 UI/L); therefore, a decision of implementing i.v. immunoglobulin administration was made. Blood sampling for

biochemical and molecular analysis of complement system was carried out before treatment in the Research Laboratory of Semmelweis' University, Department of Internal Medicine and Hematology, Hungary. Results are shown in Table 1.7, while a graphic representation of classical pathway alternative pathway, factor I and factor B antigen activity are shown in Fig. 1.14. On their basis, TTP was excluded (ADAMTS13 activity decreased, but was not deficient), and ongoing hemolysis was noted (severely decreased haptoglobin).

The results are indicative of classical pathway activation and consumption, therefore potentially related to triggering infection. In context of the absence of signs of amelioration despite advanced supportive measures including plasmapheresis and i.v. immunoglobulin, inhibitory complement therapy (Eculizumab) was started, with concomitant anti-meningococcal and H. influenzae vaccination. Recovering of diuresis, renal function amelioration, a decrease in blood pressure and increase in Hb and thrombocytes number slowly installed, confirming a complement-mediated TMA in our patient, specifically aHUS. In this context, the patient was initiated on a therapeutic protocol for aHUS consisting in administration of Eculizumab 300 mg every 2 weeks.

During the latest follow-up visit, clinical examination was normal. He presented with Hb 10 g/dL, with normal LDH, less than 4% schistocytes on peripheral blood smear, no thrombocytopenia, creatinine 0.58 mg/dL with a renal clearance (Schwartz pediatric formula) of 73 mL/min/1.73, normal C3 and C4 fractions with no proteinuria. Administration of anti-C5 monoclonal antibody had to be continued as an underlying genetic mutation in the complement system has not yet been ruled out.

Table 1.7 *Total complement activity analysis before treatment initiation for PPT*

Total complement activity
Classical pathway (hemolytic test): 45 CH50/ml (reference range 48-103 CH50/ml)
Alternative pathway (WIELISA-Alt): 104 % (reference range 70-125%)
Complement C3: 0,71 g/L (reference range 0,9-1,8 g/L)
Complement C4: 0,08 g/L (reference range: 0,15-0,55 g/L)
Factor H antigen: 375 mg/L (reference range 250-880 mg/L)
Complement factor I antigen: 89 % (reference range 70-130%)
Complement factor B antigen: 92 % (reference range 70-130%)
Anti-factor H IgG autoantibody: 16 AU/mL (reference range <110 AU/mL)
C1q antigen= 58 mg/L (reference range 60-180 mg/L)
Anti-C1q IgG autoantibody= 0 U/mL (reference range <52 U/mL)
Haptoglobin< 0,07 g/L (reference range 0,3-2,0 g/L)

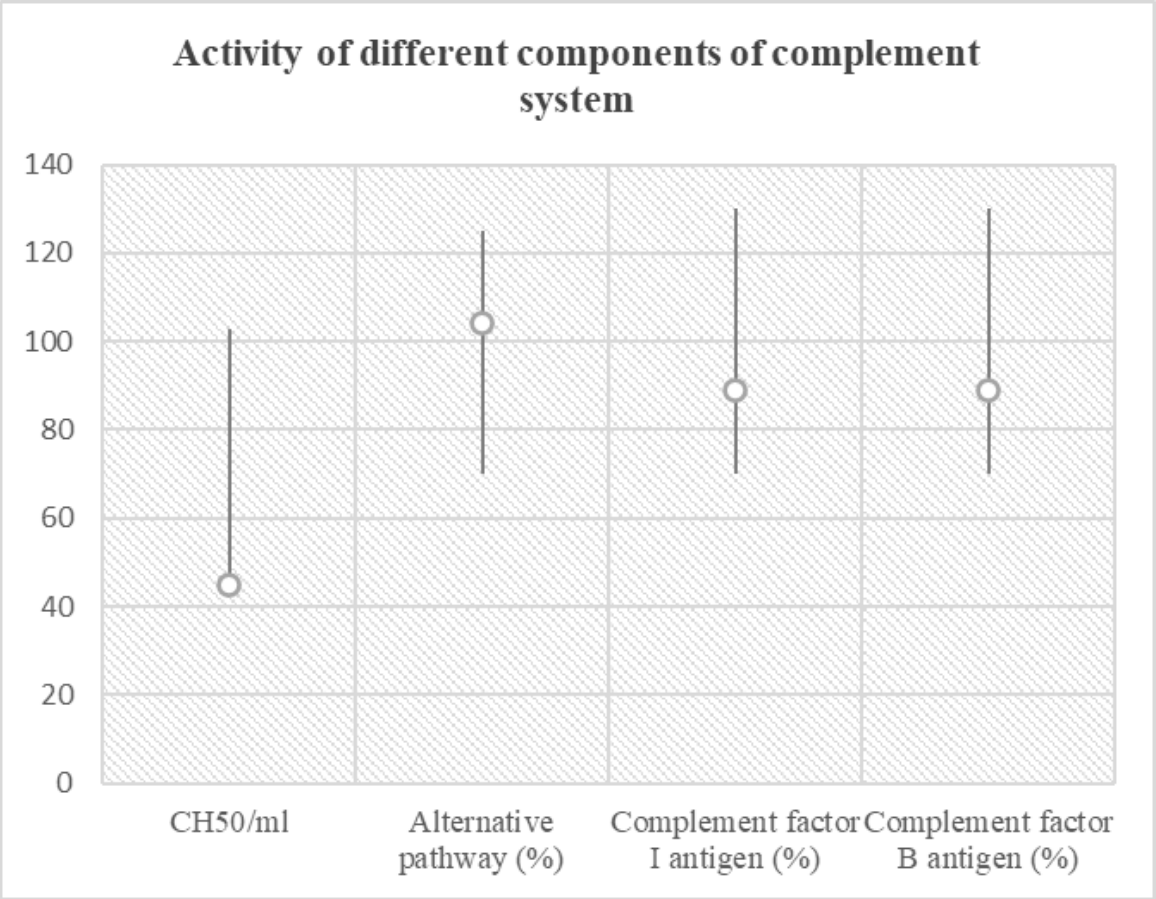

Fig. 1.13. *Classical pathway, alternative pathway, complement factor I and factor B antigen activity in relation with reference range.*

TTP case

A 16-year-old Romanian female presented to the Saint Mary Emergency Children Hospital from Jassy on 5 January 2023, complaining of asthenia, diffuse headache, odynophagia, dysphagia, fever, vomiting and a semi-solid stool, symptoms that started approximately 10 days before presentation. No recent vaccinations were observed. The patient did not have any significant medical history, nor did she report any tobacco, alcohol or drug abuse. She had not received a blood transfusion in the past and was not taking any medications at the time of admission. Additionally, there was no notable family medical history. Physical examination revealed an afebrile, normotensive female with headaches, marked asthenia, pale and jaundice, no petechia, no bleeding, discrete pharyngeal congestion observed. The patient did not exhibit any signs of splenomegaly, liver hypertrophy, or lymph node hypertrophy upon physical examination. There were no other noteworthy observations made during the examination. Abdominal ultrasound and echocardiogram did not reveal any significant findings, and the urine pregnancy test came back negative. The complete blood cell count (CBC) revealed WBC = 11,510/mmc, severe thrombocytopenia = 9000/mmc, severe hemolytic anemia with Hb = 4.7 g/dL, MCV = 92.3 fL, reticulocytosis = 14.23%, increased LDH = 1837 U/L, hyperbilirubinemia due to the indirect fraction, increased ferritin = 2269.82 µg/L, and haptoglobin was <25 mg/dL. D-dimer level was 3578 ng/mL, there was no inflammatory syndrome, normal liver and kidney functions (creatinine = 0.6 mg/dL), APTT = 24.7 s, INR = 1.16, Fibrinogen 355.8 mg/dL, PT = 84.2%. Normal immunogram,

normal triglycerides. Complement C3 and C4 within normal limits. Serum iron, amylase, total proteins, ionogram came out within normal limits. Urinalysis showed hemoglobinuria and proteinuria. Blood smear showed erythroblasts = 6/100 elements, hypochromia, anisopoikilocytosis (microcytes, normocytes, schistocytes, spherocytes, macrocytes, dacryocytes), platelets in low numbers. Schistocytes 3–4%. Bone marrow biopsy exclude an oncologic pathology. Immunophenotyping negative for tumoral markers. In addition, 0.5% B lymphoid precursors (with CD34 phenotype- cyCD79a+ CD19+) were described. The examination was completed by evaluating the thyroid function, which was normal. The antinuclear antibody (ANA) test was within normal range, while the extractable nuclear antibody profile showed a positive antibody (ANA)-HEp-2 test. The direct Coomb's test positive, while antineutrophil cytoplasmic antibodies, anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies, lupus anticoagulants, anti-β2-glycoprotein antibodies, anticardiolipin antibodies, and anti-red blood cell antibodies were negative. The tests conducted to detect the presence of various pathogens such as human immunodeficiency virus (HIV), hepatitis C virus, hepatitis B virus, Epstein–Barr virus, cytomegalovirus, influenza virus or Mycoplasma pneumoniae were negative. While RT-PCR RNA-SARS-CoV-2 was also negative, elevated titers of SARS-CoV-2 IgM and IgG were detected. In the face of hemolytic anemia and severe thrombocytopenia, blood transfusion was initially indicated. Six hours after the admission, PLASMIC score was calculated with a result of six points, indicating a high risk of TTP (Table 1.8).

Table 1.8 *PLASMIC score calculated 6 h after admission.*

Criteria and points	
Platelet count <30 x 10^9 per L	1
Hemolysis variable	1
No active cancer	1
No history of solid-organ or stem-cell transplant	1
MCV <90fL	0
INR <1.5	1
Creatinine <2.0 mg/dL	1

The PLASMIC score is a clinical prediction tool consisting of seven components that have been designed to accurately determine the pretest probability of severe ADAMTS13 deficiency (C statistic 0.96, with a 95% confidence interval 0.92–0.98) (Bendapudi, 2017, Miler 2021).

I.2.2.4 Results

TMA

The literature research revealed nine case report-styled articles (Kasturiarachi 2022, Vorster 2022, Domínguez-Rojas 2022, Kirpalani 2022, Hamza 2022, Khandelwal 2022, Dalkıran 2021, Searcy 2022, Alizadeh 2021) comprising 15 pediatric cases of MAHA related to COVID-19 infections, of which six patients were di- agnosed with TTP and nine patients were diagnosed with aHUS. Four out of six patients in TTP group were females, while six out of nine subjects in aHUS group were males. Median age at presentation for TTP group

was 15.5, in contrast to 7 for aHUS patients. One patient in TTP group eventually expired, while one patient in aHUS group has not recovered renal function, requiring chronic hemodialysis. All other cases had an evolution towards full or partial resolution. All these patients presented with schistocytes on peripheral blood smear and high LDH serum levels, as proof for MAHA.

In 2017, Goodship et al. (Goodship 2017) proposed a classification of TMA comprising TTP, HUS related to Shiga-toxin producing E. coli (STEC-HUS) and atypical HUS, multiple subgroups being described in the latter, as shown in Fig. 1.15.

This classification underlines the fact that a diagnosis of primary aHUS can only be made after excluding numerous etiologies such as bacterial and viral infections, autoimmune disease, drug-induced aHUS, malignancy and others. In this regard, a confusing factor is that in the literature, the term "aHUS" is frequently used only to describe hemolytic uremic syndrome without coexisting disease, i.e., primary aHUS.

Nevertheless, there is at least some consensus that historic terminology describing diarrhea-positive (D+) and diarrhea-negative (D-) HUS should not be used anymore, since there are multiple patients with complement-mediated aHUS who present with diarrhea or colitis (Loirat 2016, Fremeaux-Bacchi 2013), a fact also confirmed by our clinical case. Here, we refer to aHUS according to Goodhips' et al. classification.

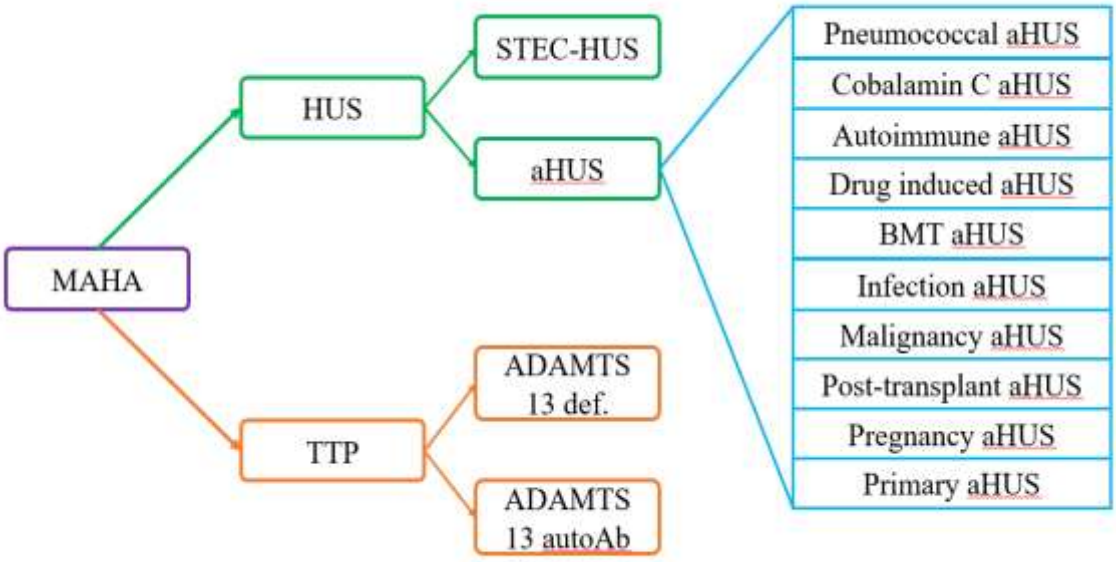

Fig. 1.14. *Pathological entities in differential diagnosis of MAHA. After Goodship et al., 2017 (21), MAHA—Microangiopathic hemolytic anemia; HUS—hemolytic uremic syndrome; STEC—Shiga-Toxin E. coli; aHUS—atypical hemolytic uremic syndrome; BMT—bone marrow transp*

MAHA, a low platelet count and renal failure, are the clinical criteria supportive of aHUS, with neurological findings and fever being less common in such patients. This is in contrast to our clinical case, in which tonic–clonic seizures were present early in the beginning.

However, from a pathophysiological point of view, thrombi formation in any organ can occur. Clinical criteria might not all be present at the same time; therefore, physical and biological evaluation at onset and in evolution provides the most important arguments for a positive diagnosis. Negative testing both for ADAMTS13 deficiency or presence of anti-ADAMTS13 autoantibodies, with a negative assessment for STEC-HUS trough Shiga-like toxin testing and STEC stool culture, supports the diagnosis of aHUS, for which further secondary causes must be ruled out in order to verify the diagnosis of primary aHUS. Complement system is the primary focus in pathophysiology of aHUS, as opposed to TTP. In aHUS, alternative pathway dysregulation seems to be implicated in more than 60% of cases (Fremeaux-Bacchi 2013, Maga 2010, Kavanagh 2013) with possible findings in complement pathways exploration being decreased in Factor H or Factor I—main regulators of complement system—decreased C3 with normal or moderately decreased C4, anti-Factor H antibodies or no identifiable biochemical modifications in complement system exploration (Liorat 2016). Important genes coding for complement-related proteins, including inhibitors of the system, must be evaluated, as they may provide relevant information for long-term management of patients. The workup should include FH, FI, MCP, C3, FB and THBD genes. Complement Factor H-related genes and other rare forms of aHUS—interesting additional genes such as diacylglycerol kinase-epsilon (DGKE) or cobalamin C metabolism dysfunction (MMACHC gene)—should also be tested for.

TTP is a rare type of thrombotic microangiopathy (TMA), distinguished by the occurrence of microangiopathic hemolytic anemia (MAHA), severe thrombocytopenia, and ischemic end-organ damage (Scully 2017).

COVID-19 represents an infectious disease caused by the coronavirus SARS-CoV-2. The novel SARS-CoV-2 virus infection has had an impact on our understanding of the previously unknown interactions between the immunological mechanism and the coagulation cascade. In a pediatric patient, the risk of developing VTE is strongly associated with the existence and advancement of underlying pathological conditions (Lazaruc 2022). Over the course of the pandemic, novel conditions and complications have surfaced, such as multisystem inflammatory syndrome in children (MIS-C), which frequently resembles other established diseases, such as thrombotic microangiopathy or Kawasaki disease (Pouletty 2020, Esposito 2021). Infection with this virus can lead to a wide range of clinical manifestations, including pediatric TMA, as shown by a growing number of clinical case reports (Hamza 2022, Khandelwal 2022, Dalkıran 2021, Searcy 2022, Richardson 2022, 124. Van Quekelberghe 2022). Although still unclear, the mechanisms behind this association might be related to loss of protection of endothelial cells and thrombocytes against complement membrane attack complexes. It is widely recognized that TMA arises due to injury to endothelial cells in small blood vessels, resulting in hemolytic anemia, thrombocytopenia and, in certain instances, organ impairment (Diorio 2020). It has been proposed that SARS-CoV-2 may cause TMA by complement activation (Skendros 2020, Yu 2020). This can result in uncontrolled formation of the C5b9 membrane attack complex, leading to the clinical features of TMA. Soluble C5b9 (sC5b9) is a biomarker that is clinically available and has been suggested as an indicator of TMA severity (Campbell 2020, Merrill 2020). All thrombotic microangiopathies are initiated by endothelial damage caused by the virus. Binding of SARS-CoV-2 to the ACE-2 receptors which are expressed in airway epithelial cells damages vascular endothelial cells. This leads to the release of pro-inflammatory chemo-attractants such as C3a and C5a, which recruit more leukocytes (Verdecchia 2020). Activated leukocytes release cytokines, including IL-6, TNF, and IL-1, causing more endothelial damage and platelet aggregation. In their study, Gralinski et al. showed that SARS-CoV-2 introduced to mice caused lung damage and complement protein deposition, which was reduced when the virus was introduced to C3-deficient mice

(Gralinski 2018). Reports have emerged that some of the vaccines against COVID-19 may be associated with vaccine-induced immune thrombotic thrombocytopenia (VITT) which is triggered by the presence of antibodies that recognize platelet factor (PF4) bound to platelets (Pavord 2021, McGonagle 2021). According to current research, it is believed that the vaccine triggers formation of neoantigens (first hit) and a subsequent systemic inflammatory response (second hit). This results in the production of anti-PF4 antibodies (platelet factor 4 antibodies) (Szóstek-Mioduchowska), which inhibit the activity of ADAMTS13, therefore unable to regulate the multimeric size of vWF. Consequently, the accumulation of ultra-sized vWF multimers can result in the formation of platelet-rich microthrombi (Petri 2019). Recent literature data suggests that there is a strong possibility that COVID-19 acts as a trigger for HUS or TTP, both of which express TMA (Matoševic 2023).

I.2.2.5 Conclusion

COVID-19 caused by SARS-CoV-2 virus may act as an immunologic stimulus that triggers the onset of MAHA. At present, there are few data in the literature that discuss TTP or aHUS caused by COVID-19 infection in pediatric patients. We report on two pediatric cases presenting with aHUS and TTP following SARS-CoV-2 infection. Our observations indicate that several manifestations of MAHA can be triggered by COVID-19 infection.

I.3 Genetic Pathology related to CKD in children

CKD is a complex disorder that encompasses a wide range of phenotypes, each of which is the result of kidney disease under pressure, as well as environmental and genetic factors with a stronger influence. The complexity of the phenotypic composition of kidney diseases makes it difficult to diagnose, predict and select the optimal treatment for each patient. The importance of elucidating the genetic basis of kidney diseases and their complications is highlighted by the effect of genetic variability on the development of renal failure.

My contribution and the team I work with in this field are illustrated below.

Articles ISI – principal author

Starcea IM, Bodescu Amancei Ionescu L, Lazaruc TI, Lupu VV, Bogos RA, Ioniuc I, Dragan F, Lupu A, Galatanu LS, Miron IC, Mocanu A. Palm-Plant Pain, Sign of a Severe Systemic Disease? Case Report and Review of Literature. Genes. 2023; 14(2):516, IF= 3.5/2022, Q2, https://doi.org/10.3390/genes14020516

Muntean C**, Starcea IM**, Stoica C, Banescu C. Clinical Characteristics, Renal Involvement, and Therapeutic Options of Pediatric Patients With Fabry Disease. Frontiers in pediatrics, 2022, 10, 908657, IF= 2.6/2022, Q2, https://www.frontiersin.org/articles/10.3389/fped.2022.908657/full

Article BDI – principal author

Lazaruc T, **Starcea IM**, Ivanov A, Scurtu G, Mocanu AM, Lupu VV, Lupu A, Bogos RA, Miron I, Bodescu AIL. Kidney involvement in Seckel Syndrome. RJOR, 2022, 14(3), 83-90, https://www.rjor.ro/kidney-involvement-in-seckel-syndrome/

ESRD is an advanced form of chronic renal failure in which kidney function has declined to 10–15% of normal before initiation of dialysis or transplantation. Blood pressure

and kidney function are closely related. Physiologically, the kidneys play an essential role in the control of chronic blood pressure, while high blood pressure affects kidney function through the pressure-nature mechanism (Elshamaa 2011). Recent advances in genome analysis technologies have had a significant impact on the laboratory and clinical practice of medical genetics. Monogenic diseases are a significant but underappreciated cause of CKD. It is estimated that they account for 70 percent of the global prevalence of ESRD in minors and 10 to 15 percent in adults (Nine 2022). These estimates are derived from extensive registries, including the European Registry of Rare Kidney Diseases (Bassanese 2021). More than 400 gene mutations are associated with inherited kidney disease. Early detection of a monogenic cause of CKD can have significant consequences for patients and their families (Stokman 2016). Numerous potential benefits are associated with molecular genetic testing for inherited renal disease (Bassanese 2021). First, genetic testing has the potential to provide an accurate diagnosis of a disease's underlying cause via a minimally invasive and increasingly time-efficient test, despite the fact that costs are still high. An early genetic diagnosis can circumvent a rare renal disease's sometimes laborious diagnostic algorithm. Although genetic testing is increasingly replacing renal biopsy and histological examination, it should still be used in conjunction with biopsy (Murray 2020).

At least one-quarter of pediatric **proteinuric glomerulopathies** are hereditary (Sadowski 2015, Trautmann 2015, Warejko 2018). The probability of identifying a causative genetic abnormality decreases with increasing disease onset age. In 80% of cases of congenital NS, screening for NPHS1, NPHS2, WT1, and LAMB2 identifies the underlying genetic defect. In Europe, NPHS2, WT1, and NPHS1 are the most common causes of hereditary SRNS that starts in childhood. In Asia, COQ8B defects are the most common cause (Sadowski 2015, Trautmann 2015, Song 2020). More than 60 genes have been linked to glomerulopathies (Murray 2020).

In a recent multicenter European study, **inherited tubulopathies** were detected in 64% of children and 28% of adults (Ashton 2018, Song 2020). More than 60 genes have been linked to tubulopathies (Murray 2020). Most of the encoded proteins are transporters, pumps or channels that can be transepithelial or paracellular and are the main cause of renal hypophosphatemia, Bartter syndrome types 1-3, hypercalciuria, familial nephrocalcinosis, distal renal tubular acidosis and nephrogenic diabetes insipidus. Other proteins regulate the expression or activity of transporters, pumps, or channels (Bartter syndrome types 4a and 5, pseudohypoaldosteronism type 2, and insulin-resistant diabetic nephrogen), while others participate in intracellular processes such as endocytosis (Dent's disease). Some metabolic disorders were included in this group because their initial manifestation was of the tubulopathy type (De Toni-Debré-Fanconi syndrome from cystinosis or Kearn Sayre Syndrome) (Murray 2020).

Rare prototypical **complement-related diseases** aHUS, immune complex-mediated MPGN (IC-MPGN), and C3 glomerulopathy (C3G) are all connected to genetic and acquired changes in regulatory proteins and the two C3 convertase components of the alternative complement pathway (Goodship 2017, Shmit 2019). Patients with aHUS and IC-MPGN/C3G should get a thorough genetic screening that looks at at least the CFH, CD46, CFI, C3, CFB, THBD, and DGKE genes. In addition to genetic testing, it is recommended to look for acquired complement abnormalities, such as anti-FH autoantibodies in aHUS and IC-MPGN/C3G and anti-C3b, anti-FB, and anti-CR1 antibodies, as well as C3 nephritic factors in IC-MPGN/C3G (Noris 2019, Marinozzi 2017, Blanc 2015).

CAKUT occur in 3–6 of 1000 newborns, representing 20% of anomalies detected antenatally (Murray 2020). CAKUT is the leading cause of CKD in children. The phenotypic spectrum is very broad and may include varying degrees of renal parenchymal defects of the kidney (agenesis, hypoplasia, or multicystic renal dysplasia), obstructive/refluxing megaureter or vesicoureteral reflux, and lower urinary tract obstruction (posterior urethral valve and urethral atresia) (Madariaga 2013). In isolated or syndromic CAKUT, pathogenic variants in more than fifty genes have been reported.

Renal ciliopathies are a heterogeneous group of hereditary disorders. Often, extrarenal manifestations are associated. The group of cystic kidney diseases includes polycystic kidney disease, autosomal dominant and autosomal recessive polycystic kidney disease and nephronophthisis (Murray 2020).

Aim

In the next few paragraphs of my thesis, I will present two interesting and rare diseases that are genetically conditioned, which were diagnosed in our department, representing true challenges for medical professionals.

First one is **Fabry disease**, an X-linked lysosomal storage disorder, results from α-galactosidase. The wide spectrum of signs and symptoms in Fabry disease represents a challenge in its management nowadays, and these include timely diagnosis and early therapy in children, the necessity for biomarkers that are correlated with the earliest changes in histology. Early enzyme-replacement therapy (ERT) and other therapeutic strategies may impact morbidity and mortality in Fabry disease patients. A delay in diagnosis of Fabry disease influences the quality of life and reduces the life expectancy in nontreated patients.

Second one is a rare form of microcephalic primordial dwarfism, alsoknown as **Seckel syndrome**. This autosomal recessive disease, although very rare, requires a multidisciplinary approach in order to manage the neurologic, cardiovascular, hematologic, endocrinologic, metabolic and kidney related complications.

I.3.1 Fabry disease

I.3.1.1 Material and methods

Also known as Anderson-Fabry disease (OMIM #301500), this is a multisystem and heterogenous lysosomal storage disease, with an X-linked inheritance pattern characterized by complete or partial deficiency of the lysosomal alpha-galactosidase A (α-Gal A) enzyme activity. The enzymatic defects result in subsequent accumulation of globotriaosylceramide (Gb3 or GL3) and glycosphingolipids within cellular lysosomes, plasma, and urine causing multiorgan damage with life-threatening manifestations (Vardarli 2020).

Fabry disease is a multifaceted condition that begins during intrauterine life. Elleder et al. stated that storage material is already present in the fetal kidney (Elleder 1998), while Vedder et al. only investigated placental storage and speculated on storage in fetal organs (Vedder 2006). Usually, even if the affected infants look normal at birth, the clinical signs of the disease will develop gradually once undigested sphingolipids (SLs) such as globotriaosylceramide and globotriaosylsphingosine (lysoGb3 or lysoGL3) accumulate in the body, as a result of the degree of the enzyme deficiency and the severity of the toxic metabolites storage within organs. The clinical impact relies on the severity of the enzyme

insufficiency and the tissues in which toxic nonmetabolized intermediates (such as Gb3) accumulate (Alkhzouz 2021).

Fabry disease recognizes two major phenotypes: "classic or early-onset" and a mild or "late- onset" phenotype. The classic forms usually occur in childhood or adolescence. Affected males with the late-onset type have residual α-Gal A activity, correlated with a later-onset cardiac and/or renal disease, and lack the major early-onset classical manifestations (Spada 2006). Fabry disease is a rare disorder with an estimated overall incidence varying from 1:17000 to 1:117000. The classic form of Fabry disease is estimated to have a prevalence of 1:22000 to 1:40000 in males, while the prevalence for atypical presentation is evaluated to be 1:1000 to 1:3000 in males and 1:6000 to 1:40000 in females (Bokhari 2022). A recent meta-analysis of dialysis patients with FD revealed that the classic forms are more frequent than true late- onset forms if pathogenic GLA mutation is considered (Capuano 2020). Also, Choi et al. found a four times higher incidence for classical vs. late-onset Fabry disease (Choi 2017). Fabry disease prevalence in different geographical areas is presented in Table 1.9.

Table 1.9 *Prevalence of Fabry disease according to region*

Region	**Evaluated period**	**No of the patients screened positive**	**Detection rate/prevalence**	**No of the subjects tested**	**Reference**
Northwestern Italy	July 1, 2003 to June 30, 2005	12	1/ 3,100 late-onset (without novel mutation 1/4.600 males); 1/3,7000 classic phenotype	37,104 boys	(Spada, 2006)
Hungary, Szeged	NL	8 (3 c.427 G>A (p.A143T) +5 intronic sequence change c.-10C<T)	1/5003 Low *α*-Gal A in 224, retesting 34	40,024 (boys and girls)	(Wittmann , 2012)
Spain; Galicia	2008	37 genetic variants 1 case p.M290I (c.870G>A)	1/7,575	14,600	(Colon, 2017)
Netherlands	1970–1996	27	1/47,6190 (0.21/100,000) (live births) 1/238,095 (0.42/100,000) (male live births)	12,634,905 No. of live births (6,495,078 No. of male	(Poorthuis , 1999)

				live births)	
North of Portugal	1982–2001	1	1/833,000 live births	NL	(Pinto, 2004)
Austria	January 2010 to July 2010	9	1/3,859	34,736 (boys and girls)	(Mechtler, 2012)
Missouri	January 1 to July 10, 2013	15	1/2,913	43,701 (boys and girls)	(Hopkin, 2016)
Japan	NL	339	1.25/100,000	NL	(Koto, 2021)
Japan (Fukuoka City and its vicinity)	April 2007 to April 2010	NL	1/7,057 14.17/100.000	21,170 (boys and girls)	(Inoue, 2013)
Taiwan	July 2006 to June 2008	75 GLA mutations (73 boys+2 girls); 86% c.936+919G >A	1/1,250 males GLA mutations; 1/1.460 males of the IVS4+919G>A splicing mutation	171,977; (90,288 males; 81,689 females) (86% had the late-onset phenotype: 1 in 1.390 males)	(Hwu, 2009)

Even if a severe phenotype is more frequent in males vs. females, heterozygous women may also exhibit symptoms of varying severity depending on random inactivation of one of the two X chromosomes. The result of a random X chromosome inactivation is represented by a mosaic of cell populations, leading to variable phenotypes from asymptomatic to severely symptomatic heterozygous females (Chimenz 2022).

Fabry disease patients require life-long follow-up to detect changes in signs and symptoms. It is characterized by progressive neurological, renal, cardiac, ocular, and dermatological manifestations (Militaru 2019). In Fabry classical disease, kidney involvement starts early, during intrauterine life by the Gb3 deposition. Even if CKD is discovered later in adult life in Fabry disease patients, a decline in GFR can occur during adolescence. So, early and close monitoring of kidney and other organ functions is required. Early diagnosis of Fabry disease is important as enzyme replacement therapy reduces symptoms, and improves clinical features, biochemical markers, and the quality of life.

More importantly, early treatment could slow or stop progressive organ damage in later life. Pulmonary involvement is usually mild and expressed by fatigue, persistent cough, obstructive lung disease, and impaired pulmonary function tests (Wang 2007). Fabry disease has an X-linked pattern of inheritance, usually, the GLA mutation is transmitted to the boys through a heterozygous mother. A heterozygous female for GLA gene mutation may have affected boys (50%) and healthy boys (50%), and each daughter has a 50% chance of being a heterozygote. An affected father will not transmit the disorder to his son. The daughters of an affected father with Fabry disease will be heterozygotes. Negative family history of Fabry disease does not rule out the diagnosis.

The lysosomal hydrolase alpha-galactosidase A (α-Gal A) deficiency will lead to the systemic progressive lysosomal accumulation of complex glycosphingolipids with terminal α-galactosyl moieties, mainly globotriaosylceramide (Gb3) and its deacylated, amphiphilic metabolite, namely globotriaosylsphingosine (lysoGb3), and to a lesser extent, galactosylceramide and other derivatives manifestations (Olivera-González 2017). Substrate accumulation within lysosomes in the cells of different tissues promotes various pathogenic mechanisms in which are implicated different mediators leading to multisystem lesions, resulting in clinical manifestations of the disease as well as the development of complications that reduce the quality of life manifestations (Nowicki 2020). Accumulation of Gb3 results in characteristic lysosomal deposits (Fabry inclusions) in different organs and cell types, known as myelin Fig.s and zebra bodies manifestations (Biegstraaten 2012) leading to cell death, with progression to fibrosis and irreversible organic damage and reducing the average life expectancy by 10 years at women and by 25 years at men manifestations (Silva 2021).

Clinical features in FD - The clinical symptoms of Fabry disease may present at any age, in children and adults (Klingelhöfer 2020, Ries 2005). According to the residual GLA enzyme activity of normal value, it may be graded as residual (1–5% of normal values) or no residual (<1% of normal values), or nearly complete deficiency of α-Gal A activity (Pisani 2018). There are two different types of Fabry disease, the early-onset type and the late-onset type. Usually, the early-onset type occurs mostly in males with absent or nearly complete deficiency of α-Gal A activity, while the late- onset type occurs mainly in cases with residual α-Gal A activity (Germain 2010). The occurrence of early symptoms during childhood is linked to the severity of α-Gal A deficiency. The early-onset type associated with classical phenotype for Fabry disease in male patients involves no residual α-Gal A enzyme activity and begins during childhood.

Clinical symptoms which appear in childhood are represented by gastrointestinal symptoms, neuropathic pain (pain attacks, chronic pain), acroparesthesia, angiokeratoma (AK), hypohidrosis, and corneal opacities (cornea verticillata). Gastrointestinal and eye involvement was reported within the first decade of life. Also, the early median age at onset was observed in males vs. females (at least 2–5 years later in girls vs. boys) (Ramaswami 2006, Laney 2015). Cardiac, renal, and skin manifestations of Fabry disease occurred in the second decade of life (adolescence) (Hopkin 2008, Ramaswami 2006). Laney et al. (Laney 2015).and Hopkin et al. (Hopkin 2016) reported the mentioned signs and symptoms and their onset early in life (during the toddlerhood and early childhood period).

The main signs and symptoms of Fabry disease observed during childhood are pain (neuropathic pain most frequently localized in palms, soles, and fingertips or acroparesthesia that begin in early childhood) (Laney 2015, Burand 2021), reduced or absent sweating (hypohidrosis or anhidrosis), heat or cold or exercise intolerance and AK that appears in children and young adolescents (Olivera-González 2018, Hopkin 2008, Laney 2015, Germain 2019, Luna 2016). The signs and symptoms of Fabry disease in children stratified by age are presented in Table 1.10. The overall quality of life (QoL) of children with Fabry is often considerably reduced and characterized by anxiety, depression, and school absences.

Table 1.10 *Signs and symptoms of Fabry disease, stratified by age.*

Signs and symptoms	**Early childhood (Luna,2016)**	**Childhood (Chimenz, 2022, Najafian, 2020)**	**Adolescence (Chimenz, 2022)**	**Age of onset (Hopkin, 2008, Laney, 2015, Allen, 2010)**
Kidney				
Proteinuria	+/-	+/-	+/-	13.8 years boys, 14.1 years girls (Laney, 2015)
Albuminuria	-	-	+	16.5 years boys, 15.9 years girls (Laney, 2015)
Low FGR (Podocyturia)	+/-	+	+	
Eyes				
Cornea verticillata (corneal whorls/retinal vascular tortuosity)	+/-	+	+	8.1 years (Allen, 2010)
Skin and membranes				
Decreased sweating (Hypo-/anhidrosis)	+/-	+	+	2.5 years (Laney, 2015)
Angiokeratoma	-	+/-	+	7 years boys, 9.5 years girls (Hopkin, 2008)
Gastrointestinal system				
Gastrointestinal symptoms	+	+	+	1–4.1 years (Laney, 2015)
Heart				
Left ventricular hypertrophy	+/-	+/-	+/-	
Arrhythmias and conduction abnormalities	+/-	+/-	+/-	9.3 years boys and 10.3 years boys, 16.9 years girls (Laney, 2015)

Heart valve disease	+/-	-	+/-	8.6 years boys, 14.4 years girls (Laney, 2015)
Nervous system				
Limb pain/Acroparesthesias	+	+	+	2–4 years (Laney, 2015)
Episodic pain crises ("Fabry crises")	+/-	+	+	
Heat or cold intolerance	+/-	+	+	3.5 years (Laney, 2015)
Hearing problems	-	-	+	4 years (Laney, 2015)

The progression of Fabry disease is concomitant with metabolite accumulation resulting in tissue involvement and progressive organs dysfunction as are depicted in Fig. 1.16.

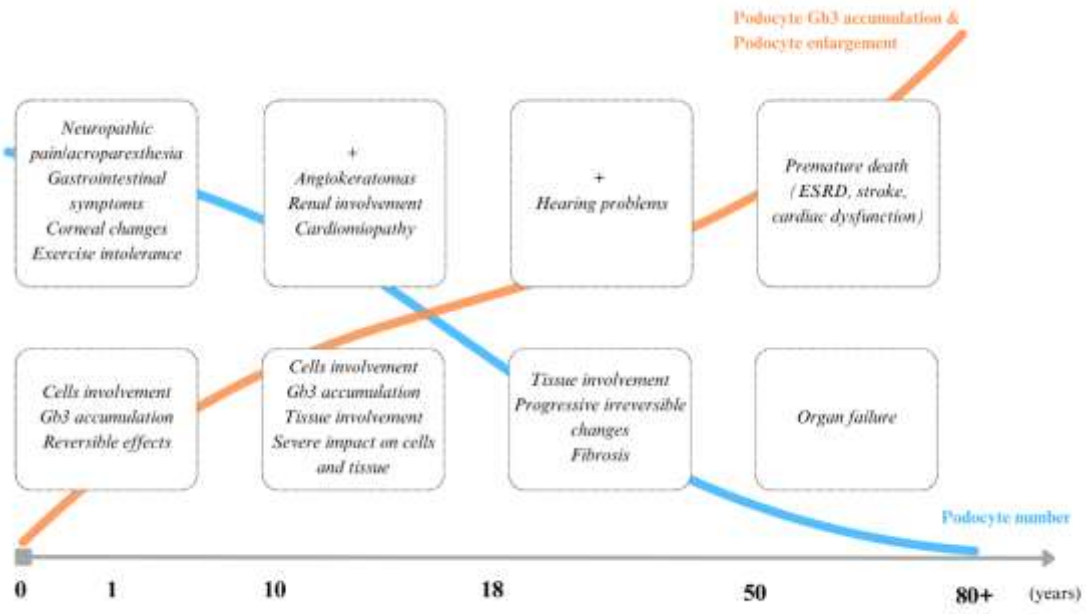

Fig. 1.16 *Progression of Fabry disease: a schematic illustration.*

I.3.1.2 Results

Fabry disease in Romanian children is rare and certainly underdiagnosed, compared to the worldwide level. Our Fabry pediatric patients with their main characteristics are presented in Table 1.11. Within our cohort, one case was diagnosed in the ESRD stage in early life (11 years). A kidney biopsy was only performed in three (43%) cases, and a characteristic FD biopsy pattern was observed. In accordance with literature data, also in our cases, kidney involvement was proved by kidney biopsy before proteinuria occurrence or GFR decline (1 from three biopsies). In our female case, the first symptoms (acroparesthesia) appeared around the age of 11 years, followed by heat intolerance and abdominal pain at the

age of 12 and 13, respectively. Non-opioid pain treatment was used only in one case and included most frequently acetaminophen but also neuromodulating anticonvulsant drugs such as gabapentin, as they proved to be efficient for neuropathic and central pain. Quality of life was evaluated in all patients with FD aged 8–17 with the Short Form 36 (SF-36) health-related quality of life survey and brief pain inventory form. ERT was proposed in four cases, but only three accepted it.

Table 1.11. *Clinical characteristics and laboratory tests of the affected patients/individuals.*

	1	**2**	**3**	**4**	**5**	**6**	**7**
Age at diagnosis	9.2 years	1.10 years	11 years	17 years	16 years	8 years	14 years
Age at kidney involvement	9 years	no	11 years	16 years	no	no	no
Sex	M	M	M	M	M	M	F
α-gal A activity (N>2.8 μmol/l/h)	0 μmol/l/h	0.1 μmol/l/h	0.25 mol/h/ml	0.17 μmol/l/h	0.91 μmol/l/h	1.68 μmol/l/h	2.2 μmol/l/h
Plasma lysoGb3 (normal range: 0.0–3.5 ng/ml)	101.1 ng/ml	-	124.5 nmol/l = 49.8 ng/ml	26 nmol/l = 10.4 ng/ml	11.24 nmol/l = 4.5 ng/ml	18.7 nmol/l = 5.88 ng/ml	2.5 ng/ml
Genetic testing GLA	c.797A>C	c.295C>T	c.317T>G	c.779G>A	c.334C>T	c.796G>A	c.644A>G
variants	(p.Asp266Ala)	(p.Gln99Ter)	(p.Leu106Arg)	(p.Gly260Glu)	(p.Arg112Cys)	(p.Asp266Asn)	(p.Asn215Ser)
Protein change	D266A	Q99*	L106R	G260E	R112C	D266N	N215S
Molecular consequence	Missense	Nonsense	Missense	Missense	Missense	Missense	Missense
Affected sibling	Mother, sister, maternal aunt, 3 cousins (2 M, 1 F), Maternal aunt and 2 deceased cousins with severe cardiac + renal illness (dialysis)	Mother and maternal grandfather	Mother	Mother	no	no	Father, Paternal grandmother, parental uncle; 3 parental grandmother sisters

Family history of stroke, heart failure, arrhythmia, etc	Cardiac illness: two maternal aunts and two maternal cousins	Maternal Grandfather: Cardiac insufficiency deceased after stroke	no	no	no	no	Father-deceased with heart failure, Parental grandmother-deceased after stroke; Uncle with CKD
Heat/cold intolerance	no	no	Heat intolerance	no	no	no	Heat intolerance
Hypo / anhidrosis	no	no	no	no	no	no	Hypohidrosis
Gastrointestinal	no	no	Nausea, epigastralgia	no	no	no	Abdominal pain
Daily neuropathic pain and tingling in hands and feet, acroparesthesia	Burn-like pain in the upper and lower limbs, mostly in the fingers of the lower limbs	Lower limbs paresthesia	Severe burn-like pains in hands and feet	Burn-like pain in hands	no	no	Burn-like pain in hands, acroparesthesia
Depression/ anxiety	no	no	depression	no	no	no	Mild depression
Hearing loss	no	no	no	no	no	no	no
Skin	no	no	no	AK (palms, anterior trunk)	AK (umbilicus, upper limbs, posterior trunk)	no	no
Eye	no	Corneal opacities, hypermetropia	Cornea verticillata	Cornea verticillata	no	no	no
Cardiac involvement	mild LVH	no	Subendocardial ischemia, malignant HTN	no	no	no	no

Others	Diabetes mellitus Type 1	no	Acute pulmonary edema	no	no	no	Urinary incontinence
Heart ultrasound	Mild LVH, mild mitral regurgitation	N	Mitral, tricuspid, aortic regurgitation Mild left ventricular and atrial dilation	N	N	N	N
ECG	N	N	ST depression, T wave inversion	Repolarization anomalies	N	N	N

*M, male; F, female; AK, angiokeratoma; GFR, glomerular filtration rate; UPCR, urine protein/creatinine ratio; ERT, enzyme replacement therapy; N, normal; NP, not performed; HCM, hypertrophic cardiomyopathy; HD, hemodialysis; HTN hypertension; Lyso-Gb3, Globotriaosylsphingosine; LVS, left ventricular hypertrophy; CKD, chronic kidney disease; PD, peritoneal dialysis. *Translation stop codon.*

Investigations of Renal Involvement in FD

Albuminuria and/or proteinuria, serum creatinine, GFR, and cystatin C, together with urinary microscopy and renal biopsy are often assessed for diagnostic, evaluation of kidney damage, monitoring of disease progression, and monitoring of treatment (Levstek 2020). Tubular dysfunction is often underestimated in children with Fabry but it should be analyzed in routine clinical care. All children with Fabry disease should undergo a renal assessment: albuminuria, proteinuria (from 24-h urine collection), and GFR. Other parameters that should be considered are serum urea, creatinine, uric acid, and Cystatin C. For early detection of microalbuminuria, the measurement of the albumin/creatinine ratio in spot urine is recommended.

In addition, the creatinine and cystatin C-based GFR-calculation is indicated for the estimation of renal function.

Also, abdominal ultrasound should be carried out in these cases. These procedures should be evaluated at the initial clinical workup and follow-up monitoring (Germain 2019).

Considering that early kidney involvement is clinically silent and that early specific therapy is more likely to prevent the progressive damage of the kidney, alternative markers of renal dysfunction are required. Therefore, the research of biomarkers that are correlated

with the earliest pathological findings is essential, as these biomarkers can become a non-invasive method of diagnosis in Fabry disease (Riccio 2019a, Riccio 2019b).

Kidney Biopsy

Different studies recommend that kidney biopsy should be considered in selected pediatric cases, especially in children with significant proteinuria or a fast decline in renal function, a variant in the GLA gene, when the decision to start ERT is doubted and an uncertain diagnosis of Fabry disease (Hopkin 2016, Levstek 2020, Maga 2010). Kidney biopsy may be considered in selected pediatric cases, especially in children with significant proteinuria or a fast decline in renal function, when the decision to start ERT is doubted; or when it is necessary to rule out a second renal disorder (Hopkin 2016). Kidney biopsy may be considered in patients where the diagnosis can be challenging and in those cases where there is uncertainty about whether to start ERT to identify the Gb3 accumulation (Carnicer-Cáceres 2021). In the study of Choi et al. that investigated Fabry disease pediatric patients from South Korea, it was observed that all children presented no proteinuria and normal serum creatinine levels. Kidney biopsy performed in three pediatric male patients before ERT revealed global sclerosis (as seen on light microscopy), while in two cases the accumulation of Gb3 was observed in the mesangial cells on electron microscopy (Choi 2017). Electron microscopy images may show characteristic/ pathognomonic zebra bodies lamellar deposits (lamellar lipid inclusion bodies) in podocyte cytoplasm and tubules (Waldek 2016). It is very important to have an early diagnosis of Fabry nephropathy whereas the early initiation of treatment may stop or delay progressive renal dysfunction more effectively compared with the late therapy initiation. Different studies considered that the kidney biopsy with electron microscopy analysis represents the only diagnostic for confirmation or exclusion of Fabry disease nephropathy and recommend to be considered for all patients with CKD, a variant in the GLA gene, and an uncertain diagnosis of Fabry disease (Levstek 2020, van der Tol 2015). The study of Thurberg et al. observed after kidney biopsy in children higher storage of Gb3 in distal tubular epithelial cells and podocytes, with the widening of their foot processes (Thurberg 2002).

Case Presentation

We present the case of an 11-year-old male boy who was transferred to the Pediatric Nephrology Department for burning pain in the palms and plants, marked asthenia, selective anorexia for meat, eyelid edema, and vertigo. The medical history attests the presence in the last 2 years of moderate normocytic normochromic anemia (Hb 8 g/dL), associated with proteinuria and microscopic hematuria. He also had repeated episodes of acute angina. From the family history, we recall both parents diagnosed with tuberculosis 4 years ago, which is why the patient underwent a prophylactic treatment with isoniazid for 6 months. The patient was investigated in a regional hospital, where facial edema, high blood pressure 155/90 mmHg, severe anemia (Hb 7.2 g/dL), market nitrogen retention (urea376 mg/dL, creatinine 14.7 mg/dL, GFR 4.71 mL/min/1.73 m), proteinuria, and microscopic hematuria in the urine summary were prominent.

Anthropometric data at the presentation in our clinic showed a marked height-weight hypotrophy, 2.5 standard deviations. The patient had a poor general condition, significant palmo-plantar pain with a burning character, pale skin and mucous membranes, and

palpebral and pretibial edema. It also associated high blood pressure (140/90 mmHg, +10 mmHg up to the 97.5th percentile for the waist), with systolic murmur III/6 at the apex, as well as oliguria—200 mL urine/24 h. Biological investigations revealed the presence of an important nitrogen retention (urea 270 mg/dL, creatinine 16 mg/dL and a GFR of 4 mL/min/1.73 m2) associated with severe hypo regenerative normochromic normocytic anemia (Hb 6.8 g/dL, Ht 20.5%, MCV 80.8 μ3, MHC 29.7 pg%, MCHC 36.8%, Reticulocytes 20‰), with high serum iron 125γ%, and ferritin 611 ng/mL, metabolic acidosis (13 mmol/L), hypocalcemia (0.4 mmol/L), hyperphosphatemia (6.64 g/L) and high alkaline phosphatase—1897 IU/L. These changes attested an advanced renal failure, complicated with renal osteodystrophy and severe anemia. We tried to correct with erythrocyte mass transfusion, and after that initiated erythropoietin treatment for secondary renal anemia. There were no changes in the liver tests, proteinemia and lipid profile. He associated nephritic range proteinuria (1.2 g/24 h). Due to the poor medical condition, with advanced renal failure, acidosis, arterial HTN, the patient required the urgent initiation of hemodialysis. At the same time, we continued investigations for the etiology of renal failure (Table 1.12.). We excluded the reflux nephropathy (secondary to primary or secondary vesicoureteral reflux, or posterior urethral valve) by voiding cystourethrogram.

Table 1.12. *Investigations for the etiology of renal failure and their results.*

Investigation	Results
Abdominal ultrasound	• Bilateral renal hypotrophy, RK 6.5/2.1 cm, LK 7.1/2.56 cm (normal size at 11 years - 10 cm). • Multiple homogenous hyperechoic nodular formations; at the lower pole of the left kidney a solid, homogeneous nodular formation with a diameter of 2.9/2.8 cm.
Abdominal-pelvic computed tomography with contrast substance (fig. 1.17)	• Delayed and symmetrically reduced renal secretion. • Describes expansive renal formations replacing renal parenchyma, with a mass effect on it.
Kidney biopsy	• Chronic glomerulonephritis with segmental and diffuse glomerular hyalinization (fig. 1.18). • Rare glomeruli with fibrinoid deposits in the mesangium and outstanding endothelial cells with a swollen appearance are observed (fig. 1.19.).

	• Renal tubes have vacuolated cytoplasm (possible in the context of lipid storage), negative PAS coloration. There are rare foci of chronic inflammation around some tubes (fig. 1.20). • Arteriole-type vessels have thickened walls due to swelling of the endothelium and vacuolization of muscle cells. Arterioles with fibrinoid deposits also appear (fig. 1.21). • IF: IgA and IgM present in massive glomerular deposits and in the hyaline cylinders in the tubules. C3, kappa, lambda and Fg present in glomeruli.
Chest X-ray (fig. 1.22.)	• Accentuated pulmonary pattern and a heart with an increased transverse diameter
ECG (fig. 1.23.)	• Sinus rhythm 75/min; QRS axis at + 30◦*;* QRS = 0.10 s; • Subendocardial myocardial ischemia
Echocardiography (fig. 1.24.)	• Mitral insufficiency second degree aortic insufficiency first degree tricuspid insufficiency first degree dilatation of the left heart • Ejection fraction 50% • Fine pericardial reaction, 3 mm
Voiding cystourethrogram (fig. 1.25.)	• Excluded the presence of a posterior urethral valve or primary vesicoureteral reflux
IDR test (tuberculin intradermal reaction)	• Value of 22 mm Palmer III – suggests tuberculin turn
Uroculture for Koch's bacillus	Negative
Gastric lavage for Koch's bacillus	Negative

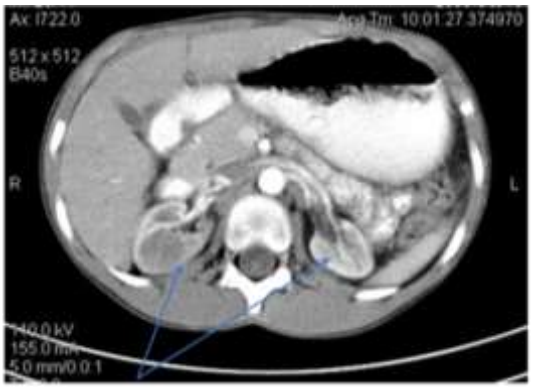

Fig. 1.17. *Abdominal CT scan - expansive renal formations replacing renal parenchyma with a mass effect (blue arrow).*

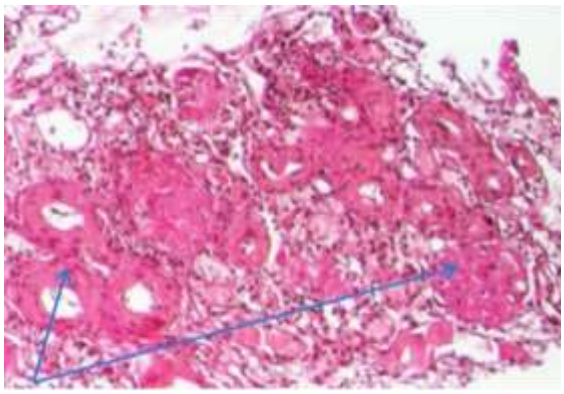

Fig. 1.18. *Kidney biopsy (hematoxylin-eosin staining × 100)—Glomeruli and hyalinized vessels*

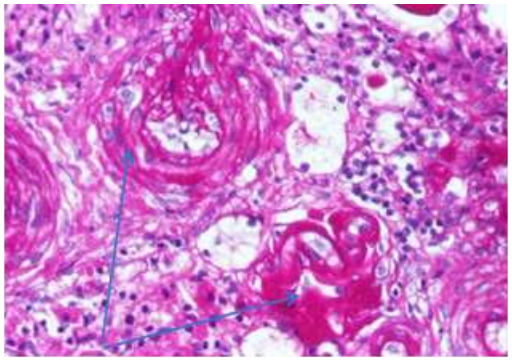

Fig. 1.19*. Kidney biopsy (PAS staining × 200)—Fibrinoid deposits in the glomerulus and PAS+ wall thickened vessel (blue arrow).*

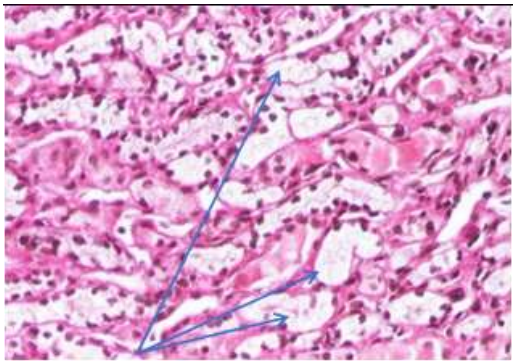

Fig. 1.20*. Kidney biopsy (hematoxylin-eosin staining × 200)—Distal tubes with intracytoplasmic vacuoles (blue arrow).*

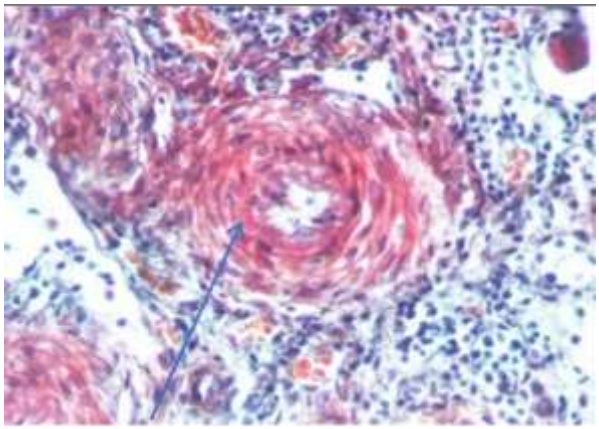

Fig. 1.21. *Kidney biopsy (Trichrome staining × 200)—Vessel with thickened wall (blue arrow).*

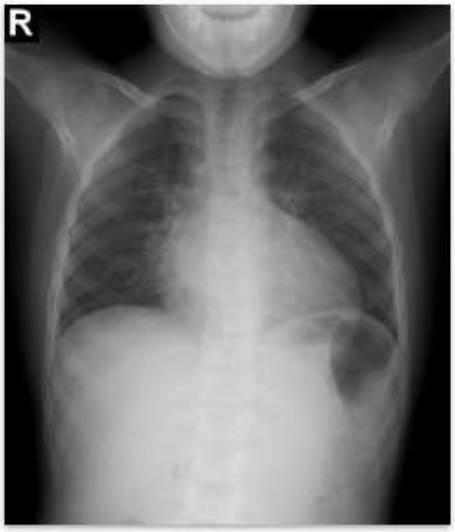

Fig. 1.22*. Chest X-ray*

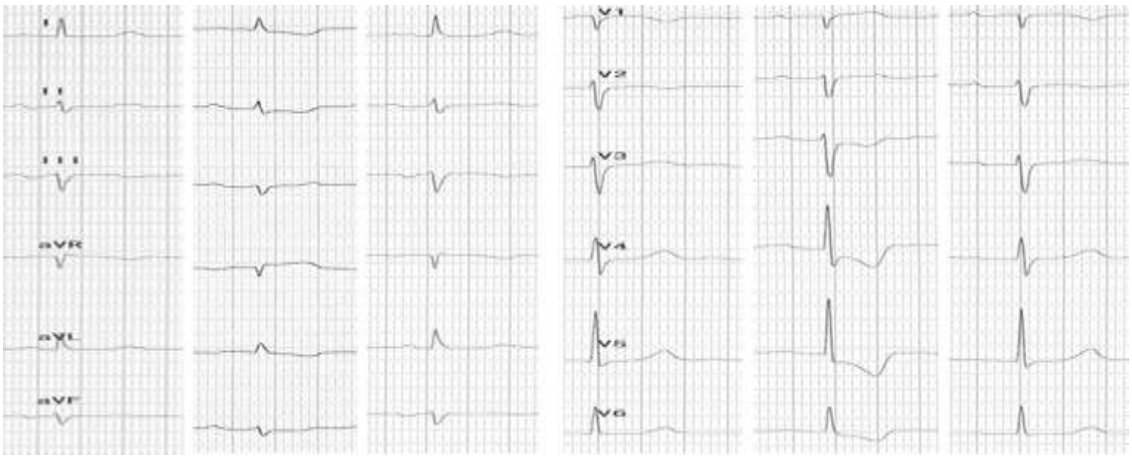

Fig. 1.23. *ECG—ST-segment depressions and T-wave inversions.*

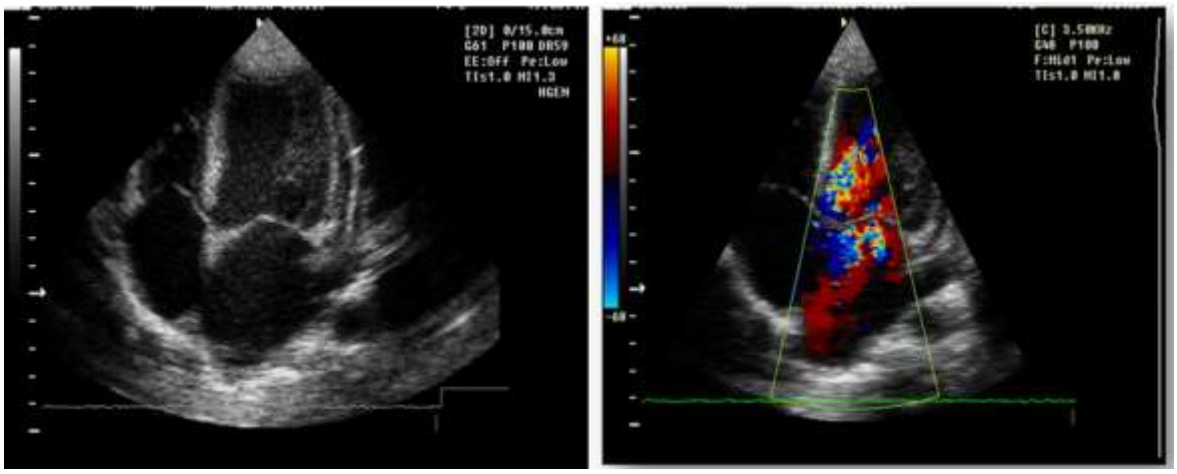

Fig. 1.24. *Echocardiography 4 chamber transthoracic apical view: echodense mitral and aortic valve, II-degree mitral regurgitation and Ist degree aortic regurgitation, pulmonary and tricuspid valve echodense, with I degree regurgitation. Left atrium and Left ventricle dilatation, normal kinetics, EF 70%, inferior vena cave not dilated, with inspiratory collapse, E/A > 2.*

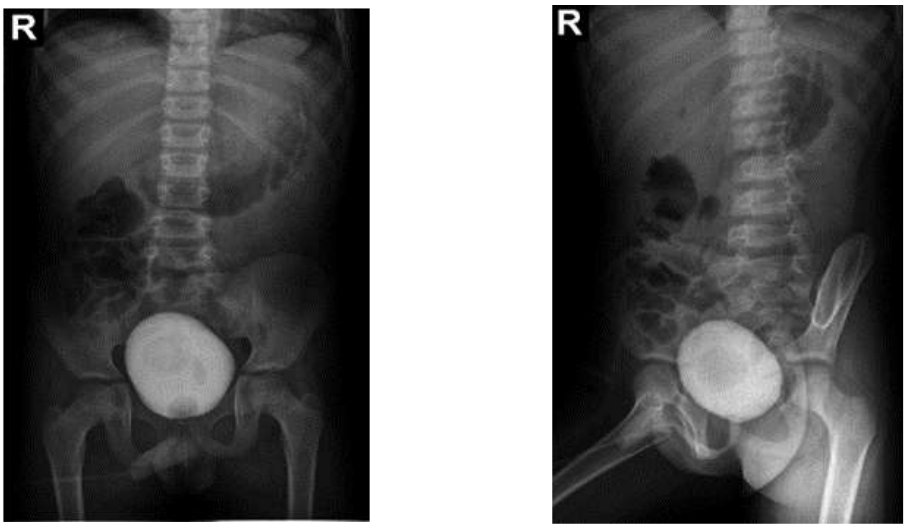

Fig. 1.25*. Voiding mictional cystourethrogram*

Following the evaluations for the etiology of end stage renal disease (ESRD) we recommended abdominal ultrasound and CT scan. The abdominal ultrasound showed multiple homogenous hyperechoic nodular formations. The CT scan showed expansive renal formations replacing renal parenchyma, with a mass effect on it (Fig. 1.17).

We thought in that moment of a bilateral nephroblastoma, but the clinical and biological dates excluded it. There remained a possibility of extrapulmonary renal tuberculosis (due to his personal and family history). Even if the culture was negative for Koch Bacillus, while a value of 22 mm Palmer III—suggests tuberculin turn, the treatment was initiated according to the international guidelines (Faivre 2002) by the phthisiologist: triple combination of isoniazid, rifampicin and pyrazinamide in doses adjusted to his clearance, in the 7/7 scheme for 2 months, then isoniazid and rifampicin in the same doses 7/7 for another 7 months (Faivre 2002).

Two months after the initiation of the tuberculostatic treatment, a CT reevaluation was performed, which showed no changes in the renal formations, although biologically the inflammatory syndrome was absent. The child continued the chronic dialysis program and still had important palm-plant pain burning type.

The suspicion of chronic glomerulonephritis with evolution towards end-stage renal failure remained, so, we decided to perform the kidney biopsy who showed Chronic glomerulonephritis with segmental and diffuse glomerular hyalinization (Table 1.12, Fig. 1.18 – 1.21). In evolution, the patient's HTN acquired a permanent character, being observed both in manual measurements and in continuous recordings (Fig. 1.26), with arterial HTN values of 150–170/100–120 mmHg. It was necessary to start antihypertensive treatment in a quadruple combination: ACE inhibitor (Enalapril) + selective calcium channel blocker (Amlodipine) + selective β blocker for β1 receptors (Metoprolol) + α1 blocker (Prazosin), simultaneously with weight reduction by dialysis to ideal weight preset by Body Composition Monitoring (BCM).

Forty-six days after admission, the patient suddenly complained one morning of epigastric pains, nausea and palmo-plantar burning, associated with a hypertensive episode (BP 180/110 mmHg), for which reason a hemodialysis session was performed urgently, extracurricular. In the same evening, at a BP value of 160/100 mmHg, at rest, the patient presented a sudden and severe worsening of the general condition, dyspnea with orthopnea, intense wheezing, SaO2 89–91%, tachycardia 140/min, subcrepitants disseminated on both lung areas. The suspicion of cardiogenic acute pulmonary edema was confirmed by imaging (chest X-ray—Fig. 1.22, Table 1.12).

Electrocardiographic evaluation (Fig. 1.23, Table 1.12) revealed subendocardial myocardial ischemia, and echocardiography revealed acute dilation of the left heart, as well as a fine pericardial reaction, 3 mm, without signs of cardiac tamponade (Fig. 1.24, Table 1.12). At that moment, we made 2-h ultrafiltration, during which the signs of acute pulmonary edema subsided. After 60 min an increase in blood pressure up to 160/120 mmHg is noted, with the maintenance of negative T waves on the monitor. Hemodialysis was stopped and iv Nicardipin was administered, with good results.

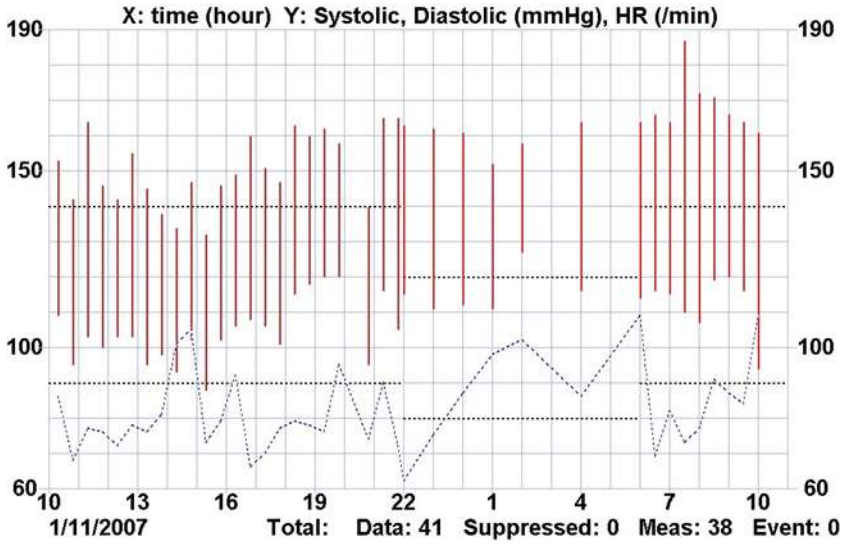

Fig. 1.26. *24-hours Arterial Blood Pressure Monitoring (ABPM)*

The patient repeated in the following days lower precordial and retrosternal pain with radiation in the epigastrium, accompanied by nausea and vomiting and palmo-plantar burning, associating ECG changes of subendocardial ischemia, not significantly influenced by the sublingual nitroglycerin administration, especially during extrarenal hemodialysis. Repeated determinations of creatine kinase (CK), CK-MB, Troponin I, Alanine aminotransferase, Glutamate oxaloacetate transaminase, LDH were normal and ruled out an acute coronary syndrome.

Considering the deterioration of cardiac function with the maintenance of changes on electrocardiography and the lack of a favorable response to treatment, it was decided to reanalyze the case and the following possible diagnoses were raised: periarteritis nodosa, collagenosis, secondary amyloidosis, storage disease or light-chain deposition disease.
Serological tests (Table 1.13) were negative.

Table 1.13*. Serological tests*

Investigation	Results
HBs Ag	**Negative**
Anti-HVC antibodies	
Anti-HIV antibodies	
ASLO	
Rheumatoid factor	
ANA-9	
p-ANCA antibodies	
c-ANCA antibodies	
Cryoglobulins	

At the same time the child needed to be converted to peritoneal dialysis, because allthe cardiac manifestations developed in the hemodialysis sessions. On the occasion of

the placement of the peritoneal dialysis catheter, a lymph node was sampled, which was later analyzed by optical microscopy, PAS staining and hematoxylin eosin staining. The result showed complete deletion of the normal architecture of the ganglion (Fig. 1.27, Table 1.14), nests of lymphocytes and remnants of lymphoid follicles, areas of macrophages with foamy cytoplasm (Fig. 1.28, Table 1.14), beaches of macrophages with eosinophilic, homogeneous cytoplasm, like in storage disease.

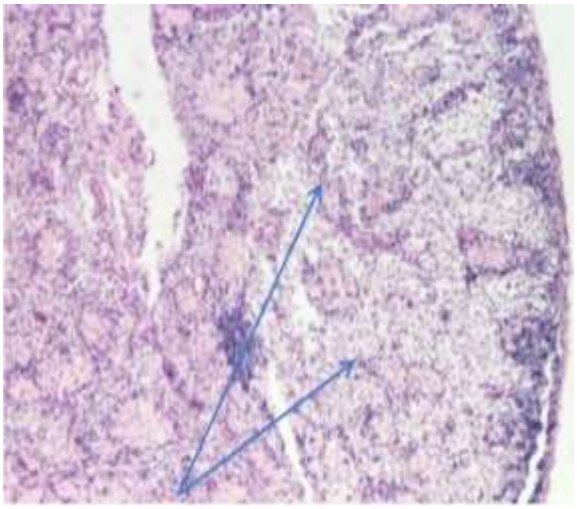

Fig. 1.27. *Mesenteric ganglion biopsy (PAS staining × 100)—Lymph node with obliterated architecture (blue arrow).*

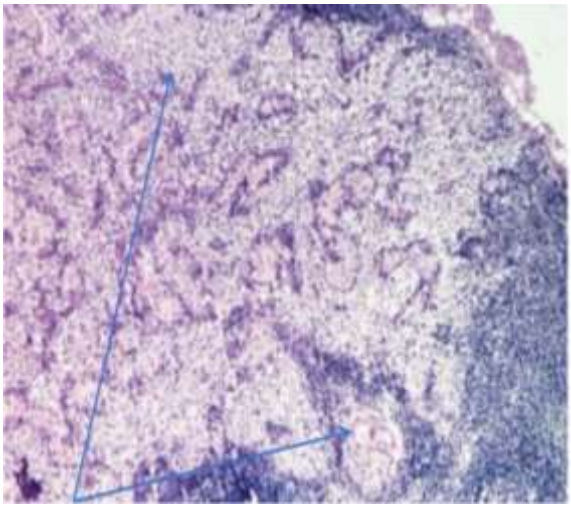

Fig. 1.28*. Mesenteric ganglion biopsy (PAS staining × 100)—areas of macrophages with foamy cytoplasm (blue arrow)*

Analysis of biopsy samples and ophthalmological examination (Table 1.14) were performed, with the outline of a possible storage disease, which is why we tested the enzymes responsible for neurolipidosis (Gaucher disease, Schindler, Fabry, Landing/Morquio B, Sandhoff, Tay Sachs, metachromatic leukodystrophy, multiple sulfatase deficiency), mucopolysaccharidoses, glycoproteinoses (α fucosidosis, α mannosidase, β mannosidase), and mucolipidoses.

After recording a significant reduction in serum α-galactosidase activity 0.25 nmol/h/mL (N: 7–20 nmol/h/mL plasma) and leukocyte α-galactosidase activity 1.68 nmol/h/mg proteins (N: 100–800 nmol /h/mg proteins) the positive diagnosis of Fabry disease is established, which includes renal (ESRD), cardiac (valvular and myocardial damage, left heart hypertrophy), neurological (acroparesthesia) and ocular (vortex keratopathy — Table 1.14) damage.

Genetic testing GLA variants revealed c.317T>G mutation, variant p.Leu106Arg, and the molecular consequence was Missense. The same mutation was detected in his mother also. Enzyme replacement therapy (ERT) (Agalsidase β) was subsequently initiated, un- der which the patient showed a favorable evolution, with the disappearance of palmo-plantar burning acroparesthesias after 3 months of therapy, the normalization of the echocardiographic appearance and the disappearance of left ventricular hypertrophy after 6 months and the disappearance of renal hyperechoic formations on CT-scan after 12 months (Fig. 1.29).

Enzyme activity was also tested on the mother and the sister, the mother showing α-galactosidase deficiency. In evolution, the patient benefited from a kidney transplant after 2 years of renal substitution therapy.

Table 1.14 *Other investigations*

Investigation	Results
Lymph node biopsy	• Complete deletion of the normal architecture of the ganglion (fig. 1.27), nests of lymphocytes and remnants of lymphoid follicles • Areas of macrophages with foamy cytoplasm (fig. 1.28) • Beaches of macrophages with eosinophilic, homogeneous cytoplasm
Ophthalmological examination	• "Swirling" subepithelial opacities in the lower half of the cornea. • No tortuosity or vascular dilatations on the retina or conjunctiva. Visual acuity was normal in both eyes • No signs of hypertensive retinopathy

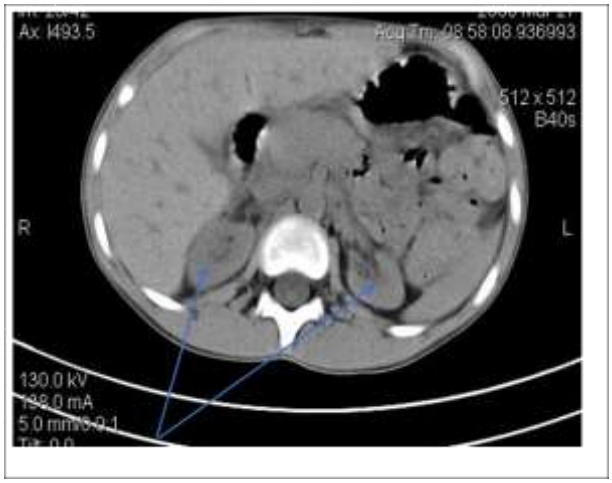

Fig. 1.29. *Abdominal CT scan—disappearance of renal hyperechoic formations (blue arrow).*

I.3.1.3 Discussion

Diagnosis of index cases of Fabry disease is usually delayed and rarely occurs during childhood, and this is due to the lack of specific symptoms (Germain 2019, Duicu 2019). The diagnosis of Fabry disease in a proband should include immediately a clinical examination, but also a biochemical and genetic investigation of the relatives both in males and females' gender (Wang 2007). For boys with clinical signs and symptoms of Fabry disease, it is recommended to investigate α-Gal A activity, a value of < 1% being highly suggestive of Fabry disease and molecular testing for GLA gene mutation is necessary. Identification of a known mutation confirmed the diagnosis of Fabry. If a VUS is identified in the GLA gene, analysis of lysoGb3 is useful (Vardarli 2020). If Fabry disease is suspected in girls GLA gene mutation analysis should be performed. In case of identification of a VUS in girls, lysoGb3 is recommended (Vardarli 2020). In their research, Wang et al. stated that heterozygous Fabry females should not be considered just carriers, as they may be symptomatic with severe organs involvement and risk of premature death similar to male Fabry disease patients (Wang 2007). Similarly, Fernando et al. demonstrated a significant and severe affection for women with Fabry disease. Different studies that included children and adolescents diagnosed with Fabry disease are listed in Table 1.15. Fabry disease was independently reported by Johannes Fabry and William Anderson in 1898. Fabry disease is most frequently diagnosed in adulthood. This is one of the reasons why the diagnosis is often made late in children.

Table 1.15 *Renal involvement in children and adolescents with Fabry disease in different studies.*

Study	Geographic area	Fabry children included in the study (no)	Mean age at diagnosis years (range)	Sex Males Female	Renal involvement of ERT n (%)		Extrarenal findings	Additional remarks
Hopkin, 2008	Fabry Registry patients	352	12 (<1–17 years)	194 M, 158 F	16 (4.5%)	Included before ERT's initiation	NP, GI, angiokeratomas, cardiac manifestations	3 cases with very low eGFR values, 9 with proteinuria, 4 with microalbuminuria
Laney, 2015	Review/Europe, China, Fabry Registry	34	2.8 (0.16–4 years)	23 M, 8 F, 3 NL	2 (5.9%)	NL	Acroparesthesia/NP, GI, CV, heat/cold intolerance, cardiac signs, angiokeratoma,	globotriaosylceramide inclusions in renal glomerular cells on biopsy, low GFR
Ramaswami, 2006	11 countries in Europe	82	12.9 (0.7–17.9 years)	40 M, 42 F	23 (28%)	NL	Acroparaesthesia, NP, GI, CV heat/cold intolerance, anhidrosis hypohidrosis, angiokeratoma,	Urinary sign: proteinuria, albuminuria, hematuria
Najafian, 2011	Norway, USA	14	12 (4–19 years)	8 M, 6 F	14 (100%)	0	Acroparesthesia, corneal opacity, angiokeratoma	Gb3 inclusions in glomerular cells, normal GFR, absent/ low-grade proteinuria
Ries, 2003	Germany, UK, Italy, Sweden	35	12.6 (1–21 years)	15 M, 20 F	5 (14.3%)	NL	Acroparesthesia, hypohidrosis, CV, NP, GI, depression	5 cases with proteinuria and / or low creatinine clearance
Tøndel, 2008	Norway	16	12.7 (5–18 years)	9 M, 7 F	9 (56.25%)	8	Acroparesthesia, typical eye changes, hypohidrosis, GI, angiokeratomas	all renal biopsies (9 cases) with Gb3 inclusions in podocytes and distal tubules; proteinuria and albuminuria (5 cases) hyperfiltration (8 cases)
Shen, 2021	China	10	7.7 (0.1–16 years)	9 M, 1 F	1 (10%)	4	Pain, early-onset, stroke, hypohidrosis, angiokeratoma, GI symptoms, LVH, arrhythmia	neurological symptoms in 1 boy at 0.7 years; cardiac symptoms in 1 girl at 3.6 years
Furujo, 2013	Japan	2	12 (11–13 years)	2 M	0 (0%)	2	Hypo- /anhidrosis, angiokeratoma, CV	urine sediment Gb3 levels were elevated at baseline
Auray-Blais, 2008	Canada	32	2–17 years	15 M, 17 F	2 (6.3%)	8	acroparesthesia, hypohidrosis, pain, heat intolerance, diarrhea	massive excretion of Gb3 in cases with nonsense mutation
Marchesoni, 2018	Buenos Aires, Argentina	44	14.6 (7–21 years)	20 M, 24 F	3 (6.8%)	3	NP, CV, abdominal pain	Abnormal brain MRI in 7 cases (5 F), 3 received ERT
Present work	Romanian	7	10.6 (1.10–17)	6 M, 1 F	4 (57.1%)	4	NP followed by GI, heart, skin, and eye symptoms	Dialysis and kidney transplant in 2 cases

M – male;, F – female; MRI - magnetic resonance imaging; NP - Neuropathic pain; CV - cornea verticillate; GI - gastrointestinal symptoms; NL - not listed; GFR - glomerular filtration rate.

Another reason would be the non-specific symptomatology present at the beginning: acroparesthesias, abdominal pain, changes in intestinal transit or urinalysis (presence of proteinuria or microscopic hematuria). Therefore, in the absence of a positive family history, these changes are not associated with Fabry disease at the beginning (Ellaway 2016, Ries 2003). The delay in diagnosis affects the patient both on a psychosocial level (leads to marked anxiety) and on a medical level (leads to the appearance of irreversible changes). This also includes the case presented above, where, although the patient had disease-related changes (palmo-plantar acroparesthesias, proteinuria and microscopic hematuria) for about three years, the diagnosis was only considered at the time of the association of progressive cardiac damage. Severe neuropathic pain is a hallmark of Fabry disease. Patients with Fabry disease experience acute and chronic pain commonly in their hands, feet, and abdomen. The pain experienced by these patients significantly affects their quality of life and their ability to perform everyday tasks. Patients with Fabry disease suffer from acute pain attacks, sensory abnormalities, peripheral neuropathy, or continuous pain throughout life. Although there is pain therapy depending on its scale and enzyme replacement therapy, the pain persists in many of these patients even after starting the specific therapy.

Although progress has been made in recent years in understanding the pathogenesis of Fabry disease pain, there is still no consensus on the pain and sensory abnormalities in these patients, nor on the most recommended therapy. Our knowledge is limited in part due to the lack of adequate preclinical models to study the disease. In a recent review, Burand et al. reviewed with the aim of providing an overview of pain in Fabry disease and how preclinical models reproduce aspects of pain seen in patients to better aid future studies of mechanical pain as well as therapy development (Burand 2021).

Accumulation of globotriaosylceramides in neurons is one of the most important pathological ways to peripheral neuropathy in Fabry disease. The peripheral neuropathy affects over a quarter of patients with Fabry disease and is characterized by loss of small myelinated and nonmyelinated fibers, whereas larger fibers are largely unaffected (Burand 2021, Rickert 2020). This loss of fibers is most prominent in the long distal axons of the lower extremities but can also be found proximally in the thigh. Interestingly, studies suggest that fiber loss is substantially greater in the skin than in the peripheral nerve trunk. Previous studies in patients with diabetic peripheral neuropathy have shown a good correlation between intraepidermal nerve fiber density and neuropathic pain intensity (Timar 2016 2020).

Lower nerve fiber density correlates with greater pain. This negative correlation between intraepidermal nerve fiber density and pain intensity is also observed in patients with chemotherapy-induced neuropathy. However, in Fabry disease, it is not yet clear whether the lower density of intraepidermal nerve fibers is associated with increased pain intensity (Rickert 2020, Boyette-Davis 2013).

Considering that pain is an important clinical feature in Fabry disease, clinicians should thoroughly evaluate this manifestation as an integrating part of peripheral nervous system assessment, that should also include somatosensory evaluation, such as quanti- tative sensory testing, nociceptive evoked potentials and analysis of skin biopsies. Pain should be evaluated with regard to localization (primarily reported in fingers, palms and soles), character and its temporal course, while a quantification can generally be obtained using particular tools, such as Fabry-specific Pediatric Health and Pain Questionnaire (children/adolescents), FabryScan or Wurzburg Fabry Pain Questionnaire (adults) (Politei 2016). Among multiple pathophysiological mechanisms generating this symptom, deposits of GL-3 in the dorsal root ganglion neurons are one of the most important, as pain in patient with Fabry disease usually manifests as neuropathic (Politei 2016).

However, nerve fiber conduction is also modified, mainly implying functional deficits in small unmyelinated fibers (Burand 2021).

The complexity of these mechanisms give birth to a large spectrum of clinical manifestations, as pain can manifest itself as inflammatory pain, evoked pain, chronic pain or pain crises. The latter install spontaneously in the extremities, frequently as burning pain spreading proximally, being triggered by exercise, fever, exhaustion or changes in ambient temperature (Burand 2021). From a somatosensory point of view, taking in consideration the associating sweating disfunction (hypophoresis), an impairment in patient sensation of warmth and cold is another clinical manifestation which might indicate Fabry disease.

An important aspect from a pediatrician's point of view is that in childhood, pain might begin as gastrointestinal in nature, entailing failure to thrive (Burand 2021) with gastro-intestinal dysmotility possibly installing later in the process. Not only the pain itself has an impact on the patient with Fabry disease still undi- agnosed.

The consequences of chronic pain affect the patient's mental balance, and the most common manifestation is depression. A study conducted in Brasilia on patients with Fabry disease showed that the rate of depression correlates with the intensity of pain (Rosa Neto 2020). Other studies found that up to 16% of Fabry patients were taking antidepressant medication, more than the general US population (Körver 2020). As the intensity of pain increases, it progressively interferes with mood and general enjoyment of life. In our case, the patient underwent depressive-type changes, in the context where the pain was quasi-continuous, long-lasting, significantly impacting the quality of life. Moreover, the child and the family requested hospitalization in the context in which the burning palmar-plantar pain could not be controlled at the level of primary medicine.

Later, the impact of the diagnosis of CKD in the dialysis stage significantly contributed to the deepening of depression in this case. Depression is generally accepted as the most common psychological problem in CKD.

Although depressive symptomatology is common in dialysis patients, clinical depression syndrome includes sadness, guilt, hopelessness, helplessness, and changes in sleep, appetite, impacting somatic development. Somatic factors such as uremic toxicity, atherosclerosis, neurological disorders, anemia, cardiovascular disorders, and metabolic disorders are also implicated in the etiology of depression (Iorga 2014).

In general, patients with Fabry disease report that their pain directly and severely affects their quality of life. Hearing loss, vertigo, cerebrovascular, ocular and dermatologic involvement are also to be noted (Ezgu 2022). Ophthalmologic manifestations can install as soon as the first decade of life and consists mainly of inferior corneal deposits, with linear pigmentation creating a specific finding named cornea verticillate.

In addition, Fabry posterior cataract might also install (Pitz 2015). The verticillate corneal appearance (vortex or spiral keratopathy) supports the diagnosis of Fabry disease and is widely considered a hallmark of the classic form of the disease (Germain 2019). After raising the suspicion of storage disease, we performed an ophthal- mological examination in the case of our patient, which revealed

"Swirling" subepithelial opacities in the lower half of the cornea, highly suggestive of keratopathy associated with Fabry disease. The major sign of cardiac involvement in Fabry disease is left ventricular hypertrophy, but conduction disturbances such as short PR interval (due to accelerated conduction in the absence of the accessory pathway) and rhythm disturbances such as sinus bradycardia have also been reported.

Cardiac ultrasound and ECG are indicated at baseline and at all follow-up visits. Holter testing is recommended only if indicated by symptoms, as severe arrhythmias are not usually encountered in early childhood (Germain 2019). In our case, the boy presented dilatation of the left cavities with secondary mitral and aortic regurgitation from the beginning. This could

not be attributed only to HTN secondary to CKD, because it regressed after the initiation of enzyme replacement therapy. During the follow-up, he did not present any rhythm or conduction disorders, but the phenomena of myocardial ischemia were observed in the context of hemodialysis, requiring a change in the method of renal replacement.

Regarding dermatologic abnormalities, AK is the most common manifes- tation followed by telangiectasia (Orteu 2007). The presented boy only had palmo-plantar pain, without the AKs considered pathognomonic, which caused the diagnosis to be delayed until presentation to our service.

Children with Fabry disease generally do not develop CKD until adulthood, when renal failure accounts for much of the morbidity and mortality associated with this disease, particularly in males. Globotriaosylceramide accumulation in renal cells and effacement of podocyte processes can be seen in renal biopsies in children with Fabry disease, even before proteinuria manifests as an early sign of renal involvement (Germain 2019, Skrunes 2017). In this situation the kidney biopsy with electron microscopy is mandatory to make a differential diagnosis between MCNS and podocyte involvement in context of Fabry disease. In NS found in electron microscopy the retraction of podocyte processes inside the cell body, with the appearance of a flat epithelial layer (Starcea 2022). Renal biopsy has been proposed and shown to be safe by several authors and should be considered in selected pediatric cases, especially when the decision to start KRT is questionable or in children with significant proteinuria where renal biopsy is essential to rule out a second kidney disease, such as in our case. FSGS is a form of glomerulonephritis that develops in various kidney lesions. Because a renal biopsy is not routinely performed especially in proteinuria in the nephrotic range, rigorous estimation of the incidence of FSGS in children is hindered (Stârcea 2018).

In our case, the child presented with nephritic-range proteinuria and severe renal failure, so we performed a renal biopsy that revealed chronic glomerulonephritis with segmental and diffuse glomerular hyalinization (sclerosis). Only after the biopsy of the lymph nodes did we find the final diagnosis.

Even though some clinical signs in Fabry disease might appear as clear indicators for diagnosis, delays in recognizing this condition are unfortunately very common, with many years passing between early symptoms and the actual diagnosis (Stiles 2020). This is due to the wide variety of symptoms that overlap with many other diseases, but also to a poor acknowledgment of this pathology as differential diagnosis in varying clinical setups. This leads to underdiagnosed children, that will finally be correctly identified as Fabry patients well into adulthood. Therefore, there is a great need of raising awareness of this fact, as ERT—if initiated as soon as possible—can positively impact these patient's outcomes to a degree where kidney transplantation for example, as in our clinical case, might be avoided.

Another way to overcome the issue of underdiagnosis is to implement newborn screening programs that can identify patients before developing symptoms.

Newborn screening for Fabry disease, the best way to detect the disease early, before the onset of symptoms, is currently being implemented in Taiwan and several states in the United States of America (Sawada 2020). However, these are not available world-wide and their sensibility and specificity must also be taken with caution so clinical suspicion is of the essence and must be cultivated. Diagnosis of Fabry disease can be established by genetic testing (GLA gene located on Xq22.1), measurement of α-Gal A enzyme activity or analysis of either Globotriao- sylceramide (Gb3) in peripheral blood mononuclear cells or Globotriaosylsphingosine (LysoGb3).

Various mutations, including missense/nonsense mutations, splice defects, regulatory abnormalities, small deletions and insertions, small indels, gross deletions and insertions, and complex rearrangements associated with the GLA gene, have been discovered over the last 30 years (Wu 2018).

Pathogenic mutations of the GLA gene can lead to a decrease to the disappearance of enzyme activity by affecting the synthesis, processing and stability of α-Gal A or by modifying the hydrophobic core of the protein (Tuttolomondo 2015, Saito 2013). Certain mutations of GLA gene (OMIM 300644) cause complete loss of function, being linked to classical form of Fabry disease with severe phenotypes, while other mutations might cause late-onset disease with milder clinical manifestations. These can be searched either by genotyping or trough sequencing analysis.

The latter might reveal variants of unknown significance which must always be well documented and analyzed in relation to a-Gal α-Gal enzyme activity and clinical manifestations, to determine their pathogenicity. α-Gal A enzyme activity measured in dried blood spots, serum or plasma is useful in evaluating males, but not reliable for detecting manifesting heterozygous females, as in their case an only slightly decreased α-Gal A or even normal activity might be present. For this situation, measurement of LysoGb3—a degradation product of Gb3—might be more efficient while also representing an indicator of disease activity, along with Gb3 detection in peripheral blood mononuclear cells (Stiles 2020).

Considering the renal involvement in Fabry disease, apart from classical investigations such as albuminuria, proteinuria, β2-microglobulin, urinary microscopy, creatinine, serum urea, uric acid, GFR, ultrasound and kidney biopsy, one should also take in consideration potential new biomarkers such as urinary Gb3, uromodulin, prostaglandin H2 D-Isomerase and bikunin (Muntean 2022).

Regarding treatment in Fabry disease, there are two kinds of therapies: enzyme replacement therapy (agalsidase alfa; agalsidase β) and chaperone therapy (migalastat). Substitution trough ERT has been shown to decrease Gb3 accumulation in liver and in tubular epithelial cells, with a consequent reduction of Gb3 excretion in urine and reduction in podocytes Gb3 inclusions (Duicu 2019).

Moreover, a decrease in glomerular hyperfiltration was also linked to ERT. The initiation of ERT therapy as early as possible gives the best clinical outcome, but the effect depends on the stage of the disease (Duicu 2019). ERT should be considered in cases of Fabry disease of both sexes, symptomatic cases, in acute cases where neuropathic pain predominates, pathological albuminuria (3 mg/mmol creatinine), severe gastrointestinal symptoms or cardiac involvement (Germain 2019, El Dib 2017).

Unfortunately, in the case of our patient, the referral was late, after the onset of renal failure, with the appearance of hypertensive complications and the development of cardiopathy secondary to the disease. Recent studies reveal that ERT can reduce Globotriaosylceramide deposits in the kidney, heart and skin, being particularly effective in endothelial cell clearance. On the other hand, podocytes, distal tubular cells, and smooth muscle cells showed less reduction in Globotriaosylceramide than that observed in other cell types, therefore, it appears to be more resistant to ERT (Guérard 2018).

The clinical benefit of ERT is mainly observed in patients who initiate ERT before the presence of irreversible organ damage, as happened in the case of the patient presented (van der Veen 2020). He was presented to our service when the kidney damage was irreversible, and kidney transplantation was the only curative option in his case. Arends et al. observed that, despite treatment with ERT, disease progression is predicted by the presence of renal failure and proteinuria at the time of initiation of therapy (Arends 2017). Unfortunately, a downside of ERT is the development of Immunoglobulin G antibodies that might limit its positive effects (Tuttolomondo 2015). Immunoglobulin G antibodies may be generated in about 40% of Fabry males with no α-Gal A activity in response to ERT, and lead to inhibition of enzyme activity that may negatively influence the clinical outcome of Fabry patients (Felis 2019).

Chaperone therapy with Migalastat stabilizes α-Gal A mutated protein, protecting it from degradation in the lysosomes. However, this kind of treatment can only be used in certain patients showing specific mutations (Weidemann 2022). Migalastat (Galafold, Amicus Therapeutics), was approved in 2016 in Europe and 2018 in the USA, respectively. Chaperone therapy may be used in patients with missense mutations, with reduced catalytic activity (https://galafoldamenabilitytable.com, 2022). The patient of the study presents a non-amenable mutation, so is not indicative of this therapy for him.

Moreover, Migalastat is significantly eliminated by the kidneys and is not recommended in Fabry cases with GFR < 30 mL/min/1.73 m2 or ESRD that requires dialysis, as in in our case (Ricio 2020). In the case of GFR >30 mL/min/1.73 m2 is not necessary the dose adjustment (Silva 2021). Based on the review of Weidemann, it is important to classify the GAL gene mutation for amenability to treatment with Migalastat in each new Fabry case (35,36).

In this moment Migalastat is the only alternative to ERT in cases where ERT response is lost or in cases of antibody formation (McCloskey 2018). Additional therapy is substrate reduction therapy that targets glycosphingolipid synthesis to reduce the formation of metabolites that cannot be degraded. At this time, it is only available in clinical trials and is not authorized to treat patients (Muntean 2022, Felis 2019, Schiffmann 2019). For Fabry disease patients with amenable mutations, chaperone treatment is the appropriate approach, while for the rest of Fabry disease patients, combination therapy, such as ERT with substrate reduction therapy, might have a beneficial effect (Muntean 2022).

The management of these cases must include a multidisciplinary teamwork, which includes the geneticist, nephrologist, cardiologist, neurologist, gastroenterologist and ophthalmologist. In the present case, one of the problems of therapeutic conduct following the diagnosis was the kidney damage. Although cardiac and neurological damage improved significantly following substitution therapy and while renal formations disappeared, kidney function did not resume, the patient subsequently needing a kidney transplant.

I.3.1.4 Conclusion

FD is a multisystemic and multifaceted disease that starts early in life, with symptoms occurring during childhood with progressive evolution that worsens throughout adulthood.

Nowadays with early diagnosis of kidney involvement in FD and new proposed therapies a better outcome is expected.

We presented the rare case of an 11-year-old male patient who came to our clinic in end stage renal failure. We found out that he had palmo-plantar pain for three years, without any identifiable cause until that moment.

During the investigations, the presence of multiple organ dysfunction was proven: neurological, cardiac, renal and ophthalmological damage, in the context of which the dosage for multiple storage diseases was reached and the late diagnosis of Fabry's disease was established. This 3-year delay led to the total compromise of renal function.

I.3.2. Seckel syndrome

Microcephaly is a clinical finding estimated to be present in 1.74 per 10.000 children when a criteria of -3 standard deviations (SD) is used, and 1.21 per 10.000 children with -2SD as a cut-off value (Morris 2016). Seckel syndrome is a very rare disease, that should be taken in consideration when children with microcephaly also show small height and weight

for gestational age, with an abnormal intrauterine and postnatal growth velocity. These findings were corroborated by Seckel in 1960 through a very fine case- series review covering 13 patients described in literature as nanocephalic dwarfs and two patients he had personally studied (Sekel 1960). These children are prone to be readily recognized and diagnosed because of their specific aspect, consisting in a "bird-like" appearance that was firstly described by Virchow in 1882, as "bird- headed dwarfs" because of their beak-like noses and micrognathia (Virchow 1882). Thanks to McKusick and his collaborators, we now know this is an autosomal recessive disorder (McKusick 1967) linked to multiple mutations on different chromosomes, as many research teams uncovered (Goodship 2000, Faivre2002). Table 1.16 showcases these mutations, as classified by the Online Catalog of Human Genes and Genetic Disorders (Online Mendelian Inheritance in Man 2017). From these, the archetypal mutation involves the ATR gene which according to Tanaka et al. is an essential regulator of genomic integrity, controlling and coordinating DNA- replication (Tanaka 2012).

Table 1.16*. Genetic Heterogeneity of Seckel Syndrome according to OMIM classification (adapted from Online Mendelian Inheritance in Man 2017)*

Chromosome	3q23	18q11	13q12	15q21	3q22	14q22	10q21	3p21	8q24
Mutated gene	ATR	RBBP 8	CENPJ	CEP15 2	CEP63	NIN	DNA2	TRAIP	NSMCE 2
Seckel Type	SCK L1	SCKL 2	SCKL 4	SCKL5	SCKL 6	SCKL 7	SCKL 8	SCKL 9	SCKL10

I.3.2.1 Material and methods

Here, we present the case of an adult patient who was diagnosed during childhood, who needed specialized nephrological pediatric assistance because of her anthropometrical characteristics and ESRD of an uncertain etiology, which required extra-renal epuration.

I.3.2.2 Results

Patient B.M., a 29 years old female, sought medical assistance because of nausea, vomiting and malaise with insidious onset. Clinical examination revealed very short stature with proportional dwarfism, with a height of 95 cm (- 12 SD), weighing 10 kilograms (- 7.62 SD) with - 11.75 SD in occipital-frontal circumference. Following biological investigations, a serum creatinine of 8.71 mg/dl in association with increased urea levels up to 306 mg/dl were found. Extra-renal epuration being needed and taking in consideration patient's anthropometrical characteristics, she was transferred to Saint Mary's Pediatric Emergency Hospital for further medical assistance. Her medical history was of great importance: she was born from a medically unsupervised pregnancy at normal gestational age, weighing only 900g.

At two years and a half she was diagnosed with Seckel syndrome in our hospital, with only a partial follow-up during childhood and adolescence. Later on, installing severe cardiovascular complications: at 23 years old she presented with anterior myocardial infarction that had not undergone thrombolysis. Consequent she developed left ventricle apical aneurism and class II New York Heart Association cardiac insufficiency at 27 years of age. In this aspect, her evolution is in accordance with other reports of similar

cardiovascular complications related to Seckel syndrome: complete heart block with status epilepticus (Abohelwa 2021), dilated cardiomyopathy, multiple septal ventricular (Donmez 2022) and intracranial aneurisms (D'Angelo 1998) are cited in literature in association with this syndrome. Furthermore, our patient also had a history of primary thrombophilia trough protein S deficiency, hyperuricemia and chronic normocytic, normochromic anemia. Due to her medical antecedents, she was on treatment with acenocoumarin, beta-blocker, an angiotensin converting enzyme inhibitor and atorvastatin.

Clinically, she presented with mild intellectual disability, dysmorphic features consisting in microcephaly, micrognathia, protrusion of the nose in a beak-like fashion (Fig. 1.30), 4 inferior molars, strabismus (Fig. 1.31), short fingers, nail clubbing (Fig. 1.32) and little to no subcutaneous adipose tissue, with a stage II Tanner classification. Although hemodynamically stable, but with severe HTN (160/100 mmHg, > 97,5th percentile of BP for height), oliguric and in general distress, with hypertensive encephalopathy. Biological data at time of admission is summarized in Table 1.17.

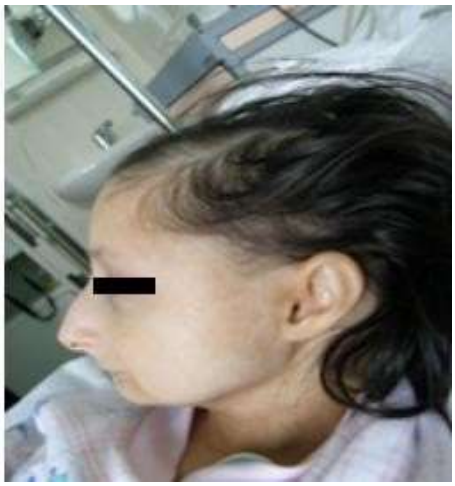

Fig. 1.30. *Microcephaly with "bird-like" appearance*

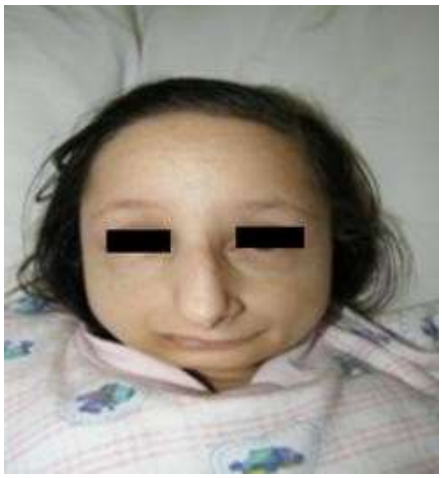

Fig. 1.31. *Strabismus and protrusion of the nose*

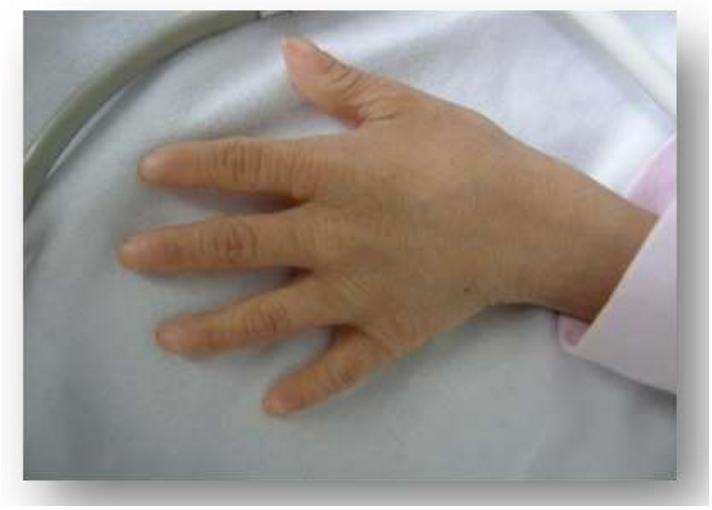

Fig. 1.32*. Clubbing of the nails and short fingers*

***Table 1.17** Biologic evaluation at time of admission*

Hemoglobin	3.9 g/dL	**K**	5.15 mmol/L	**TGO**	29 U/L
Leucocytes	13.300/mmc	**Cl**	102.7 mmol/L	**TGP**	13 U/L
Neutrophils	82.9%	**Total calcium**	7.07 mg/dl	**LDH**	689 U/L
Lymphocytes	8.9%	**Ionized calcium**	3.45 mg/dl	**GGT**	42 U/L
Thrombocytes	168.000/mmc	**Phosphorus**	9.13 mg/dl	**CPK**	118 U/L
Creatinine	9.64 mg/dl	**Magnesium**	1.41 mg/dl	**Cholesterol**	156 mg/dl
Urea	306 mg/dl	**Alkaline phosphatase**	188 U/L	**Triglycerides**	288 mg/dl
Alkaline reserve	5 mmol/L	**Total proteins**	57.55 g/L	**CRP**	38.88 mg/L
Na	131.5 mmol/L	**Albumin**	28.8g/L	**Fibrinogen**	726 mg//L

We underline the serum urea of 304 mg/dl and serum creatinine of 9.64 mg/dl, for which the GFR calculated using Schwartz's pediatric formula was 1,4 ml/min/1.73 m2. Metabolic acidosis, electrolyte disturbances (hyperkaliemia, hyperphosphatemia, hypocalcemia), severe normocytic normochromic anemia, mild inflammatory syndrome and osteodystrophy were present as specific consequences of ESRD. Renal ultrasound revealed normal kidney measurements when adjusted for height, but with poor corticomedullary differentiation on both sides in the context of CKD. Cardiac evaluation consisting in electrocardiography and echocardiography confirmed the presence of myocardial infarction sequels: pathological Q waves aspect in V1 and V2, negative T waves and prolonged QT intervals in frontal and left- sided leads, inferior dyskinesia of interventricular septum, left ventricular diastolic disfunction with second degree mitral, aortic and tricuspid insufficiency. Moreover, left ventricular hypertrophy was confirmed by chest-X ray (Fig. 1.33).

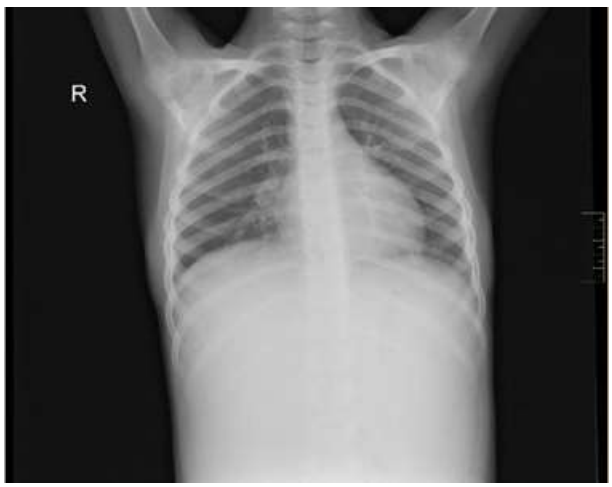

***Fig. 1.33**. Chest X-ray showing an increase of left inferior arch, proof of left ventricular hypertrophy.*

We initiated continuous KRT via left femoral vein, blood transfusions and antihypertensive treatment (association of an angiotensin receptor blocker, ACE inhibitor and a cardio selective beta-blocker) with slow, favorable evolution. There was no history nor clinical or paraclinical arguments for any event that would precipitate a transitory acute renal insufficiency. In light of persistent high serum creatinine, we initiated chronic dialysis. Because of her anthropometrical characteristics, the only possible way of extra-renal epuration was by peritoneal dialysis, which we began after placement of a Teckhoff catheter, 6 days after the first hemofiltration session. Fig. 1.34, 1.35, 1.36 and 1.37 show the evolution of arterial blood pressure, Hb, urea and creatinine levels, with a good overall outcome and remission of uremic gastritis symptoms. The patient's immediate prognosis is favorable, but on the long term, complications of peritoneal dialysis, cardiac insufficiency, thrombotic events because of primary thrombophilia and other Seckel syndrome related events can heavily influence her evolution.

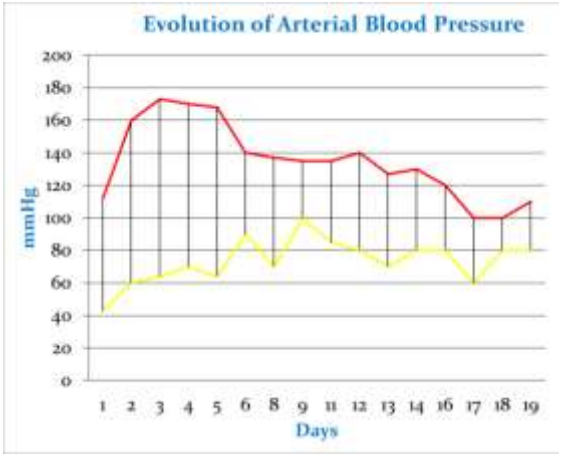

Fig. 1.34 *Evolution of arterial blood pressure. Red curve – systolic pressure; Yellow curve – diastolic pressure*

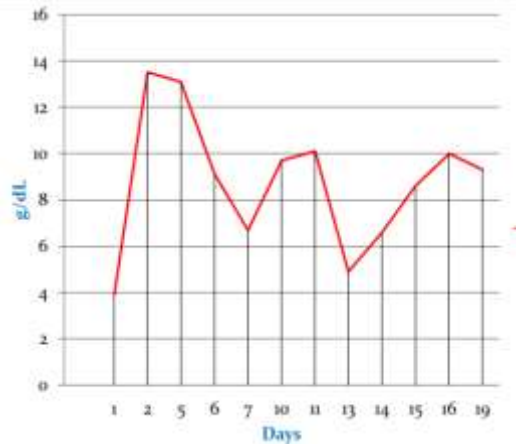

Fig. 1.35 *Evolution of serum Hb (red curve)*

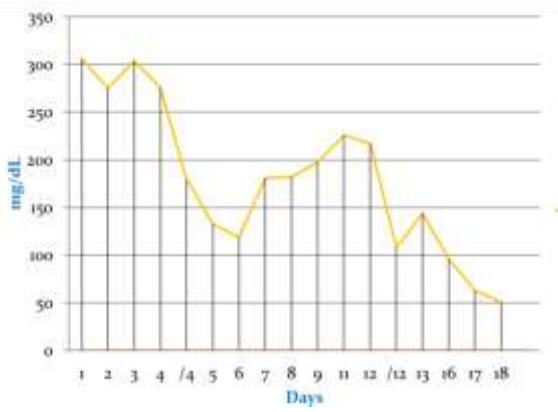

Fig. 1.36 *Evolution of serum urea (yellow curve)*

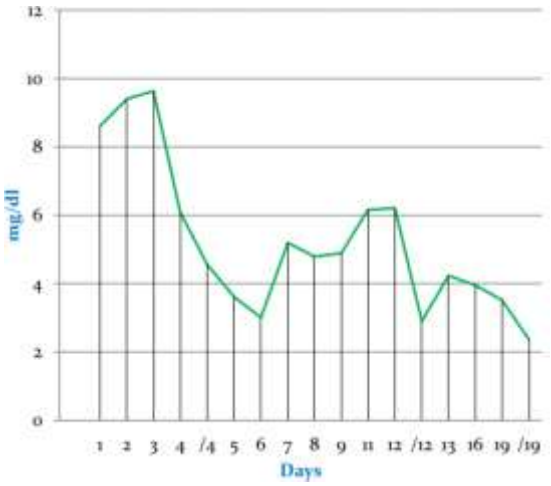

Fig. 1.37 Evolution of serum creatinine (green curve)

I.3.2.3 Discussion

The association between Seckel syndrome and CKD is very scarce. We note the case of a horseshoe kidney with nephrolithiasis in such a patient (Jung 2018) and ESRD in a Pakistani patient (Rajamani 2005), but no generally accepted relation between the syndrome and renal disease is recognized.

The etiology of ESRD in our patient was hard to come by. Based on our evaluation and patient's evolution, renal dysplasia, tubulointerstitial nephritis and glomerulosclerosis are took in consideration as possible causes. The last pone has a great probability because the patient had developed malignant HTN, with secondary encephalopathy.

The literature discuses about children with chronic renal disease, who develop hypertensive encephalopathies, in the context of primary renal disease, or secondary to immunosuppressive treatment, at particular risk of developing PRES. We thought about this possibility in our patient also, because of severe evolution of HTN, but the IRM exam didn't confirm that supposition (Stârcea 2018).

Differential diagnosis of Seckel syndrome is mainly made with other types of primary dwarfism, in which we must always include microcephalic osteodysplastic primordial dwarfism types I, II and III. These are also autosomal recessive diseases, but they all present with specific bone lesions and varying degrees of intellectual disability.

Moreover, as Khetarpal and his colleagues have shown (Khetarpal 2016), this group of genetic disorders also include Silver-Russell syndrome and Meier-Gorlin syndrome,with different overlapping features. Numerous findings were reported to be associated with this disease, such as a cleftlip (Rajamani 2018), dental anomalies (Ouattara 2020), agenesis of corpus callosum (Shanske 1997) and others that are more or less accurately documented.

I.3.2.4 Conclusion

There is a great need for diagnosis standardization regarding Seckel syndrome, but this cannot be achieved without continuously documenting the genetical substrate of the disease, which is still financially prohibitive throughout the world.

Treatment of these patients remains mainly of palliative nature, but careful management of related complications are ofthe essence. Extra-renal epuration poses serious technical issues because of specific anthropometric characteristics of these patients, with peritoneal dialysis being the preferred method in such cases.

I.4 Acute pathology related to CKD in children

AKI occurs frequently in critically ill children, having an incidence of up to 26.9% (Kaddourah 2017) and is associated with high morbidity and mortality in pediatric intensive care units (PICU).
Although not considered anymore as a true gold standard, the serum creatinine based GFR is still the most widely used appreciation of renal function. This is particularly challenging in the children population due to the variability with age, gender, and body mass (Mian 2017). Personal contributions related to AKI, with possibility to progress to CKD are listed below.

Articles ISI – principal author

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Article BDI – principal author

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The term AKI was coined by experts in the field in order to better describe the molecular, biochemical, and structural changes that occur in a kidney with acute injuries, long before the onset of acute renal failure. The term AKI reflected a broad clinical syndrome with multiple etiologies and manifestations spanning from subtle biochemical and structural alterations to anuric renal failure (KDIGO Clinical Practice Guideline for AKI, 2012, Devarajan 2013). The field of acute renal failure has seen dramatic changes in the last two decades thanks to the increasing recognition of the idea that small changes in kidney function, previously considered of little importance, can have a significant impact both in the short term (length of hospital stay, morbidity), but also in the long term, by the development of CKD. The old, all-or-nothing concept of acute renal failure has been replaced by the term AKI. It highlights the progressive nature of an attack on the kidney, the result of which is the failure. The clinician can thus promptly recognize and rapidly intervene in the development of AKI, rather than waiting for the onset of organ failure. GFR increases slowly daily after birth, doubles at 2 weeks of age, and reaches full maturity at 2 years of age (Table 1.18) (Bakr 2018).

Table 1.18. *GFR at different gestational and postnatal ages (after Bakr, 2018)*

Age	Mean GFR±SD (ml/min/1.73m2)
29-34 weeks GA – 1 week postnatal age	15±5.6
29-34 weeks GA – 2-8 weeks postnatal age	28.7±13.8
29-34 weeks GA – above 8 weeks postnatal age	51±4
1 week in term males and females	41±15
2-8 weeks in term males and females	66±25
Above 8 weeks in term males and females	96±22
2-12 years (males and females)	133±27
13-21 years (males)	140±30
13-21 years (females)	126±22

GFR = glomerular filtration rate; SD = standard deviation; GA = gestational age

Definitions and standardized stages

AKI represents the sudden deterioration of kidney function, which causes a decrease in the GFR, the loss of the ability to maintain electrolyte (HE) and acid-base (AB) balance, and in the ability to eliminate toxic products resulted from metabolism (Bakr 2018). The development of a standardized, multidimensional classification of AKI stages has revolutionized the understanding of the epidemiology and impact of AKI on the long-term prognosis.

The definition of AKI stages is currently based on:

- Changes in serum creatinine level (or estimated creatinine clearance), starting from a previous patient's baseline;
- Diuresis.

The current staging uses the Schwartz formula (Schwartz 1987) to define AKI:

Creatinine clearance (ml/min/1.73 sq m) = **k*** x **height** (cm)/**serum creatinine** (mg/dl)

*k=0.45 for 0-1 years old; k=0.55 for 1-12 years old; k=0.55 for 12-18-year-old girls; k=0.7 for 12-18-year-old boys

Previous baseline creatinine is an important parameter in the staging of AKI, hence the importance of including creatinine in the routine analysis of an evaluation. If this value is not known, it can be calculated in reverse, using the formula:

eGFR normal = **0.413** x **height** (cm)/**creatinine** (mg/dl)

Since the beginning of the 2000's, pediatric nephrologists have been using the AKI Network classifications (AKIN classification, 2007) and the "stag- ing system and the risk, injury, failure, loss and end- stage renal disease classification" (RIFLE classification, 2004), which allows an improved diagnosis and staging of AKI according to severity (Lopes 2013). Later, in 2012 and 2013, Jetton and Askenazi (Jetton 2012). and Ricci and Ronco (Ricci 2013) respectively, proposed a standardized definition of neonatal renal failure based on the KDIGO definition for adults and children. The estimation of baseline serum creatinine is challenging in neonates because serum creatinine declines rapidly in the first week of life as nephron function matures and maternal creatinine is cleared. A change in diuresis is the earliest clinical sign of AKI and it is the simplest method of diagnosing AKI in newborns, there- fore oliguria is considered a specific sensitive marker of AKI in newborns. Table 1.19 compares the pediatric and neonatal RIFLE criteria (Bakr 2018).

Table 1.19. *RIFLE classification for neonatal and pediatric AKI (after Bakr, 2018)*

	Creatinine criteria		**Urine output criteria**	
	pRIFLE	**nRIFLE**	**P RIFLE**	**nRIFLE**
Risk	eCCL decrease by 25%	?	UOP<0.5 ml/kg/h x 8 h	UO<1.5 ml/kg/h for 24 h
Injury	eCCL decrease by 50%	?	UOP<0.5 ml/kg/h x 16 h	UO<1 ml/kg/h for 24 h
Failure	eCCL decrease by 75% or eCCL<35 ml/min/1.73 m2	?	UOP<0.3 ml/kg/h x 24 h or anuric for 12 h	UO<0.7 ml/kg/h for 24 h or anuric for 12 h
Loss of function	Persistant failure >4 months	Persistant failure >4 months	Persistant failure >4 months	Persistant failure >4 months
End stage	Persistant failure >3 months	Persistant failure >3 months	Persistant failure >3 months	Persistant failure >3 months

eCCL = estimated Creatinine Clearance; UOP = urine output; hr = hour; Question mark ("?") is intended to mean uncertain thresholds; RIFLE = risk, injury, failure, loss; pRIFLE = pediatric RIFLE; nRIFLE = neonatal RIFLE

Etiology of AKI in children

30% of all children who were hospitalized went through an episode of AKI (Nawaz 2018). In newborns, the leading causes are sepsis, hypoxic-ischemia, hypernatremic dehydration, and severe obstructive malformations such as posterior urethral valve and ureterocele, as well as post-cardiac surgery occurrences (Duzova 2010, Jetton 2014, Mishra 2021 - 248). Among infants and older children, AKI is associated with acute gastroenteritis accompanied by severe hypovolemia, sepsis, hemolytic uremic syndrome, diabetic ketoacidosis, infections like Hantavirus and malaria, poisoning from substances like ethylene glycol, and situations such as bone marrow or stem cell transplantation (Mishra 2012, Krishnamurthy2013, Mishra 2021 -251, Prasad 2016). It's worth noting that serum creatinine might not be a dependable indicator for detecting AKI, as its levels increase only when about half of the glomerular function is already impaired, and it can also be influenced by factors such as height, sex, body mass, and hydration status (Mishra 2022). The implementation of new biomarkers, among which urinary neutrophil gelatinase-associated lipocalin (uNGAL) have apparently proven their utility in predicting AKI compared with changes in creatinine clearance, in pediatric and adult studies, particularly in cardiac surgery patients (Tuan 2020). Less studies have been performed in children, particularly with the aim to demonstrate the role of uNGAL in the assessment of critically ill children. Renal angina index (RAI), a combination of patient AKI risk and early signs of in- jury, was created to stratify the risk in patients for whom biomarker testing would be most optimal.

Aim

In the paragraphs below, I want to present our clinical experience with children's AKI with diverse etiologies. The first discussion will be about the renal angina index and the role of biomarkers in the early diagnosis of AKI in children. The emphasis will be on uNGAL, with our aim being to study the utility of using this marker in the management of critical pediatric patients admitted to our hospital in a six-month period, more specifically, its capacity to predict AKI development, alone and in association with the RAI. In the second part of this section, I will make a short mention of neonatal AKI, a common cause of admission to neonatal intensive care units (NICU), and a major factor in neonatal mortality and morbidity. Next will be our clinical experience with AKI in children in a short series of 35 patients and the presentation of two cases of acute tubular necrosis with an unexpected evolution. In the last part of this section, I will present our department's experience with AKI induced by infection with Hantavirus in children, the first series of pediatric patients in our country.

1.4.1 uNGAL Predictive Value for S Cr Decrease in Critically Ill Children

I.4.1.1 Material and methods

Critically ill children admitted to PICU were enrolled over 6 months (January 2021–July 2021). Inclusion criteria were a predicted discharge of >48 h of PICU admission (prediction discharge date was estimated by the attending ICU provider as part of the PICU daily clinical routine).

Patients with history of end-stage renal disease, urinary tract infections, and congenital or acquired kidney disease were excluded from the study. Data were collected at the first calendar day of PICU admission and on day 3. Urinary NGAL was assessed the day after PICU admission between 12 and 24 h after time of admission (Day 1). Day 3 was defined as the time period between 72 and 96 h after PICU admission. Other collected variables at the

time of admission were: demographic information, admission diagnoses, comorbidities, height, weight, available laboratory values, and vital signs. Daily collected variables included vital signs, laboratory values, vasopressor use, mechanical ventilation support level, and total ICU fluid intake and output. Creatinine clearance (CrCl) on day 1 was calculated according to the Schwarz formula):

A normal renal function was defined if the eGFR was >90 mL/min/1.73 m^2. All patients were also classified according to the criteria for renal angina fulfilment. The RAI score was calculated on day 1 of PICU admission. We recorded the RAI index in both ways: as a continuous variable from 1 to 40 as well as a categorical variable (dichotomous); a RAI score of ≥8 was considered as a positive index. We were looking for associations of uNGAL values from day 1 with CrCl from day 1 and from day 3 as well as the RAI score with the day 1 CrCl, and multiple regression RAI + NGAL as the independent and CrCl as the dependent variable.

We determined the cut-off point of uNGAL by the ROC (receiver operating characteristic) analysis to decide on a CrCl lower than 90/1.73 m2/min. Statistical analysis was performed using SPSS, version 18 (SPSS Inc.

Released 2009. PASW Statistics for Windows, Version 18.0. Chicago). Variables were presented as the number and percent or average and standard deviations, and for some, also the 95% confidence interval. Relations between variables were assessed by means of correlation (Spearman and Pearson), and by linear or logistic regression.

To compare the samples, the nonparametric Mann–Whitney test was operated. $p \leq 0.05$ was considered significant. Multiple logistic regression analyses were performed to check the relation between independent factors (uNGAL and RAI) and CrCl > 90/1.73 m2/min as the output on different days.

The coefficients were exponentiated to compute the adjusted odds ratio for the effect measures. The protocol study was approved by the research ethics committees of the University of Medicine and Pharmacy “Grigore T Popa” Iasi, Romania.

I.4.1.2 Results

Twenty-eight critically ill children aged from 1 day to 15 years were included. The underlying pathology of the patients admitted in our PICU included both surgical (severe burning, diaphragmatic hernia, giant ovarian cyst, intestinal malformations, polytrauma, hydrocephalia, tumors (pancreato blastoma, ovarian teratoma, Ewing sarcoma), hydropneumothorax) and medical conditions: pancreatitis, congenital cardiac malformation with cardiac failure, respiratory failure, upper gastrointestinal bleeding, adreno-genital syndrome, foreign body aspiration, and transverse myelitis. A total of 11/28 children (39%) had a CrCl between 22 and 87 mL/min/1.73 m2 on day 1 of PICU admission, and 8/28 children had a CrCl between 23 and 83 mL/min/1.73 m2 on day 3 of PICU admission. The mean uNGAL value was 7.32 ng/mL, with a large standard deviation of 10.33 ng/mL.

We found a negative relationship between uNGAL and day 1 CrCl. The nonparametric Spearman’s rho correlation coefficient was 0.523 (with 95% CI: 0.763, 0.205, bootstrap method) and had a significance of $p < 0.01$. We also computed the linear trend and found a Pearson coefficient of 0.486 (with 95% CI: 0.688, 0.252) with a significance $p < 0.05$. (Fig. 1.38, Table 1.20).

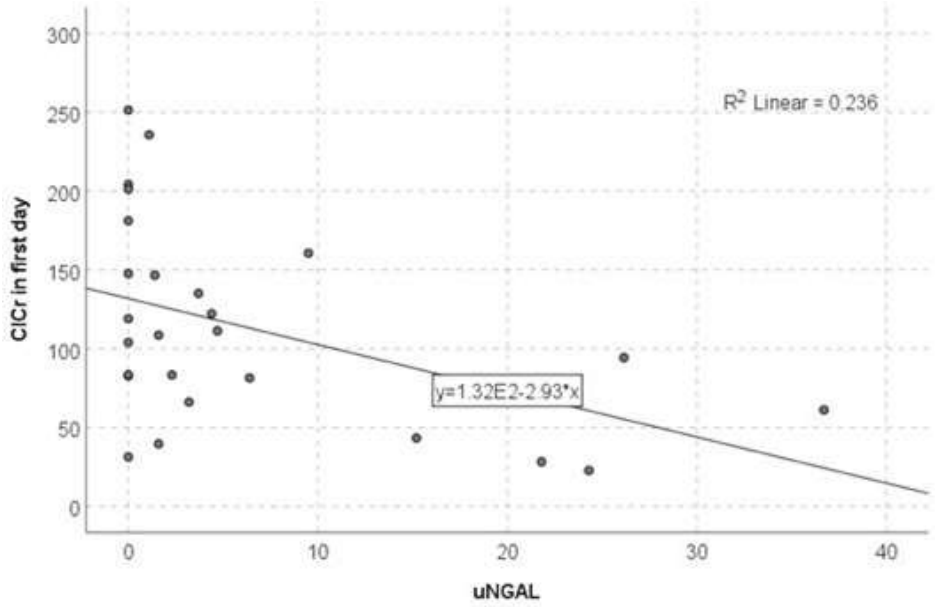

Fig. 1.38. *The CrCl–uNGAL relationship on day 1 of PICU admission.*

Table 1.20. *The logistic regression coefficients for the dependent variable for day 1 CrCl < 90/mL/1.73m^2.*

Variables Involved (Type)	Correlation Confidence Interval (95%)	Significance *p*
uNGAL; CrCl day 1 (S)	-0.523 (-0.763;-0.205)	0.002
uNGAL; CrCl day 2 (P)	-0.486 (-0.688;-0.252)	0.004
uNGAL; CrCl day 3 (S)	-0.139 (-0.531;-0.286)	0.24
uNGAL; CrCl day 4 (S)	-0.318 (-0.621;-0.073)	0.05

Spearman correlation (S), Pearson correlation (P).

However, we did not find a significant relationship between uNGAL and CrCl from day 3 (Spearman's correlation r = −0.139, *p* = 0.240) (Table 1.21.).

Table 1.21. *The logistic regression coefficients for the dependent variable for day 1 CrCl*

Covariate/Factor	B	Sig. *p*	OR EXP (B)	95% Confidence Interval for EXP (B)	
				Lower	Upper
uNGAL	0.096	0.056	1.101	0.997	1.215
RAI ≥ 8	0.088	0.923	1.092	0.182	6.564

B – coefficient; OR – Odds Ratio

The uNGAL ROC curve analysis found a cut-off point of uNGAL = 5.55 ng/mL to predict the CrCl_1 < 90. The area under the curve (AUC = 0.708) was not statistically significant, p = 0.062. The corresponding sensitivity and specificity were 0.53 and 0.86, respectively (Fig. 1.39).

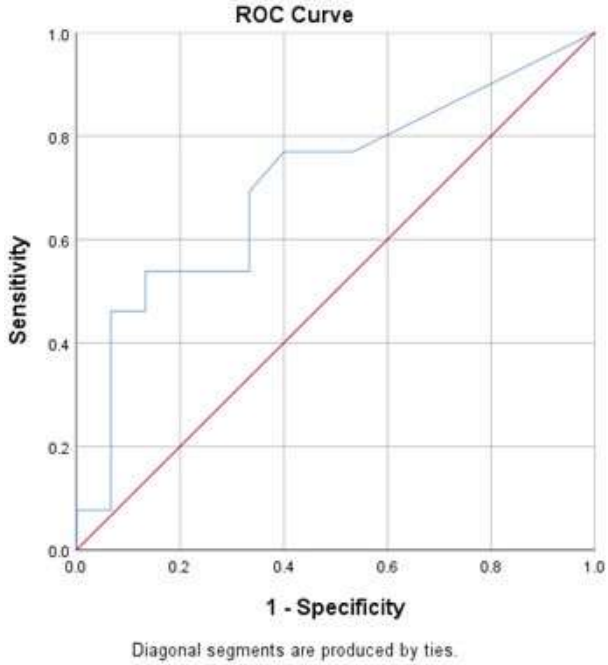

Fig. 1.39. *The ROC curve: uNGAL to predict the CrCl < 90 mL/1.73 m2/day on day 1 of PICU admission.*

The ROC analysis to predict a creatinine clearance lower than 90 on the third day, taking into account the uNGAL values, showed no significance (p = 0.265) and AUC = 0.643. For the optimum maximum sum of sensitivity and specificity, we found an uNGAL = 17.15. This cut-off point provided a sensitivity of 0.571 and a specificity of 0.905.

The relation between RAI and day 3 CrCl was estimated by the nonparametric Spearman correlation. The value was −0.318 with a significance p = 0.05. This showed a negative week relation (according to Colton classification (Vaidya, 2008)).

When comparing the creatinine clearance on day 1 in the two groups (RAI positive/RAI negative), we did not find any difference (p = 309, Mann–Whitney U test). A similar result was obtained by comparing it with the creatinine clearance on day 3 (p = 0.186) (Table 1.22).

When assessing the relation of CrCl < 90/mL/1.73 m2 on the first day (as a dependent variable) in relation to the uNGAL score and a RAI larger or equal to 8, the logistic regression coefficients by means of the odds ratio (exp of beta coefficients) were 1.10 and 1.09 with a significance of 0.056 and 0.93, respectively.

Therefore, there was no relation in this multiple logistic regression study. Correspondingly, we tested the same inputs in relation to the creatinine clearance on the third day. The odd ratios were 1.066 and 2.460 with a significance of 0.129 and 0.351, respectively.

Table 1.22. *The logistic regression coefficients for the dependent variable for day 3 CrCl*

Covariate/Factor	B	Sig. *p*	OR EXP (B)	95% Confidence Interval for EXP (B)	
				Lower	Upper
uNGAL	0.064	0.129	1.066	0.982	1.157
RAI ≥ 8	0.900	0.351	2.460	0.371	16.315

B – coefficient; OR – Odds Ratio

I.4.1.3 Discussion

The role of uNGAL in AKI has been previously studied in small samples of children admitted to the PICU. We synthetized the main results of these studies investigating the predictive role of uNGAL (Table 1.23).

Table 1.23*. Relevant studies depicting the role of urinary NGAL in AKI.*

Authors	Study Type	Sample Size and Age	Aims	Main results
Abu Zeid, 2019	Prospective study	53 children, 3 months to 7 years	To test the hypothesis that association of uNGAL and RAI improves the prediction of severe AKI.	- Individual uNGAL demonstrated marginal discrimination for severe AKI (AUC = 0.877, little higher than prediction by RAI (AUC = 0.847). Incorporation of uNGAL significantly added to the renal angina index AKI prediction (AUC = 0.847, increased to 0.893).
Acuna, 2018	Prospective study	34 children, 1 month–18 years	To determine the association of uNGAL and RAI for AKI prediction in critically ill children	- Significant relationship between uNGAL and creatinine (p = 0.034) and no associated relationship between RAI and creatinine (p = 0.071). - When combined, it only showed a slight increase in the detection of AKI. (p = 0.067).
Agarwal, 2021	Prospective cohort study	35 children with contrast induced AKI, 1 month – 12 years	To study the diagnostic role of uNGAL AND evaluate the outcome of contrast induced (CI) -AKI in critically ill children.	- There was no significant difference in NGAL 6 h after contrast-enhanced CT scan for AKI prediction (AUC 0.41, 95% CI 0.29 to 0.54) - There was no significant difference in mean plasma NGAL level before and 6 h after contrast enhanced CT scan in CI-AKI and Non-CI-AKI groups

Assadi, 2019	Prospective cross-sectional study	86 children, 7 months– 14 years.	To assess the ability of IL-17, KIM-1, uNGAL IL-18, KIM-1), uNGAL to predict AKI in critically ill children with circulatory collapse.	- IL-18, KIM-1, and NGAL rose significantly from the day of admission to the sixth day of hospital stay ($p < 0.001$). - KIM-1 displayed the highest AUC (AUC = 0.81, 95% CI, 0.76–0.93; $p < 0.001$) for the early detection of AKI after circulatory collapse, followed by NGAL (0.77 CI, 0.70–0.84) and IL-18 (0.69, CI, 0.48–0.64)
Di Nardo, 2013	Single-center prospective observational cohort study	11 children were enrolled: 7 with severe sepsis and 4 patients with severe sepsis + AKI	As sepsis is known as a risk factor for AKI, in PICU patients, but it is also able to upregulate urinary and plasma NGAL decreasing its predicting value of AKI, this confounding factor needs to be demonstrated.	- uNGAL levels were significantly increased in patients with septic AKI compared with septic patients without AKI, while pNGAL levels were not significantly different between septic these groups.
McGalliard, 2020	Single-center prospective, Observational cohort study	657 children 0–16 years	To test the predictive value of uNGAL, and RAI (alone and combined) of stage 2 or) AKI development in PICU patients	This was a heterogenous PICU cohort in which, uNGAL and RAI alone did not find a good prediction for severe AKI: - The AUC for uNGAL and RAI were 0.75 (95% Confidence Interval (CI) 0.69, 0.81), and 0.73 (95% CI 0.65, 0.80) respectively. - When combined RAI + day 1 uNGAL, the AUC was 0.80 for severe AKI prediction (95% CI 0.71, 0.88).
Goldstein, 2021	Two center prospective study	134 patients 6–18 years	To test if a low uNGAL is a reliable tool to rule out nephrotoxic AKI in children	- uNGAL thresholds of 150 and 300 ng/mL demonstrated high specificity (92.4 and 97.1%, respectively) and negative predictive values (93.3 and 92.8%, respectively) for ruling out severe AKI.
Naunova-Timovska, 2010	Prospective study	50 newborns, 0–28 days	To assess the efficiency of uNGAL in early diagnosis of AKI in newborns	- Significant higher uNGAL values in newborn with AKI in day 1 of admission. - There was a significant higher uNGAL value in newborns with AKI and lethal outcome compared with newborns without lethal outcome ($p < 0.001$).

Currently, the estimated decrease in the GFR was calculated using the serum creatinine levels. Nevertheless, there may be a 48h delay between the renal injury and measurable increase in creatinine (Vaidya 2010). In the Bhowmick et al. study (Bhowmick 2022), the modified Schwartz formula showed a good agreement with the 99mTc-labeled DTPA method for calculating the GFR in critically ill children aged 1 month to 12 years. Nowadays, an improved equation to estimate the GFR was developed based on Scr, BUN, and cystatin C (Tang 2022). uNGAL has been validated in relation to cardiopulmonary bypass in children, being able to detect AKI before the functional change proven by the rise in serum creatinine (Meersch 2014). It is already known that new AKI biomarkers do not demonstrate a reliable prediction outside the cardiac surgery.

However, in noncardiac PICU patients, the performance of these biomarkers is variable, with an area under the curve receiver-operating characteristic (AUC-ROC) values ranging from 0.54 to 0.85 (Basu 2014).

We demonstrated that an increase in uNGAL on day 1 of admission in the PICU was significantly correlated with a decrease in creatinine clearance, but not anymore on day 3. Similar results were found by Dinardo et al. (Dinardo 2013) in a smaller sample (seven patients with severe sepsis and AKI and four patients with severe sepsis and AKI) in which uNGAL was significantly increased in children with septic AKI compared with septic patients without AKI. uNGAL was not altered by sepsis, being significantly increased in children with severe sepsis + AKI compared with those without AKI. In contrast, plasma NGAL was not significantly higher in septic patients + AKI compared with septic children without AKI.

According to our ROC, uNGAL did not show a significant predictability for AKI development. A lack of uNGAL utility in AKI was demonstrated by Agarwal et al. (Agarwal 2021) in a sample of 100 children aged 1 month to 12 years who underwent contrast-enhanced CT scan, out which 35 developed contrast induced (CI)-AKI. The NGAL did not predict contrast induced AKI while age < 2 y was an independent risk factor for CI-AKI. In studies performed on PICU patients with circulatory collapse, uNGAL has proven its efficacy in predicting AKI, with a lower performance than KIM, but better than IL18 (Acuna 2018). In a much larger sample (657 children 0–16 years), McGalliard R.J. et al. (McGalliard 2020) still did not find a good prediction of uNGAL alone. The renal angina index is a construct aiming for a better prediction of AKI by assigning point values for 'risk' (e.g., sepsis, use of vasoactives, history of transplant, and/or invasive mechanical ventilation) and 'signs' of injury (e.g., changes from baseline SCr, short periods of oliguria, and/or fluid overload). The resultant renal angina index score can range from 1 to 40. A cut-off of ≥8 is used to determine renal angina fulfilment (Naunova-Timovska 2020, Kaur 2018). When we supplementary incorporated the RAI into the prediction model, uNGAL+ RAI did not predict better either. Unlike us, other authors (Abu Zeid 2019, Basu 2014, Goldstein 2021) have demonstrated that the association of increased uNGAL + RAI ≥ 8 significantly increases the prediction for subsequent AKI. Individual uNGAL demonstrated marginal discrimination for severe AKI (AUC = 0.877, little higher than the prediction by RAI (AUC = 0.847), but the incor- poration of uNGAL to the RAI significantly increased the AKI prediction (AUC = 0.847, increased to 0.893) (Abu Zeid 2019). Other authors also did not find an increased AKI prediction of such combination (Lameire 2017).

Our study has several limitations: the sample size was not large enough to allow us to draw definite conclusions. Although our sample included critically ill patients, the underlying disease (either medical or surgical) was not extremely severe to develop a quick AKI, nor were associated risk factors for AKI detected. Another explanation for the lack of significant results is the lack of a homogenous group. Therefore, apart from cardiac surgery, the efficacy and utility or uNGAL in the management of critically ill children is still questionable. For the best prediction, we will need to incorporate not only the RAI or other PICU scores, but other biomarkers such as KIM-1, urinary cystatin, IL-18, etc.

I.4.1.4 Conclusion

The underestimation of GFR should be kept in mind while applying the Schwartz formula at the bedside in the PICU. Among the new biomarkers, bNGAL alone may not be useful in all PICUs. In our case, the day of admission NGAL levels were not found to be predictive of the day 3 creatinine clearance measurements. In our PICU, uNGAL did not prove its excellency in the management of critically ill children. This is also due to the small sample and the lack of homogeneity among the diseases that triggered the PICU admission.

We demonstrated that uNGAL is a good marker of renal injury, but not a good predictor for AKI. Depending on the disease severity and complexity of the admitted patients, uNGAL use may not always be helpful. Indeed, to clearly demonstrate its accuracy, one may need larger samples, which is not always easy to produce, usually due to a lower frequency of such diseases in pediatrics compared to adult medicine. Last, but not least, based on ethical grounds (the reluctance of parents to accept the enrollment of children in research). However, uNGAL may be potentially helpful in reno-protective interventions such as avoiding nephrotoxic exposure and contrast agents, maintaining euvolemia, thereby decreasing the morbidity and mortality associated with AKI.

I.4.2 AKI in the newborn – a challenge for the medical team

The primitive prenatal kidney appears by the third week of gestation, while the permanent kidney begins to form after the 30th day of gestation (Bakr 2018). Fetal kidneys produce dilute urine, the production of which increases from 15 ml/kg/h to 50 ml/kg/h at 40 weeks of gestation (Coca 2012). After birth, serum creatinine reflects maternal renal function up to 72 hours of life. GFR and effective renal blood flow are low in term and preterm neonates, due to the high vascular resistance in the renal vessels and, also, due to the marked decrease in systemic vascular resistance resulting from the redistribution of blood flow at birth (Moritz 1999).

Epidemiology and incidence of AKI in newborns

Neonatal AKI is common in neonates admitted to neonatal intensive care units (NICU) and is a major factor in neonatal mortality and morbidity (Coca 2012). The incidence of AKI is 6-24% in newborns in intensive care units, 25% being represented by oliguric forms, 60% being non-oliguric, and 15% anuric forms. Premature newborns (especially those with birth weight below 1500 g) and newborns with sepsis, asphyxia or cardio- vascular malformations (persistent ductus arteriosus, transposition of great vessels) are at an increased risk of developing acute renal failure. AKI associated with kidney malformations has an incidence of 50%. Genetic factors that increase the risk for AKI are mutations of the gene that encodes the angiotensin enzyme, or its receptor, which cause changes in the activity of the renin-angiotensin-aldosterone system (RAAS), which ultimately leads to AKI (Summary of Recommendation Statements 2012). AKI occurs more frequently in very low birth weight (VLBW) newborns who have mutations in the genes encoding the heat shock protein 72 (Fekete 2003). Since this protein has an important role in the production of renal ischemic injury, these findings suggest that some newborns would be more susceptible to ischemic injury. The mortality reflects trends similar to those of older children and adults. Non-oliguric acute renal failure is associated with a higher survival rate than oliguric acute renal failure. Norman and Asadi observed a mortality rate of 45% in oliguric renal failure, and other authors noted a mortality rate between 14% and 73% (Gorga 2018). The international, retrospective, observational, cohort study AWAKEN assessed the epidemiology of AKI worldwide in neonates exclusively admitted to neonatal intensive care units and who received at least 48 hours of intravenous volume resuscitation (Jetton 2017). Early AKI was defined by an increase in serum creatinine of 0.3 mg/dl, or a decrease in diuresis below 1 ml/kg per hour on post- natal days 2-7. Risk factors for AKI and the association with length of hospital stay and mortality were assessed. Twenty-one percent (449 of 2110) developed early AKI, which is associated with a higher risk of death. Factors associated with a higher risk of AKI included: preterm birth, resuscitation with epinephrine, marked hyper-

bilirubinemia, inborn errors of metabolism, or the need for emergency neonatal surgery. Risk factors varied by gestational age. The study showed that 50% of newborns with asphyxia presented prerenal damage, 17% of them presented oliguria and increased creatinine, and 11% presented only increased azotemia. The same authors observed the association of prolonged oliguria with CKD, hypoxic-ischemic encephalopathy and with long-term neurological deficits (Charlton 2019).

Etiology of AKI in the newborn

The most common form of AKI in neonates is prerenal failure due to renal hypoperfusion or ischemia. Prerenal AKI can lead to intrinsic renal failure if not treated promptly. The newborn kidney is particularly sensitive to hypoperfusion due to the physiological characteristics of the neonatal kidney, including high renal vascular resistance, high plasma renin activity, low GFR, low intracortical perfusion rate, and de- creased proximal tubule sodium reabsorption in the first days of life (Basile 2016). Thus, newborns can develop more easily acute tubular necrosis or cortical necrosis. The etiology of AKI in the newborn is multifactorial. In most studies, birth asphyxia and sepsis are the most commonly associated conditions. Other conditions associated with the development of AKI in the newborn include respiratory distress syndrome, dehydration, congestive heart failure and nephrotoxic drugs (Youssef 2015), but also the obstructive causes, like posterior urethral valve, phimosis, preputial imperforation, urethral diverticulum, blood clot, prune belly syndrome and extrinsic bladder obstructions by tumors, mesenteric cyst, adrenal hemorrhage (Stârcea 2019). A special place in the classification of AKI in the newborn should be given to hospital-acquired acute renal dysfunction. In developed countries, AKI has been intensively studied in children with operated congenital heart malformations, but also in non-cardiac patients with severe diseases from intensive care units. In them, the incidence of AKI varies between 30% and 60% (Li 2011). Thus, the term hospital-acquired AKI (HA-AKI) appeared, which signifies an episode of AKI due to a renal involvement that occurred in the patient after hospitalization, as opposed to community-acquired AKI (CA-AKI), in which the initial event occurred before hospitalization. In developed countries, nosocomial infection and primary renal disease remain the main cause of CA-AKI, instead the etiology of HA-AKI is often multifactorial and reflects comorbidities (for example, bone marrow transplantation, healthcare-associated infections, hospitalization in neonatal intensive care units).

Current role of urinary biomarkers

The early diagnosis of acute renal dysfunction in the newborn may bring new therapeutic perspectives Knowledge of serum and urinary biomarkers involved in the pathophysiology of newborn AKI may change the approach to this diagnosis, helping to differentiate causes and rapidly implement preventive interventions. Serum creatinine and diuresis are functional biomarkers of AKI, they don't assess the presence or absence of tissue structural lesions, and only quantify the decrease in the glo- merular filtration rate. In addition, their change appears after 72 hours from the onset of renal injury. Animal models have identified proteins secreted in the urine, as a result of cellular damage to the renal tubules, involved in the pathophysiology of AKI and which allow the early identification of tissue damage, before the function is affected. Studies of specific biomarkers in neonatal AKI are limited and performed mainly in risk populations, such as low birth weight preterm infants, perinatal asphyxiated infants, and those undergoing cardiopulmonary surgery (Libório 2014). Studies conducted in children who underwent heart surgery or in seriously afflicted pa- tients from intensive care units, who received substances with renal toxicity demonstrated the increase in the urinary concentration of these biomarkers 48 hours be- fore

the increase in serum creatinine. Moreover, marked increases predict a greater degree of severity of AKI (Bihorac 2015).

Practical therapeutic approach in the emergency department

Prophylaxis is preferable, of course, to curative treatment and involves early detection of the aforementioned risk factors, fetal ultrasonography to detect renal malformations, prevention of decreased renal blood flow or intravascular blood volume by administering prophylactic dopamine and furosemide or mannitol, and avoiding the nephrotoxic drugs administration during pregnancy. Theophylline infusion, which is indicated in the first hour after birth in severe asphyxia, was associated with restoring the water balance and reducing the serum creatinine level from the third day of life, with no effect on neurological or respiratory complications. But newborns receiving theophylline tend to have a high incidence of persistent pulmonary HTN. In the study published in 2019, Bhatt and colleagues established, following the analysis of nine trials, the importance of administering a dose of theophylline for AKI prophylaxis in newborns (Bhatt 2019). The treatment involves general supportive treatment with electrolytic, AB and nutritional balancing, blood pressure control, cardiac output optimization, as well as the treatment of the primary cause (asphyxia, infections, shock etc.).

Neonatal dialysis in newborns and children who have reduced muscle mass – the initiation of renal replacement is done at lower serum creatinine values. Hemodialysis has been replaced by peritoneal dialysis and hemodiafiltration, the technique of choice for the treatment of vascular overload. Peritoneal dialysis is contraindicated in newborns with respiratory distress, shock, peritonitis or ulceronecrotic enterocolitis. A recent study showed that the choice of renal replacement method by the pediatric nephrologist included 30% peritoneal dialysis, 20% hemodialysis, and 40% hemofiltration (Mian 2016). Kidney transplant is not an available option at this age. Nutrition aims to minimize the excessive catabolism. The minimum caloric intake will be 100 kcal/ kg/day, with protein in a dose of 1-2 g/kg/day. If the newborn cannot be enterally fed, with breast milk, total parenteral nutrition is instituted in which the usual amino acid solution must be replaced by essential amino acids supplemented with L-histidine in a dose of 0.5-1 g/kg/day. Dosage adjustment of drugs with renal elimination should be performed such as to avoid toxic levels either by extending the administration interval or by reducing doses. Administration of drugs such as aminoglycosides, acyclovir, amphotericin B, cyclosporins, paralyzing agents, tolazoline, antiepileptic drugs and digoxin can increase the renal damage.

Prognosis

The prognosis depends on the etiology of AKI. The factors associated with increased mortality are multiorgan failure, hypotension, the need to use vasopressors, hemodynamic instability, the need for mechanical ventilation and the need for extrarenal purification by dialysis. The immediate mortality of infants with urinary tract malformations depends on their association with other syndromes (Potter syndrome, severe pulmonary hypoplasia, renal agenesis, prune belly syndrome). The mortality rate in newborns with oliguric renal failure was 60% in cases due to asphyxia and sepsis (Gorga 2018). A higher rate was recorded in those with congenital heart malformations and multiorgan failure. In children with peritoneal dialysis for AKI, the reported mortality is 64% in those with oligoanuria, compared to 20% in those with normal diuresis (Mian 2016). The long-term follow-up of children with AKI revealed that CKD can install after 3-5 years, suggesting that the effects of AKI are in time, on nephron total mass. Newborns with renal congenital diseases (renal dysplasia, obstructive uropathy, cortical necrosis, polycystic renal disease) are at a high risk

to develop CKD. In the short term, the prognosis depends on the general condition of the newborn and the condition of all major organs and systems. It is essential to appreciate the newborn as a whole, and not just the renal pathology. The prognosis for non-oliguric renal failure or prere- nal failure is better than for those with renal failure of renal origin. The long-term effects are also related to the moment when the offending factor acts. AKI before 34 weeks of gestation leads to a reduction in the total number of nephrons. AKI in prematurity or in small for gestation age children is associated with reduced GFR, proteinuria after a few years, and with the risk of renal HTN as teenagers.

Conclusion

The association of AKI is frequent in newborns from pediatric intensive care units and markedly in- creases the risk of mortality. Contrary to the classical theory (full recovery is the rule), the patient who went through AKI has a risk of developing CKD and requires long-term follow-up. The long-term prognosis must be addressed in a team that includes a neonatologist, nephrologist, anesthesiologist and intensive therapist, urologist, clinical geneticist and radiologist. Knowing and using standardized definitions and staging of AKI in newborns contribute to a more efficient approach to the patient by the complex medical team.

I.4.3 Acute renal failure in children – a study on 35 cases

I.4.3.1 Material and methods

The medical care of children with acute renal failure and the necessity of the substituting the renal functions has dramatically modified over the past 15 years. The study has been conducted retrospectively on 35 children diagnosed with AKI, for analyzing the etiological spectrum, the evolutionary patterns and the influence factors of the disease evolution. The lot of this study included 35 children diagnosed with IRA; the criterion for inclusion in the batch was impaired renal function (clinical and biological) for a period of less than three months. The duration of follow-up ranged from 4 to 30 months. They analyzed: distribution by age, sex, AKI etiology, clinical and laboratory parameters (presence of edema, blood pressure, diuresis, digestive and neurological disorders, nitrogen retention, diselectrolytemia, and EKG changes), treatment used, complications of the disease and those related to therapy, and evolution. Indications for extrarenal clearance were: oligo-anuria after three days; nitrogen retention; hepato-renal syndrome; Arterial hypertension (HTA) with or without pulmonary edema; and uremic gastritis. As possible factors influencing the evolution, the following parameters were considered: AKI etiology, hTA/HTA (assessed by waist ratio), oligoanuria persistence, nitrogen retention level (creatinine clearance calculated by the Schwartz formula), and type of treatment (renal suppression by HD or DP, conservative treatment).

I.4.3.2 Results

Children with AKI included in the study batch were divided into three age groups, as shown in Table 1.24. The average age was 6.3 years (with limits between 5 days and 17 years). Of the 35 children with the IRA, 15 were boys and 20 were girls. The etiological diagnosis is presented in Table 1.25. The clinical parameters analyzed are presented in Table 1.26. Edema was noted in 14 cases (40%), having a generalized character. Seven of these cases showed massive edema, which, along with other parameters, constituted a criterion for inclusion in dialysis. Oligoanuria was present in 24 children, (70%) in 10 cases lasting more

than 3 days and constituting, along with other symptoms, one of the indications for extra-renal clearance. Hypotension was observed in 5 patients (14.2%) who needed treatment with vasopressor amines, of which 2 children died. Hypotension is quoted as a pejorative prognostic factor (Flynn 2002).

The size of the batch analyzed did not allow us such a correlation. HTN was noted in 13 cases (37%), in 4 children being HTA border, in 6 children HTA confirmed, and in 2 cases TA reached threatening values. Electrolytic disorders were present in 14 patients (moderate hyperpotasis - 9 cases 25.7%, hyponatremia - 5 cases 14.2%, hypernatremia – 1 case -3%), in which they could be corrected by intravenous rebalancing. The EKG changes recorded in our patients consisted of: symmetrical, high and sharp T waves in 9 children, suggesting hyperkalemia, confirmed by serum ionogram, but with values below 6,5 mEq/L. The treatment applied was conservative in 17 cases (48.5%). In 18 cases dialysis was practiced: in 15 cases (42.8%) hemodialysis was performed and 3 children (8.5%) were treated by peritoneal dialysis (DP). Indications for dialysis are shown in Table 1.27, along with the etiology that induced AKI. All cases undergoing HD were in critical condition at the time of initiation of this therapy. Hemodialysis was required mainly by persistence of oligoanuria in combination with moderate to severe HTA and neurological disorders in 11 cases (Table 1.27). Complications of hemodialysis consisted in: catheter infections in 5 cases, hypotension during the session in a 10-month-old infant, requiring administration of vasoactive amines. In a newborn with ARPKD treated by peritoneal dialysis, purulent peritonitis occurred 4 days after initiation of therapy. Following the progress of patients, it is observed that the majority (24 cases - 68.5%) have fully recovered their renal function. The follow-up period was 4 to 30 months, with an average of 8 months. Co-right, remote assessment was possible in eight cases. The time interval until recovery ranged from 5 to 70 days, averaging 17.4 days. The evolution towards CKD assessed after 3 months, was observed in 3 cases - 8.5%, respectively 2 patients with atypical HUS and 1 case of rapid progressive glomerulonephrite. In cases with aHUS, the evolution was linear towards chronization. Death occurred in 8 cases (22.80%), all due to extra-renal causes

Table 1.24 *Age distribution of study cohort*

Age group	0-1 years	1-5 years	> 5 years
No. of cases (%)	11 (31,34)	6 (17,28)	18 (51,42)

Table 1.25. *AKI etiology in study cohort*

AKI etiology	No. of cases	Percentage
Sepsis	11	31,4%
Acute dehydration	3	8,5%
Polycystic kidney	1	2,890%
Intoxications		
Mushrooms	2	5,71%
Ethylengligol	1	2,80%
Medication	1	2,80%
Cisplatin	1	2,80%
Rifampicine	1	2,80%
Hemolytic uremic syndrome	6	17,1%

Tumoral lysis syndrome	3	8,5%
Bilateral uretheral lithiasis	1	2,77%
Chronic mesangio-proliferative glomerulonephritis	2	5,55%
Rapid progressive glomerulonephritis	2	5,55%

Table 1.26*.Clinical data of subjects with AKI included in the study*

Clinical findings	**No. of cases**
Edema	14
Oligoanuria	24
Hypo/hypertension	5/13
Gastro-intestinal manifestations	10
Neurological manifestations	12

Table 1.27 *AKI etiology and dialysis indications*

Dialysis indication	**No. of cases (%)**
Mushroom intoxication	2 (11,11%)
Intoxication due to ingestion of multiple medication	2 (11,11%)
Tumoral lysis syndrome with oliguria	3 (16,66%)
Polycystic kidney – anuria and hypertension	1 (5,55%)
Septic shock **- Oliguria and neurological manifestations** **- Multisystem organ failure**	 1 (5,55%) 1 (5,55%)
Hemolytic uremic syndrome **- Anuria + kidney failure + hypertension**	5 (5,55%)
Glomerulonephritis **- Oligo-anuria + hypertension + neurological manifestations**	3 (16,66%)

I.4.3.3 Discussion

Continuous renal replacement therapy (CRRT) is enjoying a growing interest, while DP, except for very young ages, is declining (Flynn 2002). We can see that the global mortality rate in our batch is low (22.80%) compared to that shown in the literature. But, since the deaths occurred only in dialysed patients, calculating mortality in this group we note a higher percentage - 44.44%. Wei-Kin Gong et al. (Gong 2001) a mortality of 68.2%

on a batch of children who all needed dialysis. Lowrie reports a 91% mortality rate in critical patients with multiple organic suffering syndrome. So, it is difficult to compare the mortality rate in different series due to the different dimensions of the batches, their etiological heterogeneity and the different degrees of severity of the AKI.

I.4.3.4 Conclusion

The majority of cases of AKI are over 5 years (51.42%) and infants (31.42%). The symptomatology is varied and is closely related to the etiology of the disease; secondary kidney damage occurs as a consequence of the correct assessment of the critical patient. The prognosis of the disease is influenced by conditions of comorbidity (liver failure, oncological disease, neurological disorders, hemodynamic instability). Indications for dialysis, in the batch studied, were oligo-anuria over three days, nitrogen retention, hepato-renal syndrome, HTA with or without pulmonary edema, uremic gastritis. Dialysis improved therapeutic results, with death occurring in 44.44% of dialysed cases (22.80% of the entire batch studied), with extra-renal causes of death.

I.4.4 Drug induced acute tubular necrosis – rare case of NS

Multiple therapies have renal side effects. The most common form of acute renal failure is acute tubular necrosis. There are rare occasions, seldom quoted, of tubular necrosis manifesting as NS (Jason 2013).

I.4.4.1 Material and methods

We presented two cases of NS drug-induced with tubular nephrotoxicity, with different evolution in the context of etiologic diseases.

I.4.4.2 Results

Case I: 5-month-old girl admitted with NS (clinically and biological proven) and acute renal failure after another hospitalization for pneumonia. The girl was treated with ceftriaxone and gentamicin 12 days. Congenital NS suspicion was eliminated by renal biopsy who revealed renal tubular necrosis highlighting recovery phase (Fig. 1.40). The development was favorable in 7 days of peritoneal dialysis.

The positive diagnosis was **Drug-induced acute tubular necrosis**, **AKI, Secondary NS,** secondary anemia. The treatment consisted in correcting electrolyte and AB disorders, correction of anemia with red blood cell transfusion, correcting hyperuricemia with allopurinol and peritoneal dialysis for 10 days, well tolerated.

The evolution was slow, with the resumption of diuresis and decreasing of nitrogen retention. Subsequent checks revealed the disappearance of clinical and biological picture of NS and normalized renal parameters.

Case II - 16 years old adolescents treated 3 years with carbimazol for Basedow disease. Was presented with NS not influenced by corticosteroids. Histopathology revealed **toxic tubular necrosis, interstitial fibrosis, absence of glomerular injury** (Fig. 1.41). Nephrotoxic treatment was stopped, and, after thyroidectomy, edema was reduced, but kidney function continued to depreciate, while nephrotoxic therapy given for 3 years. She is now in ESRD, chronic dialysis program.

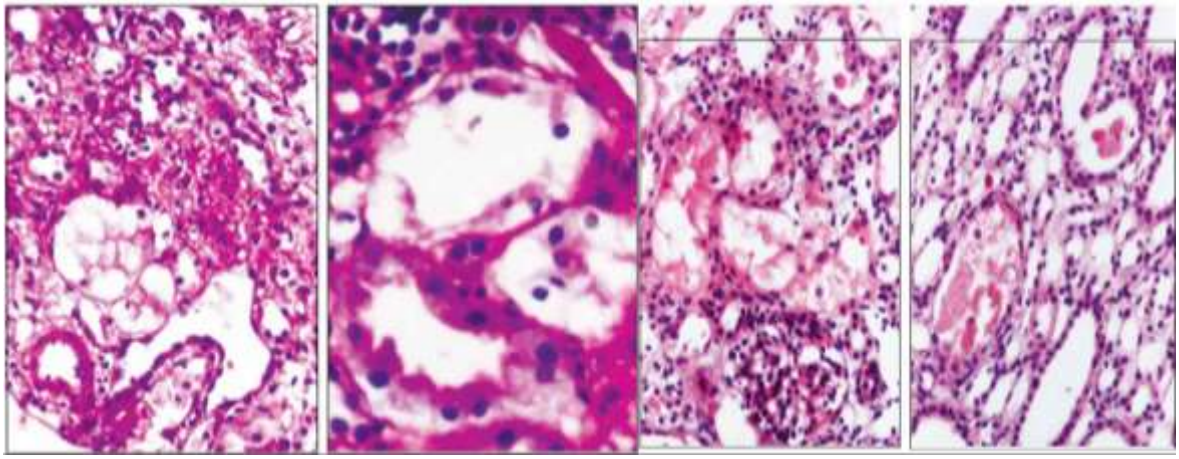

Fig. 1.40. *Degenerative changes - granulocyte-type outbreaks of patchy necrosis. From left to right: renal tubules in PAS coloration x200, renal tubules in PAS coloration x400, renal cortex in hematoxylin-eosin coloration x200, renal medulla in hematoxylin-eosin coloration x200.*

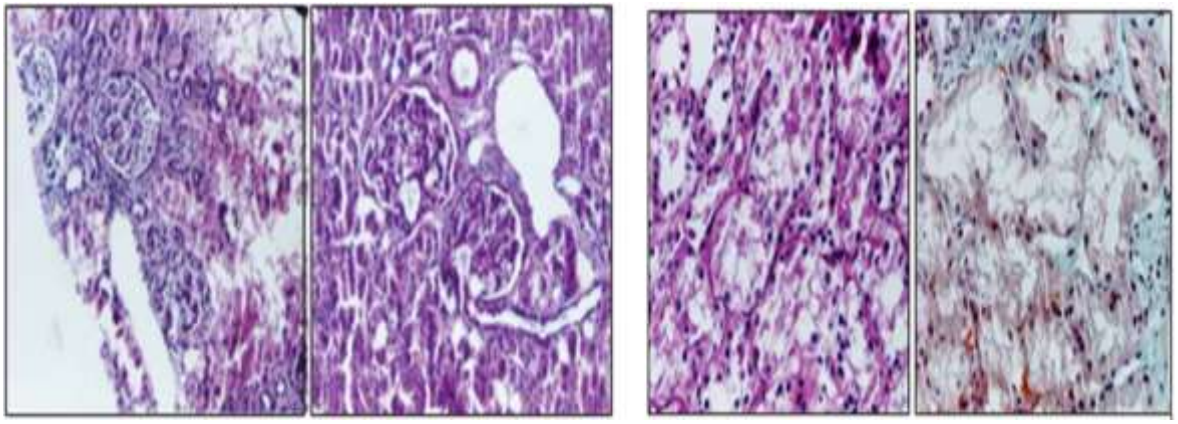

Fig. 1.41. *Histopathology aspects. From left to right: normal glomeruli in hematoxylin-eosin coloration x100 and PAS coloration x100; tubular necrosis in PAS coloration x200, tubular necrosis and interstitial fibrosis in Szekely coloration x200.*

I.4.4.3 Discussion

Both cases illustrate the renal tubular toxicity effect of the drugs used in the treatment of pediatric pathology – nonsteroidal anti-inflammatory (Jason 2013), aminoglycosides (Balgradean 2013), vancomycin (McKamy 2011), contrast media, gold salts. The peculiarity lies in clinical and biological expression of acute tubular necrosis as a NS. In the first case where the toxic exposure was of short time, there has been full recovery of renal function compared to the second case where the outcome was interstitial fibrosis as toxic acted much longer. The literature quoted numerous cases of interstitial nephritis tubulointerstitial toxicity due to aminoglycoside therapy (Balgradean 2013, Zappitelli 2011) but only one case of interstitial nephritis after carbimazol treatment (72 years old male) (Day 2003). It is known so far the link between propylthiouracil and kidney damage.

I.4.4.4 Conclusions

It is known the nephrotoxic role of aminoglycosides. Carbimazol was only incriminated in some cases of acute tubular necrosis. In very rare cases a nephrotoxic trigger causes a NS clinical and biological aspect.

I.4.5 Hantavirus Infection in Children—A Pilot Study of Single Regional Center

Hantaviruses are infectious etiological agents of a group of rodent-borne hemorrhagic fevers, with two types of clinical manifestations in humans: hantavirus pulmonary syndrome (HPS) and hemorrhagic fever with renal syndrome (HFRS). According to available statistics, the disease occurs mainly in adults, but the lower incidence in the pediatric population might also be related to a lack of diagnosis possibilities or even unsatisfactory knowledge about the disease.

Hantaviruses are the etiologic agents of a diverse group of rodent-borne hemorrhagic fevers belonging to the *Bunyavirales* order, which contains a group of single-stranded, spherical, enveloped RNA viruses. Different viral families in the *Bunyavirales* order cause hemorrhagic fever. They include *Phenuiviridae, Arenaviridae, Nairoviridae*, and *Hantaviridae* (Teng 2022).

I.4.5.1 Material and methods

Epidemiological Study

A retrospective single-center study was carried out over a period of 5 years (January 2017 to January 2022) on a group of patients of both sexes, aged between 0 months and 18 years, hospitalized in the Nephrology Department at St. Mary's Emergency Hospital for Children in Iasi, Romania, regarding HFRS. This is a tertiary hospital serving the pediatric population of 7 counties. The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of St. Mary's Emergency Hospital for Children in Iasi, Romania (34629/23.11.2022). In order to identify the eligible patients, we performed a free text search of our hospital's database using the search terms "hantavirus infection" and "HFRS", while ruling out cases of Hantavirus pulmonary syndrome. The main criterion for inclusion in the study was the definite diagnosis of hemorrhagic fever with renal syndrome beginning from the clinical aspect, and by performing serological, immunological, and pathological analysis with biopsies taken from the kidney when it was possible. Our research was based on the analysis of data from patient observation charts, hospital discharge tickets, and the pathology reports. We compiled data on gender, age, biological data, viral serotype, and renal impairment.

We have selected 79 cases of patients who presented with AKI and hematological involvement, such as thrombocytopenia/anemia. Among them, 70 were confirmed to have different types of thrombotic microangiopathy (post-diarrheic hemolytic uremic syndrome, or atypical hemolytic uremic syndrome) and one with Leptospirosis infection. After excluding other types of pathology that associated AKI and hematological involvement, we identified eight unique patients with a serology-confirmed Hantavirus infection and renal involvement. All the immunology and virology analyses necessary for the diagnosis were conducted by the Public Health Institute in Bucharest, the capital of the country.

Serological Diagnostic

The serological diagnosis of Hantavirus infections was performed at the Public Health Institute by enzyme-linked immunosorbent assay (ELISA) based on the detection of immunoglobulin G and M responses to the recombinant nucleocapsid proteins of five viral serotypes.

Kidney Biopsy

For the diagnosis of one case, we performed a kidney biopsy. We made a frozen section. The tissue staining was performed with toluidine blue and Hematoxylin Eosin on the frozen section, and the examination was in optical microscopy with the magnitude ×40 and ×200.

I.4.5.2 Results

We identified eight cases of HFRS, all of which were males, aged between 11 and 18 years (mean age 15.5 years-old), predominantly living in rural environments (7/8). All patients were referred to our clinic due to AKI, two of them having an epidemiological context—one working as a shepherd and one as a forest worker. Symptoms developed 3 to 7 days before presentation, with an average onset of 4.6 days. Sociodemographic, clinical characteristics, and biological data at onset are summarized in Table 1.28. All patients presented with gastrointestinal symptoms, while fever was present in 5/8 cases. Because of AKI with marked renal failure, 3 patients underwent a short course of dialysis, the rest receiving only supportive care. Viral serotype was assessed in all eight cases, revealing Dobrava serotype in seven patients and Hantan serotype in one patient. All patients survived, with complete restitution of renal function. The hospitalization period ranged between 5 to 22 days, with an average of 9.9 days. Assessment of renal function at onset and in dynamic revealed varying degrees of nitrogen retention, as seen in Table 1.29.

Table 1.28 *Sociodemographic, clinical characteristics, and biological findings at baseline.*

Patients	**Age, Month and Year at Admission**	**Baseline Characteristics**	*n* = 8	**Biological Findings**	*n* = 8
Patient 1	*16 y.o.*	**Gender**		***CBC***	
	November 2017	*Female*	0	*Mild anemia*	1
Patient 2	*16 y.o.*	*Male*	8	*Leukocytosis*	2
	October 2021	**Residence**		*Thrombocytopenia*	6
Patient 3	*18 y.o.*	*Rural*	7	**Inflammatory markers**	
	October 2018	*Urban*	1	*CRP > 10 mg/dL*	8
Patient 4	*16 y.o.*	**Symptoms**		*ESR > 15 mm/1 h*	5
	May 2020	*Vomiting*	8	Hepatic cytolysis	6
Patient 5	*16 y.o.*	*Abdominal pain*	6	**Urinalysis**	
	October 2019	*Fever*	5	*No proteinuria*	0
Patient 6	*11 y.o.*	*Diarrhea*	3	*Proteinuria < 30 mg/dL*	2

	November 2017	*Oedema*	3	*Proteinuria 30–100 mg/dL*	2
Patient 7	*16 y.o.*	*Oligo-anuria*	2	*Proteinuria > 300 mg/dL*	4
	January 2022	*Headache*	2	*No hematuria*	4
Patient 8	*15 y.o.*	*Cough*	1	*Hematuria < 10 RBC/μL*	4
	October 2022	*Shiver*	1	*Hematuria > 10 RBC/μL*	0

CBC = complete blood count; CRP = C-Reactive Protein; ESR = Erythrocytes Sedimentation Rate; RBC = red bloodcells; μL = microliters.

Table 1.29 *Urea and Creatinine Values at onset versus highest value during hospitalization.*

Patients	**Urea (mg/dl)**		**Creatinine (mg/dl)**	
	Onset	**Highest Value**	**Onset**	**Highest Value**
Patient 1	154	172	3.4	6.4
Patient 2	111	215	1.3	6.6
Patient 3	79	110	2.6	5.7
Patient 4	103	172	2.2	5.7
Patient 5	76	296	2.3	8.5
Patient 6	84	140	2.7	4.4
Patient 7	107	125	2.8	3.7
Patient 8	132	132	4	5.12

On one patient we performed a renal biopsy for the differential diagnosis with a glomerulonephritis. The result showed infiltrates with polymorphonuclear cells and eosinophils in the renal interstitium and tubules, tubules with fibrino-leukocyte cylinders, suggestive of interstitial nephritis and multifocal interstitial hemorrhages (subcapsular and medullar areas), as seen in Fig. 1.42 and 1.43. We also performed immunofluorescence, which was negative for C1q, C3, IgA, IgM, IgG, and fibrinogen. From 22 glomeruli resulting from a needle biopsy, 18 were normal glomeruli and the rest were with moderately increased mesangial cellularity. Unfortunately, we could not perform the electron microscopy.

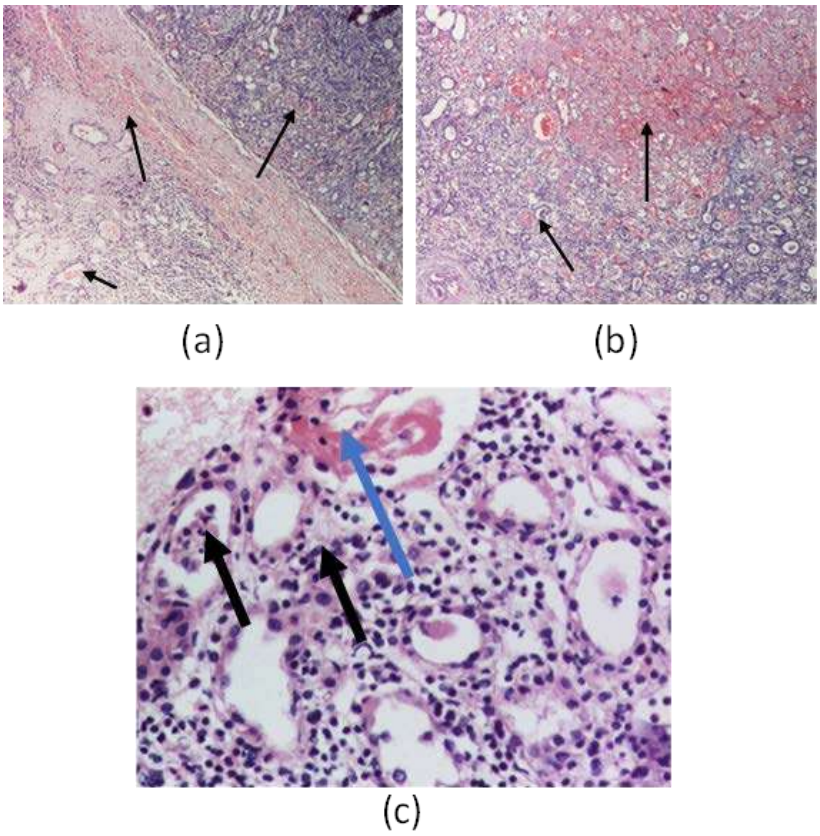

Fig. 1.42 *Kidney biopsy: (a)—Hematoxylin-Eosin (HE) coloration in optic microscopy (OM) (×40) showing multifocal interstitial hemorrhages in the subcapsular areas (black arrows); (b)—HE coloration in OM (×40), showing multifocal interstitial hemorrh hemorrhages (black arrows); (**c**)—HE coloration in OM (×200), showing interstitial nephritis infiltrates with polymorphonuclear cells and eosinophils in the renal interstitial and tubules (black arrows); renal tubules with fibrino-leukocyte cylinders—(blue arrow).*

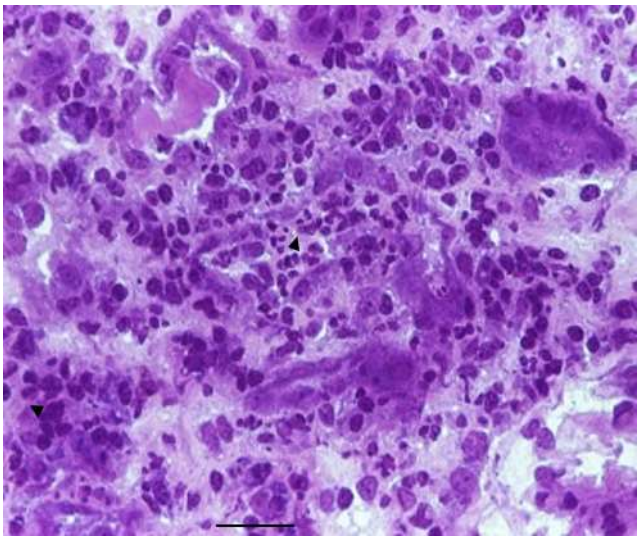

Fig. 1.43 *Kidney biopsy—Interstitial Nephritis. Toluidine Blue coloration in optic microscopy (×200) showing infiltrates with polymorphonuclear cells in the renal interstitium and tubules—black arrows).*

I.4.5.3 Discussion

Epidemiology of Hantavirus Infection

Based on the geographic areas in which they are found, hantaviruses are conventionally divided into two categories: Old World (Euro-Asia) hantaviruses and New World (America) hantaviruses. Amur virus (AMV), Seoul virus (SEOV), HTNV, Dobrava virus (DOBV), Tula virus (TULV), and Puumala virus (PUUV) are Old World pathogenic hantaviruses that cause HFRS in humans. This virus's serotypes predominantly cause HFRS, a disease characterized by renal failure, hemorrhage, and shock (Kim 2016). HTN virus and DOB virus tend to produce the most severe form of the disease, with mortality rates of approximately 5.0–10.0%, while Puumala virus is endemic in northern Europe and usually causes a less severe HFRS disease, also called epidemic nephropathy (NE), with a low mortality rate of 0.1–0.2% (Noh 2019). Breast milk may contain Andes Orthohantavirus (ANDV) - infected cells, leading to direct inoculation into the Peyer's patches of the naturally fed infant (Cabinian 2016). It is known that the newborn has a more alkaline gastric pH, and the gastric emptying is achieved quickly in the natural diet, which favors the transmission of this viral serotype through breast milk (Ferrés 2020).

The spread of hantaviruses throughout Europe is not uniform; for example, in the 2019′s Annual Epidemiological Report from the European Centre for Disease Control, from 2015 until 2019, in Romania, there were only 23 cases of HFRS reported compared to Finland with 6627 cases or Germany with 4611 cases (Hantavirus Infection—Annual Epidemiological Report for 2019).

In Romania, the first case of HFRS serologically confirmed was in 2005, in a man spending a fortnight in his forest hut (C.S. Ceianu, unpublished). There aren't many studies in our country regarding hantavirus infection in general, and almost none regarding the pediatric population. Maftei et al. published a first study in 2011 regarding the HFRS in adults from Romania since laboratory diagnosis of hantavirus infection has become available in the country, demonstrating that there are hantavirus infections in Romania and that this type of infection should not be overlooked (Maftei 2011).

We can, however, compare this with the studies made for the Balkan region in which our country is included, having been demonstrated that all the countries from this region have similarities regarding hantavirus infection (Županc 2014). Most frequently, the patients are male, with an overall male: female ratio of 2:1.

Hantavirus diseases also occur almost exclusively in rural areas, and people at increased risk of infection are those who live or work in in specific environments linked to virus reservoirs, such as hunters, farmers, forestry workers, or military.

Pathological Features of the Disease

The HFRS is characterized by hematologic abnormalities and prominent renal involvement. Damaging the micro vascularization by the virus with resulting increased vascular permeability and vasodilatation seems to play an important role in the pathogenesis of the hantavirus infection (Koskela 2021). It is assumed that vascular endothelial cells are the primary target of viral particles in a hantavirus infection. Dendritic cells, epithelial epithelial cells, and mononuclear phagocytes are invaded by the virus (32). The infection triggers an immune response by activating cytokines and cytotoxic lymphocytes. Increased CD8+ and CD4+ T cell responses were also observed (Jost 2013). More specifically, elevated levels of IL-6 have been observed to be associated with severity for both HTNV, ANDV, and PUUV (Klingström 2019). Increased levels of intercellular adhesion molecule 1 (ICAM-1) are expressed on the surface of the infected cell, resulting in endothelial cell adhesion, NK cell activation, and the release of pro-inflammatory mediators (Klingström 2019, Jost 2013, Noor 2020). The typical renal histological finding is acute tubulointerstitial

nephritis. Hantaviruses can infect tubu- lar epithelial cells, glomerular endothelial cells, and podocytes of the human kidney. A high degree of proteinuria as well as medullary hemorrhages are suggestive and specific for hantavirus infection (especially for PUUV), being found in 20–60% of renal biopsies in the acute phase (Mustonen 2017). These lead to hypotension, hemoconcentration, thrombocytopenia, proteinuria, and leukocytosis, as well as an abrupt decline in GFR, with AKI (Caramello 2006). In our case, the renal biopsy also showed interstitial nephritis with multifocal interstitial hemorrhages, a specific sign of infection.

Clinicals Features of the Disease

The hantavirus infection has to be distinguished from other acute illnesses, infectious or non-infectious. If we refer strictly to the clinical presentation, due to its diversity of signs and symptoms, there is indeed a very long list: acute abdominal pain, with vomiting and fever, can be misinterpreted as signs of acute surgical abdomen—appendicitis, inflammatory pelvic process, pancreatitis—and can lead to unnecessary surgery, acute febrile urinary infection, and bacterial sepsis (Maftei 2011). We have to include the HFRS in the differential diagnosis of AKI, associated with thrombocytopenia, such as hemolytic and uremic syndrome, acute tubulointerstitial nephritis of other etiology, and acute or chronic glomerulonephritis. One of the first illnesses to rule out when facing a child with fever, thrombocytopenia, AKI, and acute hepatitis is leptospirosis, as it has a very similar clinical picture with HFRS.

Biological Features in the Disease

A hallmark of HFRS in the Balkans is renal impairment. Elevated levels of urea and creatinine are useful in early HFRS diagnosis (Županc 2014). All of our patients had various degrees of AKI, with only three out of eight needing a short course of dialysis. Echterdiek et al. found no statistical difference between children and adults concerning the need for dialysis, one of the ideas raised by their study being that pediatricians are usually more cautious in starting dialysis in children and are more accustomed to rely on clinical presentation rather than laboratory findings (Echterdiek 2019).

Thrombocytopenia is another laboratory marker for HFRS, but it is not necessary to be present, as various studies have suggested, with a low platelet count being found between 30–100% in children (Hantavirus Infection—Annual Epidemiological Report for 2019). Generally accepted, though, is the fact that thrombocytopenia
recognized as a severity marker of hantavirus infection, with platelet count being a predictor of the severity and progression of the disease, especially marked thrombocytopenia for the subsequent severe AKI (Zeier 2005). All of our patients had proteinuria and elevated C-reactive protein, consistent with the data in the literature (Cherry 2019).

A kidney biopsy should be considered in those children where the course of AKI does not follow the expected course towards spontaneous regression. However, particular precautions should be taken regarding the risk and benefit ratio of this invasive measure, as the majority of patients are thrombocytopenic. The most frequent type of injury described is acute tubulointerstitial nephritis, also called NE (Lupusoru 2021). The only patient from our study who had a kidney biopsy was also afflicted with this histological aspect. In this case, the biopsy was necessary because the initial presentation needed a differential diagnosis with a glomerulonephritis. Moreover, the child did not have a suggestive history, was from an urban environment, and did not work in a forest or on a farm. In children, the evidence is scarce, but it suggests that kidney function also returns to normal, as happens in the adult population (Huttunen 2011). All patients from our study survived and regained complete renal function. This serves to emphasize the statement above.

Evolutive and Therapeutic Features in the Disease

Two hantaviruses, Pumala and Dobrava, are responsible for clinically manifested HFRS in patients in the Balkans (Fidan 2012). From eight children included in our study, seven were infected with the Dobrava serotype. Panculescu-Gatej et al. demonstrated in a study that there are two strains of the Dobrava virus that circulated in rodent populations and transmitted to humans in Romania, and that both belong to the group of Dobrava strains circulating in Southeastern and Central Europe (Panculescu-Gatej 2014). Till now, the literature does not specify evidence of the effectiveness of any antiviral drug for HFRS or HPS. The management of severe cases is based exclusively on supportive therapy, with correct water and electrolyte balance. HFRS patients with severe renal insufficiency may require extrarenal clearance by acute dialysis or hemodiafiltration techniques. In HCPS, patients can benefit from mechanical ventilation, and extracorporeal membrane oxygenation may even be necessary. Since hantavirus usually causes a self-limiting infection with a favorable evolution in 2–3 weeks, treatment is mainly supportive. KRT is occasionally required (in <5% of cases) and this is largely due to hypervolemia. Thus, an effective supportive treatment option is adequate, such as monitoring of fluid and electrolyte balance and the avoidance of fluid retention, especially in patients with anuria. Platelet transfusions can be provided in cases of severe thrombocytopenia with a risk of bleeding (Lupusoru 2021, Avsic-Zupanc 2019).

Prevention of the Disease

Fighting rodents in households, in the buildings of forestry operations, and in other areas where human activities are involved is considered the most important step in preventing the disease. Ventilation of rooms, use of rubber gloves and disinfectants, and use of respirators to avoid aspiration of contaminated particles during cleaning of rodent-infested areas are all important measures that can reduce the risk of exposure to the virus. Despite the worldwide spread of pathogenic hantaviruses and the constant efforts invested in vaccine development, there are currently no approved vaccines against these viruses (Saavedra 2021).

I.4.5.4 Conclusion

Hantavirus infection is a rare finding in children, but HFRS must always be considered as a differential diagnosis when facing a patient with AKI and thrombocytopenia. As far as we know, this is the first study regarding HFRS in children from Romania. Although small, our cohort reflects the predominance of this infection in males, the nonspecific clinical onset with gastro-intestinal manifestations, and a self-limiting evolution of the disease, given the proper supportive treatment is assured. The association between fever, renal failure, and thrombocytopenia prompts a serological evaluation, while their absence cannot and should not rule out this diagnosis. The Dobrava serotype is the most common subtype of the hantavirus in the Balkans, and the epidemiological context must always be searched for through a thorough medical history. The awareness regarding this rodent-borne infection should be raised both in medical personnel and for the general public, emphasizing that basic hygiene measures and reasonable precautions will greatly limit the transmission of this virus. For the specific prevention of human infections, mainly in high-risk groups, vaccines are necessary.

I.5 CKD evolution in children

CKD is a condition associated with irreversible kidney damage, which can progress to end-stage renal disease. Globally, CKD is a major public health concern. ESRD is a devastating disorder associated with excessive mortality and cardiovascular morbidity, and specific problems, such as impaired growth and psychosocial adjustment, occur in children, all of which have a devastating effect on life quality (Harambat, 2012). To make a precise and early diagnosis, identify preventable or reversible causes of progression, predict prognosis, and aid in the counseling of children and their families, a better understanding of the epidemiology of CKD in children is essential. Children with CKD stages 1–2 are typically asymptomatic and should be monitored for a decline in renal function. In contrast, children with more advanced stages of CKD experience complications associated with the disease, such as fluid and electrolyte disorders, HTN, anemia, growth impairment, and mineral bone disorder (Suh, 2020).

The most relevant contributions in this topic are presented below.

Articles ISI – principal author

Mocanu A, Bogos RA, Trandafir LM, Cojocaru E, Ioniuc I, Alecsa M, Lupu VV, Miron L, Lazaruc TI, Lupu A, Miron IC, **Starcea IM.** The Overlap of Kidney Failure in Extrapulmonary Sarcoidosis in Children—Case Report and Review of Literature. International Journal of Molecular Sciences. 2023; 24(8):7327, IF= 5.6/2022, **Q1**, https://doi.org/10.3390/ijms24087327

Aldea PL, Rachisan AL, Stanciu BI, Picos A, Picos AM, Delean DI, Stroescu R, **Starcea MI,** Borzan CM, Elec FI. The Perspectives of Biomarkers in Predicting the Survival of the Renal Graft. Frontiers in pediatrics (2022), 10, 869628, IF= 2.6/2022, **Q2**, (Author with equal contribution with first author), https://www.frontiersin.org/articles/10.3389/fped.2022.869628/full

Muntean C, **Starcea IM**, Banescu C. Diabetic kidney disease in pediatric patients: A current review. World journal of diabetes, (2022), 13(8), 587–599, IF= 4.2/2022, **Q2**, (Author with equal contribution with first author), https://www.wjgnet.com/1948-9358/full/v13/i8/587.html

Starcea, M., Gavrilovici, C., Munteanu, M., Lupu, VV., Cojocaru, E., Miron, I Miron, L., A case report of pediatric calciphylaxis-a rare and potentially fatal under diagnosed condition, MEDICINE, 2018, 97 (27), (e11300), IF= 1.870/2018, **Q3**, (Autor principal), https://journals.lww.com/md-journal/Fulltext/2018/07060/A_case_report_of_pediatric_calciphylaxis_a_rare.25.aspx

Article BDI – principal author

Stârcea I.M., Ivanov A., Mocanu A., Lupu V.V., Subotnicu M., Munteanu M., Ignat A., Miron I., Oral manifestation of renal ostheodistrophy in children, Romanian Journal of Oral Rehabilitation, Vol.10, No. 1, January- March 2018, pp. 41-45, (Autor principal), https://www.rjor.ro/oral-manifestation-of-renal-ostheodistrophy-in-children/

Aim

In the following I will go into detail about specific CKD factors in the discussion that have a significant impact on how the disease progresses and how the affected children's quality of life is. Initially, I will illuminate an immune-related pathology that infrequently correlates with severe renal impairment—extrapulmonary sarcoidosis. This ailment itself exhibits a low incidence among children, and within the realm of extrapulmonary manifestations, renal involvement is observed in only approximately 1% of cases. Subsequently, I will expound upon the realm of renal transplantation and its assessment using biomarkers to gauge survival rates. The escalating presence of diabetes in pediatric pathologies will also be scrutinized, as it can potentially become intricately intertwined with profound renal deterioration. Our focus on this juncture has been emphasized through an extensive review published on this subject. Finally, as a conclusive point in this section, I will elucidate two cases with severe complication arising from renal osteodystrophy.

I.5.1. The Overlap of Kidney Failure in Extrapulmonary Sarcoidosis in Children

I.5.1.1 Material and methods

Sarcoidosis is a systemic granulomatous disorder characterized by the accumulation of T lymphocytes, mononuclear phagocytes, and noncaseating granulomas in almost all affected tissues and organs. The clinical phenotypes vary from single-organ, sometimes self-limited, asymptomatic disease to multi-organ involvement with high-risk manifestations. The types of pediatric sarcoidosis are classified by age into two distinct forms: early onset sarcoidosis (triad: uveitis, arthritis, and rash, mainly caused by NOD2 mutation) and pediatric-onset adult-type sarcoidosis—preferentially involving the lung and mediastinum (Semenzato, 2005). Kidney involvement in pediatric-onset adult-type sarcoidosis is rare, and the incidence and prevalence of kidney involvement in sarcoidosis are still uncertain (Semenzato, 2005). The kidney can be affected by the presence of histologically proven granulomas but also by calcium metabolism alteration. For example, in adults, a cohort including more than 1200 patients with pulmonary sarcoidosis found that kidney manifestations were present in 12 percent of cases (Lhote, 2021). In 116 cases of pediatric sarcoidosis, renal involvement was found in only 3 patients (Gedalia, 2016, Hoffmann, 2004, Nathan, 2015).

I.5.1.2 Results

We illustrate the case of a 10-year-old boy who presented for weight loss (4 kg in 12 months), fatigue, and feeling sick with an insidious onset in the last year. His past medical history includes multiple respiratory infections during early childhood and non-specific enterocolitis one year before the current presentation. On this latter occasion, hypercalcemia, as well as elevated serum urea and creatinine levels, were detected but were considered secondary to dehydration, although they did not improve with adequate hydration. Hepatic cytolysis was also constantly present in the last year. Clinical examination revealed massive hepatosplenomegaly, pallor, and oliguria, while biologically, elevated serum creatinine was noted, corresponding to an eGFR of 25 mL/min/1.73 m^2 (Schwartz's pediatric equation). A follow-up evaluation revealed pancytopenia with a normal bone marrow assessment and no immunophenotyping abnormalities. Therefore, we concluded that the pancytopenia was in the liver damage. A negative carcinoembryonic antigen ruled out neoplastic dis- ease. Moderate hepatic

cytolysis and cholestasis were observed, with normal coagulation parameters. Hypercalcemia, low plasma parathyroid hormone levels, and metabolic acidosis were present, while urinalysis revealed hematuria, proteinuria, leukocyturia without hypercalciuria, and a negative urine culture. All of the differential diagnoses made upon admission to our department are summarized in Fig. 1.44(a) and 1.44(b).

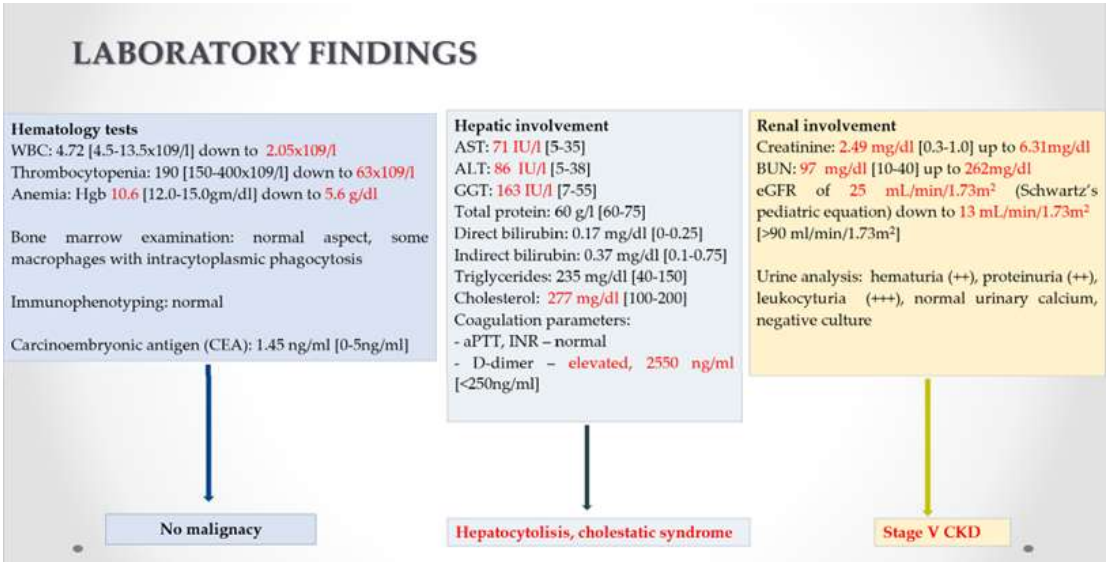

***Fig. 1.44(a)**. Differential diagnosis at presentation.*

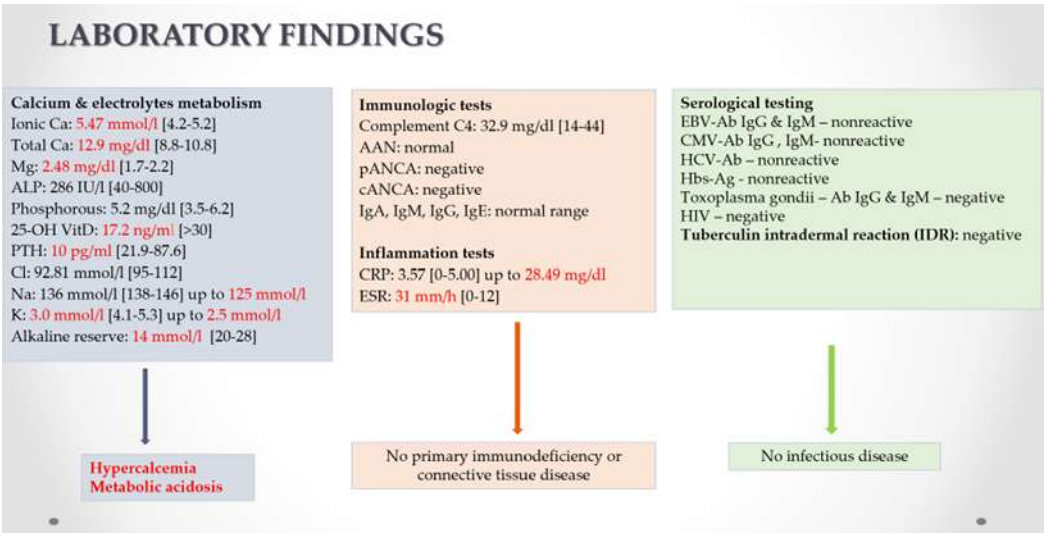

***Fig. 1.44(b).** Differential diagnosis at presentation.*

Renal function deteriorated rapidly to a creatinine clearance of 10 mL/min/1.73 m2, requiring hemodialysis on day 5 after admission. A history of drug ingestion that could cause acute interstitial nephritis was negative. Serologic tests for Epstein–Barr virus, cytomegalovirus, hepatitis C/B, human immunodeficiency virus, Toxoplasma gondii, and tuberculin skin reaction were negative. In the absence of specific immunological findings, a marked inflammatory syndrome or antibodies such as p-ANCA, c-ANCA or antinuclear antibodies, primary immunodeficiency, a connective tissue disease or vasculitis were

excluded. Renal ultrasound evaluation was highly suggestive of nephrocalcinosis. After this preliminary evaluation, the diagnosis of advanced renal disease was made; there- fore, the patient started chronic hemodialysis. Thoracic–abdominal computed tomography confirmed renal medullary calcifications, hepatosplenomegaly, hyperdense splenorenal and splenogastric masses as indicators of portal HTN (Fig. 1.45 and 1.46).

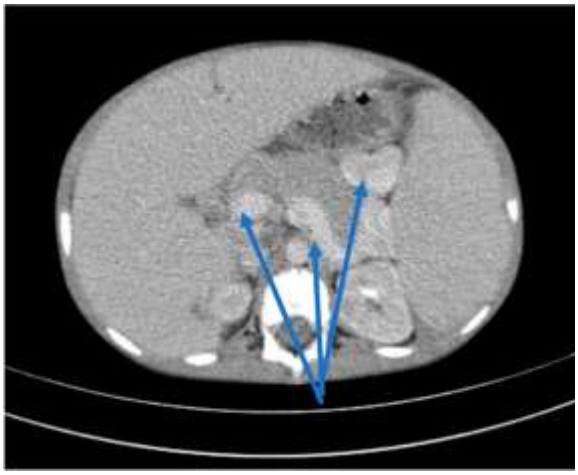

Fig. 1.45 *Axial CT scans, bilateral medullary nephrocalcinosis (blue arrow)*

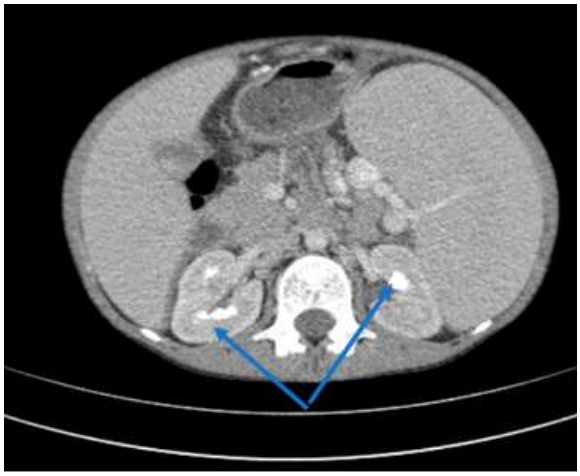

Fig. 1.46 *Axial CT scans, portal hypertension and bilateral nephrocalcinosis (blue arrow)*

In this context, we performed a hepatic biopsy that described chronic giant cell granulomatous hepatitis, highly evocative for sarcoidosis (Fig. 1.47a, b and 1.48a, b).

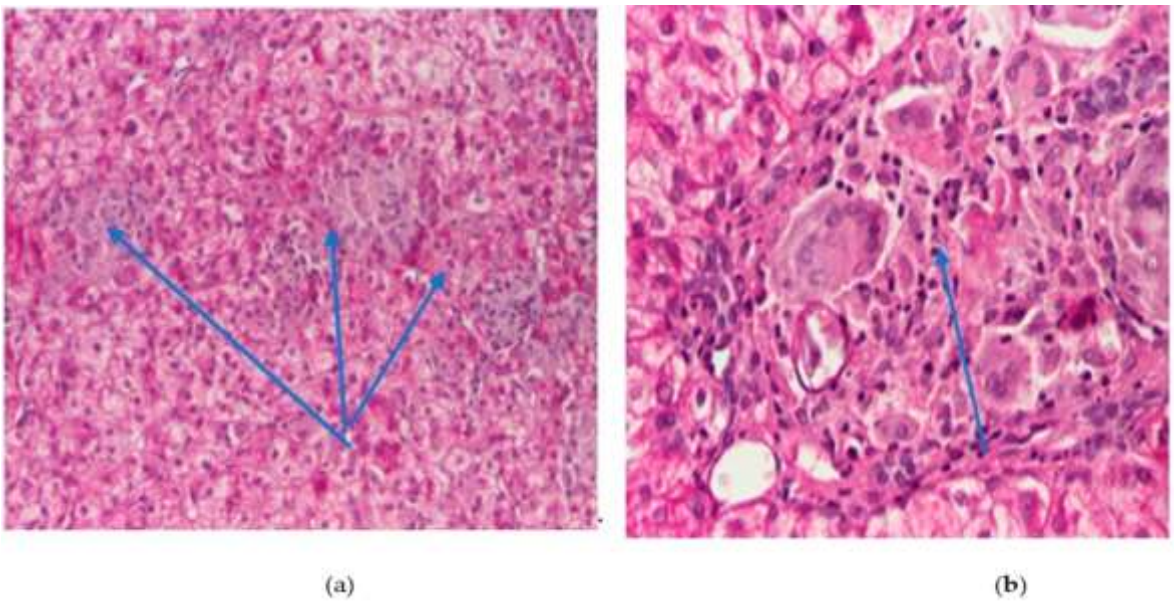

Fig. 1.47 (a)*: PAS coloration ×100;* ***(b):*** *PAS coloration ×200. Liver tissue showing chronic giant cell granulomatous hepatitis (blue arrows) (personal collection, St. Mary Emergency Children's Hospital, Iasi).*

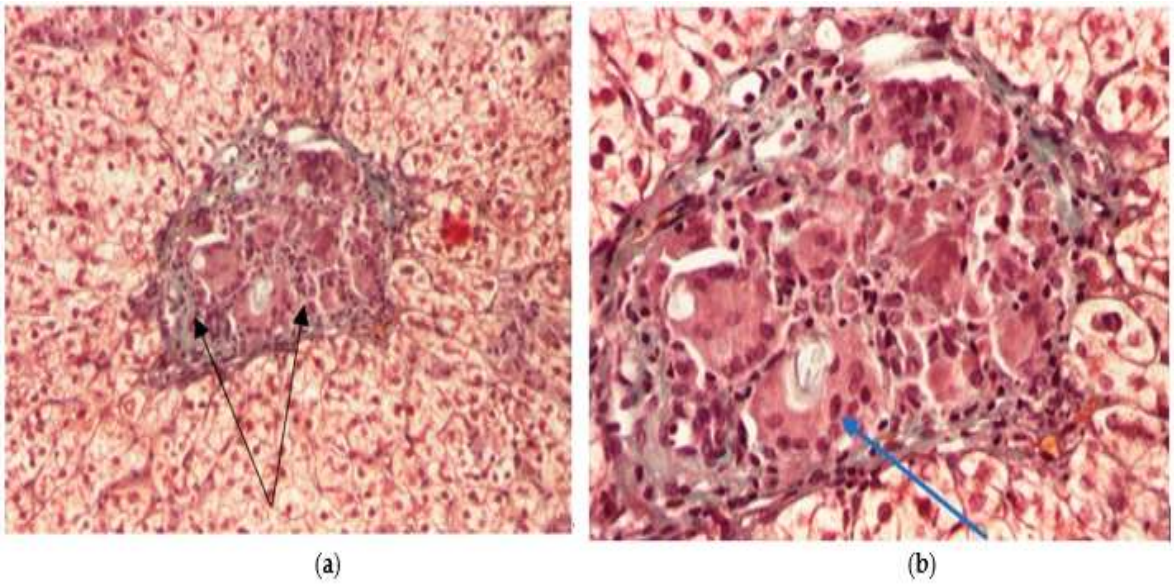

Fig. 1.48 (a) *Szekely trichrome staining ×100,* ***(b)*** *Szekely trichrome staining ×200. Liver biopsy: tight, well-formed epithelioid granuloma of sarcoidosis, not directed at the bile duct. There is a cuff of lymphocytes (black arrows) and Langhans giant cells are characteristic of sarcoidosis (personal collection, St. Mary Emergency Children's Hospital, Iasi).*

To support this diagnosis, serum amyloid A and serum ACE were measured, revealing high concentrations. Peripheral band opacities resulting from calcium deposits on the Bowman's subepithelial layer were also detected, as band keratopathy is a sarcoidosis-associated entity.

Considering the renal, hepatic, and ophthalmic involvement in our patient, the diagnosis of extrapulmonary sarcoidosis was made. Our therapeutic approach was initially supportive, including the correction of hydro– electrolytic and AB imbalances, blood transfusion, and hemodialysis.

Hepatic and portal involvement required the administration of ursodeoxycholic acid, beta-blockers, and ornithine. Specific therapy with prednisolone daily (1 mg/kg/day) was initiated, with positive results after 3 months of treatment, as presented in Table 1.30

However, because of corticoid-related side effects (secondary Cushing syndrome), we decided to decrease the dose of prednisolone up to the maintenance dose of 0.25 mg/kg/day. Even though a clear histopathological diagnosis was made through hepatic punction, and renal involvement was almost certainly a consequence of sarcoidosis, this evolution prompted us to perform a renal biopsy.

This showed non-granulomatous interstitial nephritis, nephrolithiasis, and interstitial fibrosis, as shown in Fig. 1.49–1.51 These images show no immune deposits in immunofluorescence, and no glomerulonephritis aspects, such as crescents or extent of mesangial proliferation.

Table 1.30 *Clinical, biological, and histopathological parameters at onset and 3 months after prednisolone*

	Onset	**After 3 Months**
General symptoms	Fatigue, HSM	Cushing syndrome, no HSM
Laboratory		
TGP	71 U/L	34 U/L
TGO	86 U/L	25 U/L
Alkaline phosphatase (ALP)	286 U/L	213 U/L
GGT	163 U/L	54 U/L
CRP	28.49 mg/dl	4 mg/dl
ESR	61 mm/1h	10 mm/1h
ACE	105 U/L	20 U/L
Calcium	12.9 mg/dl	9.8 mg/dl
Nephrological		
Serum creatinine	6.31 mg/dl	1.56 mg/dl
Egfr (Schwart's pediatric equation)	13 ml/min/1.73 m^2 before dialysis initation	49.2 ml/min/1.73 m^2 dialysis discontinuation
Hematuria	+	+
Proteinuria/24h	848 mg/day	627 mg/day
Leukocyturia	+	+
Urinary Calcium/creatinine ratio	0.7	0.21
Urinary 24h calcium	5.19 mg/kg/day	2.9 mg/kg/day
B2M	437 mcg/L	325 mcg/L
Hemodialysis	3 times/week	Dialysis discontinuation
Hepatic histology	Granulomatous aspect	Not repeated
Ophtalmology	Band keropathy	Not repeated

HSM = hepatosplenomegaly; HD = hemodialysis; TGP = transaminase glutamico piruvica; TGO = transaminase glutâmico oxalacética; GGT = gamma-glutamyl transferase; CRP = C-reactive protein; ESR = erythrocytes sedimentation rate; ACE = angiotensin-converting enzyme; eGFR = estimated glomerular filtration rate; B2M = urinary beta 2 microglobulin.

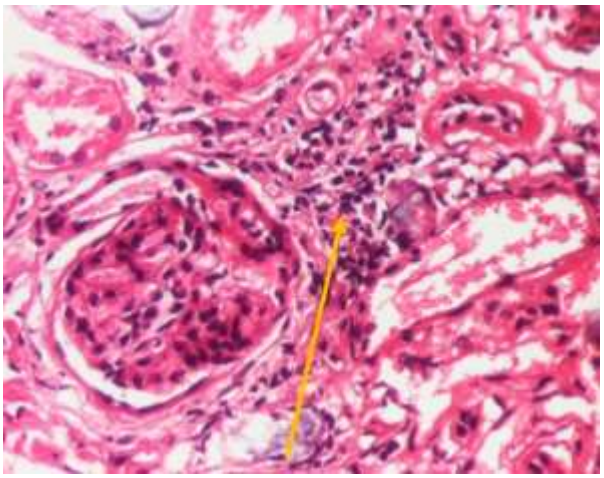

Fig. 1.49 *Hematoxylin-eosin staining ×200; renal tissue showing interstitial inflammation (yellow arrow) (personal collection, St. Mary Emergency Children's Hospital, Iasi).*

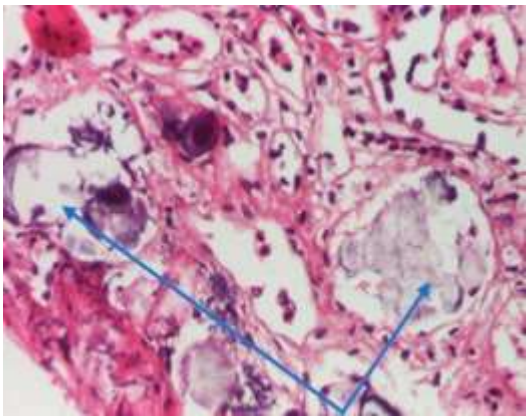

Fig. 1.50 *Hematoxylin-eosin staining ×200; renal tissue showing calcifications (blue arrows) (personal collection, St. Mary Emergency Children's Hospital, Iasi).*

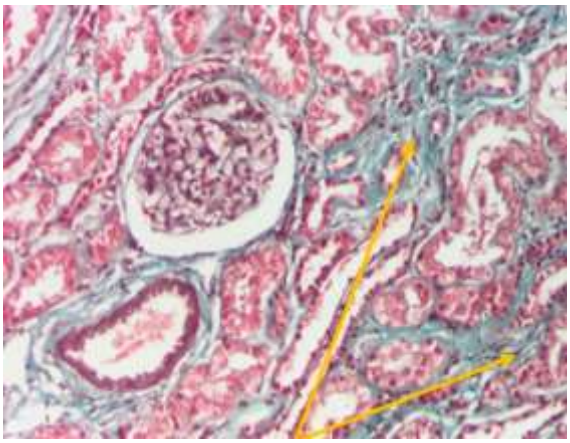

Fig. 1.51 *Szekely trichrome staining ×100; renal tissue showing interstitial fibrosis (yellow arrow) (personal collection, St. Mary Emergency Children's Hospital, Iasi).*

Disease activity can be followed by ACE serum levels. We note an improvement of this parameter 3 months after cortisone therapy as well as an overall improvement of renal function, with dialysis discontinuation and hepatosplenomegaly diminution (Fig. 1.52).

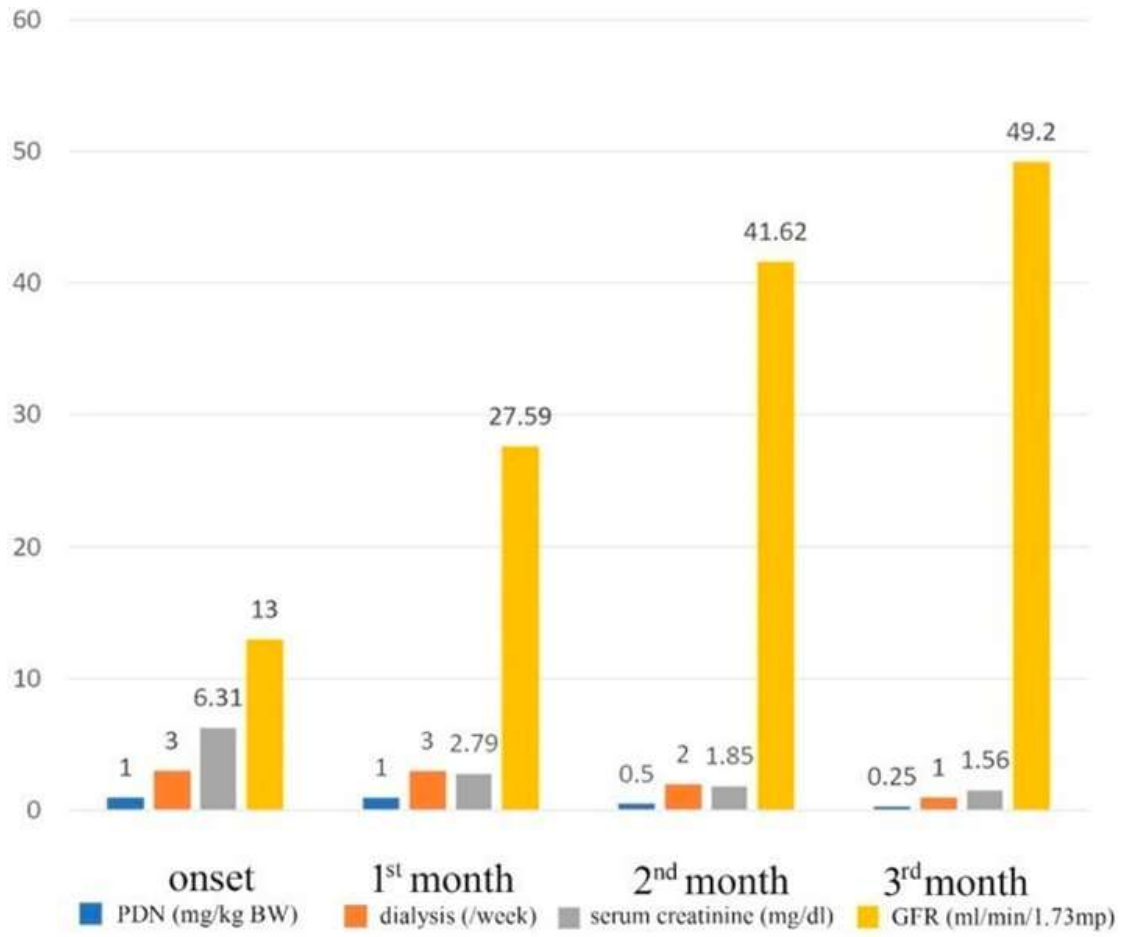

Fig. 1.52 *Characteristics of our patient at presentation, 1, 2 and 3 months after therapy initiation.*

Our evaluation concluded with the diagnosis of extrapulmonary pediatric-onset adult-type sarcoidosis with nephrocalcinosis, nephrolithiasis, non-granulomatous nephritis, granulomatous hepatitis, portal HTN, hepatic insufficiency, splenic infarctions, and band keratopathy.

I.5.1.3 Discussion

Sarcoidosis is a disease characterized by the formation of nodules of inflammatory cells or noncaseating granulomas in any part of the body—most commonly in the lungs and lymph nodes. However, it can also affect the eyes, skin, heart, kidneys, central nervous system, or sense organs. Sarcoidosis, or Besnier-Boeck-Schaumann disease, was first identified by the English doctor Johnathan Hutchinson in 1877, and although more than a hundred years have passed since that first description, the disease still remains an enigma (Kashyap, 2022) The incidence of sarcoidosis in adults appears to be biphasic (Gedalia, 2016). Historically, it was thought to affect young adults between 30 and 50 years, but recent studies have reported that more than half of cases are patients over 55 years of age (Gedalia, 2016, Levin, 2013). About 25% of people affected by the disease develop a chronic and progressive disease, which contributes to the increasing disease burden on health systems (Gerke, 2017, Spagnolo 2018).

Pediatric Sarcoidosis—Epidemiology

Pediatric sarcoidosis is extremely rare, with only three reported cohorts: Danish (Caucasian), French (Afro-Caribbean), and Louisiana (Afro-American) patients. Most patients were aged 11–13 years. The disease seemed severe in children, involving multiple organs, and was often persistent in adulthood (Nathan, 2022). The diagnosis of sarcoidosis is relatively uncommon in children, and the manifestations of the disease may be different in children compared to adults (Chiu, 2019). Sarcoidosis is 3–4 times more common and more aggressive in black than in white patients (Lee, 2022). Furthermore, the lifetime risk of developing sarcoidosis is higher in African Americans (2.4%) than in whites (0.8%) (Heinle, 2014), although the true incidence and prevalence are unknown due to the limited number of reported cases in children. A recent study among Danish patients estimated an incidence of approximately 0.29 per 100,000 person-years in children under 15 years of age. The incidence of pediatric sarcoidosis ranged from 0.06 per 100,000 person-years for children under 5 years of age to 1.02 per 100,000 person-years for children aged 14 to 15 years (Rose, 2021). Most pediatric cases have been reported in children between 13 and 15 years of age. At the onset, our patient had an age close to the maximum incidence of the disease in children.

Sarcoidosis—Etiopathology

Sarcoid granulomas represent an intensely interconnected network of immune cells, including macrophages, dendritic cells, T helper lymphocytes, T regulatory cells, and their mediators. After years of investigations and advances in medical science, the immunopathogenesis of sarcoidosis remains evasive. One or multiple antigens may trigger an exaggerated cell-mediated immune response resulting in granulomatous inflammation. These antigens, possible etiologic agents, vary from occupational or environmental factors to infectious agents, and, of course, genetic contribution may play an important role (Thomas, 1987, Agostini, 2000, Hunninghake, 1984). Infectious agents, such as

lymphotropic viruses (HHV6, HHV8, HIV, HTLV1, and cytomegalovirus), have been documented in patients with sarcoidosis but apparently represent generalized B cell activation rather than being a sign of an etiology (Chen, 2015). Genetic contribution in sarcoidosis was suggested due to the occasional occurrence of sarcoidosis in more than one member of a family (Fritz, 2021). The major histocompatibility complex antigens were most closely linked with genetic susceptibility in sarcoidosis (Chen, 2011). Drug-induced sarcoidosis (antiretroviral therapy, TNF-α antagonists, interferon therapy, and immune checkpoint inhibitors) can only be speculated because of the surprising clinical and histological similarity between the two entities in terms of immunopathogenesis (Chopra, 2018).

Sarcoidosis—Laboratory Diagnosis

Sarcoidosis is diagnosed based on clinical and imaging manifestations as well as the histopathological detection of non-caseating granulomas at the level of the affected organs after excluding other diseases. No laboratory marker can be conclusive for the diagnosis of sarcoidosis, although serum ACE is among the most commonly used diagnostic biomarkers for sarcoidosis; however, the test is nonspecific and lacks sensitivity (Alsarhan, 2020). Regarding sarcoidosis, vitamin D and its metabolism are noteworthy due to their crucial involvement in immune system regulation and granulomatous inflammation.

The expression of 1-α-hydroxylase is present in numerous tissues, but only the kidneys, activated macrophages, and placenta have the ability to affect plasma 1,25(OH)2D3 levels through hydroxylation (Gwadera, 2019). Hypercalciuria, hypercalcemia, and elevated levels of 1,25- dihydroxy vitamin D (1,25(OH)2D) may also occur in patients with sarcoidosis due to the overproduction of 25-hydroxy vitamin D-1 α-hydroxylase (Shetty, 2008, Eurelings, 2019). Recent studies involving adult patients have suggested that serum levels of soluble interleukin-2 receptor (sIL-2r) represent a superior and more sensitive biomarker than serum ACE levels in supporting the diagnosis of systemic sarcoidosis (Gundlach, 2016, Thi Hong Nguyen, 2017).

It seems that the level of sIL-2r correlates with the level of disease activity and may indicate multisystem involvement (Chauveau, 2020). Patients diagnosed with sarcoidosis should be evaluated in terms of kidney function.

Renal biopsy remains the gold standard for confirming renal sarcoidosis, although histological lesions are not specific for sarcoidosis, necessitating the exclusion of infection and drug hypersensitivity, which are more common causes of interstitial nephritis (Al-Kofahi, 2016).

Pediatric Sarcoidosis—Renal Involvement

Kidney lesions associated with sarcoidosis are represented by specific histological changes in the disease or by abnormal calcium metabolism, nephrolithiasis, and nephrocalcinosis. The renal manifestations in sarcoidosis are represented by hypercalcemia and hypercalciuria, nephrolithiasis and nephrocalcinosis, granulomatous or non-granulomatous interstitial nephritis, glomerular and tubular disease, and ureteral obstruction (Rosé, 2005). A variety of glomerular lesions, including membranous nephropathy, focal segmental sclerosis, mesangioproliferative glomerulonephritis, IgA nephropathy, or crescentic glomerulonephritis, are described as glomerular damage in sarcoidosis, without being able to distinguish it from the primary form of these entities. Tubular dysfunctions can affect the isolated proximal or distal renal tubule, but also in the context of tubulopathy

Fanconi syndrome. Polyuria is a common clinical feature, mostly due to hypercalcemia (Correia, 2020). Our patient had the same types of manifestations at the onset. Initially, we considered our case to be end-stage kidney disease (ESRD) because he had a chronic evolution over one year.

Pediatric Extrapulmonary Sarcoidosis—treatment and prognosis

Depending on the involvement, extrapulmonary sarcoidosis may benefit from local treatment, escalation of systemic treatment, or multimodal interventions (Löffler, 2014). The majority of studies regarding the treatment of symptomatic sarcoidosis have focused on pulmonary disease (Papanikolaou, 2022).

The goals of treatment in sarcoidosis are to prevent permanent end-organ dysfunction, reduce mortality, and preserve the quality of life. Corticosteroids remain the first-line treatment, although they have significant cumulative side effects. Therapies such as alkylating agents, immunosuppressive medication, calcineurin inhibitors, and TNF-α inhibitors can be used in refractory or relapsing diseases or when corticosteroids cause unacceptable toxicity. Methotrexate and infliximab have demonstrated significant efficacy and an acceptable safety profile in cardiac sarcoidosis, for example, (Terasaki, 2019).

CKD is a contraindication for treatment with methotrexate. Thiopurine S-methyltransferase (TPMT) deficiency is a contraindication for the use of azathioprine (Srivastava, 2012). Renal sarcoidosis after kidney transplantation is rare, usually follows a mild clinical course and is responsive to increased immunosuppression. It has been recently reported that it is safe to perform renal transplantation in sarcoidosis with close clinical and histological monitoring (Drent, 2022).

For children, the outcome is variable for sarcoidosis, ranging from spontaneous remission to end-stage renal disease. Early diagnosis and prompt treatment with corticosteroids can improve prognosis (Calatroni, 2023).

I.5.1.4 Conclusion

Sarcoidosis with extrapulmonary involvement in children is rare, which leads to a delayed diagnosis. In our case, renal sarcoidosis was diagnosed in advanced CKD, with severe GFR impairment at onset, offering unfavorable outcomes.

Renal biopsy is mandatory in this case for a better understanding of the disease course and reassessment of the treatment. Oral or pulses of intravenous corticosteroids are the mainstay of the treatment of sarcoidosis in children. Relapses are frequently observed in the evolution of this pathology, mainly extra thoracic, so even in cases of initial remission, long-term follow-up is required. There are some clinical, radiological, and laboratory factors that determine the prognosis of the disease.

The clinical phenotype of the disease can be presented with self-limited acute sarcoidosis and/or chronic, progressive multisystemic involvement. Laboratory factors are nonspecific and may not always be useful in clinical practice. New biomarkers would be useful for accurate diagnosis. New multicenter prospective studies are needed to shed light on this pathology, especially in children.

I.5.2. The Perspectives of Biomarkers in Predicting the Survival of the Renal Graft

I.5.2.1 Material and methods

Kidney transplantation (KT) is the elective approach in CKD stage V, and it provides a better quality of life compared to extrarenal epuration methods (e.g., hemodialysis) (Irish, 2010). The first year after transplantation is not absolved by complications. Although the surgical techniques are safe and the immunosuppressive protocols are standardized, patients with KT are unique and can develop complications from acute tubular necrosis to delayed graft function (DGF). Therefore, the development of long-term complications after KT is still seen (Matas, 2013). DGF is defined based on the creatinine levels and the need for dialysis after KT (Yarlagadda, 2008).

Among all the definitions, the most used and accepted one is based on the need of minimum one dialysis during the first week after KT (Helfer, 2019). DGF was associated with higher rejection rates and worse in the short-term and long-term results due to miscellaneous factors including donor-related factors (donation after brain death, cold ischemic time, shipping distance, donor age, body mass index, and others), recipient-related factors (preemptive or non-preemptive KT, previous KT, the presence of antibodies, ABO incompatibility, history of diabetes, recipient sex, and so on), and perioperative risk factors. DGF is usually associated with innate immune response because of complement activation and other molecular pathways activated during ischemic injury.

The proposed mechanism suggests the release of inflammatory mediators via endothelial cells upregulating cell adhesion molecules (Redfield, 2015).

I.5.2.2 Results

Currently, the evaluation of the renal graft is based on creatinine levels, the calculation of GFR, and the appearance of proteinuria. Being the gold standard assessment of the kidney function, creatinine and GFR are nonspecific markers, and the reliability is affected by several factors (Waikar, 2009).

Studies have focused on kidney injury molecules such as neutrophil gelatinase-related lipoprotein (NGAL), beta 2 microglobulin (β2MG), kidney injury molecule 1 (KIM1), and others, as the potential markers for the prognosis of graft durability (Eikmans, 2019) (Table 1.31)

Table 1.31 *Biomarkers in kidney transplantation.*

Biomarker	Abbreviations	Type of sample
Creatinine	-	Serum/urine
Cystatin C	CYS-C	Serum/urine
Neutrophil gelatinase-related lipoprotein	NGAL	Serum/urine
Beta 2 microglobulin	B2MG	Serum/urine

Kidney injury molecule 1	KIM1	Urine
Uromodulin	UMOD	Serum
Clusterin	-	Serum/urine
Chitinase-3-like protein 1	YKL-40	Serum/urine
Liver-type fatty acid-binding protein	L-FABP	Urine

I.5.2.3 Discussion

Novel biomarkers of kidney injury

Neutrophil Gelatinase-Associated Lipocalin (NGAL) - also known as siderocalin, lipocalin 2 oroncogene 24p (Teo, 2017), it is a 25 kDa protein associated with human neutrophil gelatinase being a part of the lipocalins family (Beker, 2018).

NGAL has a bacteriostatic role: it binds to bacterial iron siderophores, inhibiting the bacterial iron uptake. Besides its bacteriostatic effect, NGAL exerts an antiapoptotic effect and stimulates renal tubular cell proliferation, suggesting a potential protective effect in AKI.

NGAL was found in many organs, such as kidney, lung, large intestine, uterus, prostate, salivary gland, trachea, and stomach (Teo, 2017). Its biodisponibility augments with age and levels are higher in women compared to men (Beker, 2018).

NGAL is a urinary marker produced especially by neutrophils, loop of Henle, and collecting ducts, but can also be detected in the epithelium of the proximal convoluted tubule (due to megalin-mediated malabsorption of NGAL). NGAL has been the most widely investigated of the available AKI biomarkers (An, 2013).

Scientific proofs showed that plasma and urine NGAL are present approximately 2 days before the AKI develops, therefore being an early diagnostic biomarker in kidney injury and a useful tool for the risk stratification in CKD (Shang, 2017).

Moreover, urinary NGAL measured at the onset of AKI can precisely predict persistent AKI, new-start CKD, and CKD progression in patients with AKI; therefore, it is a valuable instrument for the better assessment of AKI risk stratification (Lumlertgul, 2020, Törnblom, 2020). Multiple studies showed the use of NGAL in the diagnosis of DGF (Table 1.32).

Hall et al. (Hall, 2011) noted that serum NGAL was ineffective to distinguish injury in DGF patients and those with normal graft function. Bataille et al. (Bataille, 2011) studied the accuracy of NGAL in the prediction of DGF with a sensitivity of 93.3% and a specificity of 88.5%, being more predictive than the plasma creatinine.

A more rapid decrease in serum NGAL compared to creatinine was observed in the first days post-transplant. NGAL has also been shown to be a useful and superior marker to creatinine in monitoring nephrotoxicity of calcineurin inhibitors (tacrolimus) in the post-transplant period (Cantaluppi, 2015).

Table 1.32 *Comparison of studies on serum NGAL for the diagnosis of DGF after kidney transplantation.*

Group/year	Study characteristics	Time of measurement after KT	Remarks
Hall, 2011	78 KT 26 DGF	0-24-48h	NGAL was not different between KT with DGF and others
Bataille, 2011	41 KT 15 DGF	24h	NGAL level early and precisely predicted DGF after KT
Lee, 2012	59 KT 14 DGF	24h	NGAL is higher in DGF patients at any time after KT
Buemi, 2014	97 KT 20 DGF	6-24-48h	NGAL levels were notably lower in LDs than in DDs. No DGF was found among LD kidney recipients, but DGF was seen in 25% of patients in the DD group

** LD, living donors; DD, deceased donors*

Beta 2 Microglobulin (β2MG) is a low molecular weight protein (11, 8 kDa) (Parikh, 2015) consisting of 100 amino acid proteins. β2MG is produced by all cells expressing MHC-1 antigens, but lymphocytes and tumor cells are presumed to be major biosynthetic sites (Wang, 2020).

During normal cell turnover, β2MG is released in blood, synovial, cerebrospinal, amniotic, and seminal fluid, as well as in aqueous humor, colostrum, and saliva (Parikh, 2015). Even though low levels of β2MG are found in urine and serum of normal subjects, these levels might increase in the context of kidney injury due to decreased reabsorbance by the damaged tubules (Srisawat, 2020).

Serum β2MG level may be used as a prognostic biomarker of renal decline in patients with type 2 diabetes (Colombo, 2019), whereas β2MG mRNA expression in cells of the urinary sediment is higher in patients with type 1 diabetes with diabetic kidney disease in comparison with healthy subjects, demonstrating a tubulointerstitial damage promoted by albumin (Monteiro, 2016).

Kidney Injury Molecule 1 (KIM1) is a transmembrane protein, which consists of two portions – an extracellular portion and a cytoplasmic one. The KIM1 gene can be found on chromosome 5p33.3 and contains 14 exons (Song, 2019). Another names for KIM1 are T-cell immunoglobulin mucin receptor 1 (TIM1) or hepatitis A virus cellular receptor 1

(HAVCR1). This biomarker is not expressed only in the kidney, but also in the liver and spleen. Recent studies showed that KIM1 is expressed only in renal injury, so this biomarker can be used for early diagnosis of kidney damage (Yang, 2015). Under conditions that cause AKI (conditions such as ischemia, hypoxia, toxicity, tubular interstitial diseases, and polycystic kidney disease), urinary and renal KIM1 levels increase depending on the extent of the damage (Song, 2019).

In a study conducted on 140 renal transplanted patients, 37 of whom had DGF, Zhu et al. (Zhu, 2017) demonstrated that urinary KIM1 levels among DGF patients were higher than among IGF (immediate graft function) patients at 0 h post-transplantation, as well as on the first day post-transplantation, indicating that recipients with increased urinary KIM1 levels after the first post-transplant day have a 23.5% higher risk of developing DGF and a 27.3% higher risk of long-term graft dysfunction (Zhu, 2021).

Yadav et al. (Yadav, 2015) concluded that urinary KIM1 is higher in DGF patients compared with IGF patients at 6–12–18–24 and 48 h after transplantation, having the 100% specificity and 89.9% sensitivity to predict DGF in the first 18 h after KT. Tavernier et al. (Tavernier, 2017) in a large study with 244 kidney graft recipients determined the urinary KIM1 10 days after transplantation and found a significant correlation with time of cold ischemia and DGF and also the serum creatinine.

Uromodulin (UMOD), also known as Tamm–Horsfall protein (THP), is exclusively produced by renal epithelial cells. Levels of UMOD in the urine and in the blood are the valuable biomarkers to assses the tubular mass and renal function (Bokhove, 2016, Weiss, 2010). Uromodulin also plays the role in kidney insult (acute and chronic) and innate immunity (by binding immunoglobulins) (Devuyst, 2017).

In humans, uromodulin is encoded by the UMOD gene, which is located on chromosome 16. Some mutations in UMOD can cause autosomal dominant tubulointerstitial kidney disease (ADTKD), leading to the acummulation of mutant uromodulin in the endoplasmic reticulum of tubular cells, causing decresed levels of urinary uromodulin and tubulointerstitial injury. Mutations in UMOD gene can be also associated with the autosomal dominant renal disorder medullary cystic kidney disease-2 (MCKD2). Urinary uromodulin was associated with rapid decline of eGFR, being an independent predictor of rapid kidney function loss (Steubl, 2019).

Clusterin, also named apolipoprotein J, is an omnipresent glycoprotein present in three isoforms, all of them differing in their functions. Discovered almost four decades ago in ram rete testis fluid with the ability to cause clustering of red blood cells – hence the name, this multifunctional protein as of today is still an enigma (Fritz, 1983).

In humans, clusterin is coded by a gene localized on the chromosome 8 (Dietzsch, 1982). Due to its molecular size, the urinary clusterin level is specific for kidney (Dieterle, 2010). One study – regarding different biomarker levels in drug-induced kidney insult, suggests that clusterin levels can be consistent with the severity grades of proximal tubular injury (Musiał 2020). Moreover, clusterin appears to be an encouraging biomarker in the management of diabetic kidney disease as the urinary levels of clusterin are associated with the severity of diabetic nephropathy in patients with diabetes (Zeng, 2017).

YKL-40, also known as chitinase-3-like protein 1, is a glycoprotein encoded by the CHI3L1 gene located on chromosome 1. YKL-40 is expressed and secreted by different cell types with high cellular activity (Schultz, 2010, Kazakova, 2009). Studies show that YKL-

40 modulates renal repair mechanisms after ischemic kidney injury in mice and showed to be a useful marker of kidney damage in kidney transplantation in man (Schmidt, 2013).

In patients with NS, serum YKL-40 levels are associated with endothelial dysfunction and increased arterial stiffness and may predict proteinuria levels for these patients (Kocyigit, 2014). In hemodialysis patients, YKL-40 levels significantly improved risk prediction for all-cause and cardiovascular mortality compared to other cytokines thus better reflecting inflammatory activity (Lorenz, 2018). YKL-40 is a protein that can be measured in urine on the first day of clinically manifested AKI and combining with other biomarkers – such as NGAL – could refine AKI prognosis and better assess renal injury repair (Hall, 2014).

Liver-Type Fatty Acid-Binding Protein (L-FABP) is a 14 kDa protein, which was at first identified in the hepatocytes and afterward was expressed in the human renal proximal tubule epithelium (McMahon, 2013, Ferguson, 2010). Numerous studies have demonstrated that L-FABP is a useful biomarker for both CKD and AKI. Furthermore, Nakamura et al. found that urinary L-FABP levels are elevated in patients with septic shock and are not correlated with the requirement for extrarenal epuration (Ferguson, 2010).

In patiens with kidney transplant (KT), Yamamoto et al. (Yamamoto, 2007) concluded that urinary L-FABP levels were higher in the immediate period after KT. Przybylowski et al. (Przybylowski, 2011) indicated that urinary L-FABP could be a possible early marker for damaged kidney function in patients with KT. Nevertheless, Yang et al. (Yang, 2014) showed that urinary L-FABP could be useful for predicting poor graft outcome for ≤2 years; they showed that 0-h urinary L-FABP level was independently associated with DGF in patients with KT after 2 years. Their data indicate that urinary L-FABP might be useful for predicting adverse long-term graft outcomes.

Donor-derived cell-free DNA (ddcf-DNA) is typically encountered in the body fluids of post-transplant individuals and refers to cell-free DNA that arises after apoptosis or necrosis of the allograft tissue. Therefore, ddcf-DNA can be used as a prospective biomarker to evaluate the status of donor tissues. In patients with DGF and acute rejection, ddcf-DNA levels have been shown to drop and follow a comparable pattern in the early postoperative stages. However, when plasma ddcf-DNA levels in patients with DGF remain >1%, it might indicate acute rejection in renal transplanted patients. . In conclusion, ddcf-DNA acts as a marker of allograft injury, but it is not specific to any form of rejection. Increased levels could occur in allograft-limited conditions, including rejection, but can also be raised in systemic conditions, such as malignancy and infection (Yang, 2021, Jaikaransingh, 2021).

I.5.2.4 Conclusion

These potential DFG biomarkers need supplementary validation and require more understanding. Although the roles of described molecules have been established as the markers of renal injury, there is limited application to translate benchwork to clinical use. We consider that there is no ideal renal injury biomarker, and only the combination of a panel containing different biomarkers can elucidate the DGF mechanism and can predict earlier this event to maximize the therapeutical strategies.

I.5.3 Diabetic kidney disease in pediatric patients: A current review

I.5.3.1 Material and methods

Diabetes mellitus (DM), a chronic metabolic condition, is characterized by complete or insufficient insulin production. The main form of DM in childhood and adolescence is type 1 DM (T1DM) compared to type 2 DM (T2DM), which is more frequent in adulthood. Within the last 20 years, DM prevalence increased significantly worldwide. In the last decades, we have also assisted in an ascending trend in the prevalence of T2DM in childhood and youth because of the outbreak in juvenile obesity prevalence (Zhao, 2017). T1DM and T2DM have similar symptoms upon diagnosis, and both include polyuria, polydipsia and polyphagia. While obesity and insulin resistance signs (acanthosis nigricans and polycystic ovarian syndrome) are typical hallmarks of T2DM, loss of weight may be present in both types of DM (Zhao, 2017).

Both T1DM and T2DM, with lasting inadequate glycemic control, are associated with long-term vascular complications (Stoian, 2014) and a significant increase in mortality, especially in those who develop kidney disease (Afkarian, 2015). While DM represents the main worldwide cause of end-stage kidney disease in adults, this is uncommon during childhood (Stoian, 2014, Afkarian, 2015).

I.5.3.2 Results

Epidemiology of DM in children

From 2002 to 2015 the Centers for Disease Control and Prevention reported a 4.8% increase per year for T1DM and a 1.9% increase per year for T1DM in youths aged < 20 years (Divers, 2020). A very recent study, comprising six areas of the United States from 2001 to 2017, reported an important increase in estimated prevalence for both T1DM and T2DM (T1DM from 1.48 to 2.15 per 1000 youths < 19 years and T2DM from 0.34 to 0.67 per 1000 youths among those aged 10-19 years) (Lawrence, 2021).

Up-to-date research that included a large cohort of Hungarian children and teenagers during the period 2001 to 2016 (covering 16 years), showed that T1DM is still the most common type, and its prevalence is rising, with a significant male predominance (male/female ratio: 1.25).

Also, there is a high prevalence of T2DM, affecting more females every year (female/male ratio: 2.86) (Barkai, 2020). A Danish study showed no increase in T2DM prevalence in children and adolescents (Oester, 2016) while in the United Kingdom a rising incidence and prevalence of T2DM have been observed in youths, especially in some ethnicities (Candler, 2018).

Contributing risk factors to this major increase in incidence are obesity, race, ethnicity, exposure to maternal obesity and diabetes as well as exposure to environmental contaminants (Lawrence, 2021).

There is an increased morbidity and mortality rate, mainly in T1DM and in those with early T2DM onset. DM represents the main cause of ESRD worldwide in adults (Narres, 2016). Diabetic nephropathy affects 20% (1 in 5) of adults with diabetes (Murphy, 2016). Within the pediatric population, a significant increase in the incidence of DKD was also observed, the prevalence rate being three times higher in 2013 compared to 2002 (1.16% to 3.44%) (Li, 2016).

A 4-fold higher risk of kidney failure was found in a large cohort of youth with T2DM vs those with T1DM (Dart, 2012). Also, compared with the control group, those with youth-

onset T2DM had a 16-fold higher risk of a kidney disorder, a 23-fold higher risk of severe renal injury and a 39-fold increased risk of ESRD (Dart, 2012). A multicenter study reported that more than a quarter (28%) of T2DM youth aged under 20 years developed microalbuminuria (Rodriguez, 2006).

Pathophysiology

Chronic hyperglycemia leads to the occurrence of diabetic nephropathy, retinopathy and neuropathy as well as macrovascular complications (cardiovascular disease: Stroke, coronary artery disease, peripheral vascular disease) (Zhao, 2017, Lin, 2018, Uwaezuoke, 2020). DKD recognizes four major pathogenic mechanisms: Glomerular damage, tubular injury, inflammation and oxidative stress (Salem, 2020) (Fig. 1.53).

In DKD patients there are important alterations in tubules as well as in the interstitium. These findings may pave the way, or they may appear concomitant with glomerular changes (Fu, 2019). There is a greater risk for complication occurrence in youths with T2DM vs adults with T1DM and T2DM (Zhao, 2017).

The main microvascular complication of diabetes is represented by DKD and later by diabetic nephropathy, which finally leads to ESRD. In time, with diabetes evolution, clinical and biological changes will be observed (Fig. 1.54).

Children with T1DM may have damaged renal function at the disease onset as acute complications through AKI and renal tubular damage as well as chronic complications by diabetic nephropathy development (Hurs, 2017).

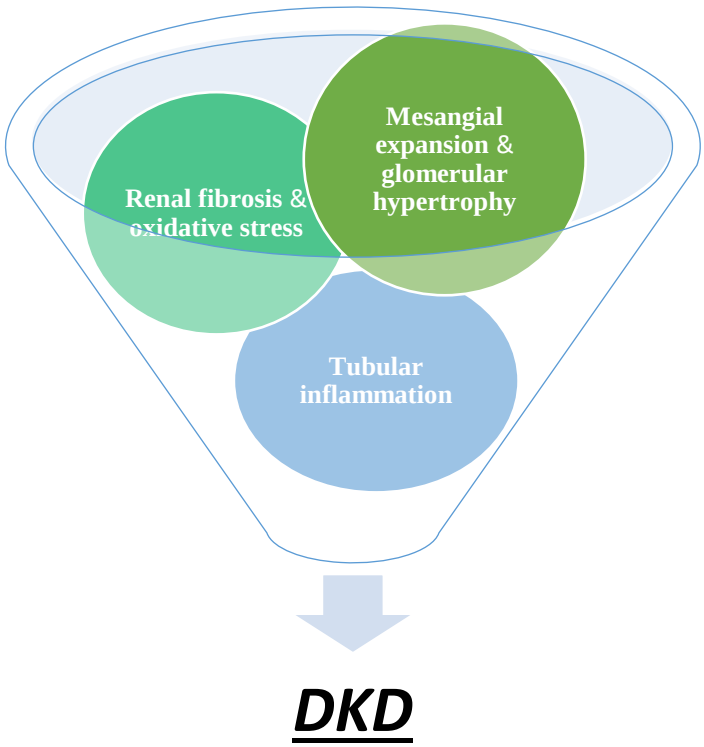

Fig. 1.53 *Pathogenesis in diabetic kidney disease. DKD: Diabetic kidney disease*

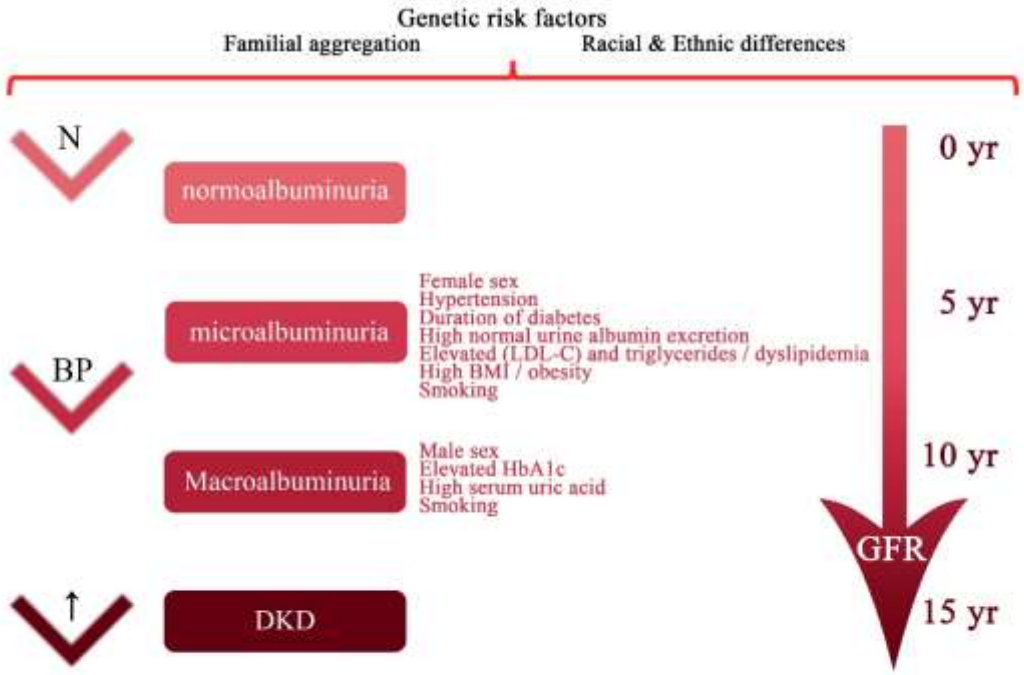

Fig. 1.54 *Changes in diabetic kidney disease: Blood pressure evolution and GFR decline along with albuminuria level. Influence of factors involved in diabetic kidney disease occurrence and progression. N: Normal; DKD: Diabetic kidney disease; BP: Blood pressure; GFR: Glomerular filtration rate; LDL-C: Low-density lipoprotein cholesterol; BMI: Body mass index; HbA1c: Glycated hemoglobin.*

DKD, one of the most important and frequent complications of DM, recognizes a wide spectrum of risk factors, some of which are modifiable. Therefore, DKD occurrence or evolution may be considerably influenced by strict control of these factors that are listed in Table 1.33.

Table 1.33 *Risk factors for diabetic kidney disease development*

Non-modifiable	**Modifiable**
Small/young age at DM onset	Poor glycemic control
Diabetes duration	Glucose variability: Hypo/hyperglycemia
Puberty	Overweight/obesity
Family history of diabetic complications and insulin resistance	Dyslipidemia
Genetic factors	High blood pressure
Race/ethnicity	Microalbuminuria
	Smoking, alcohol
	Intrauterine exposure (maternal diabetes, obesity)
	Low birth weight

I.5.3.3 Discussion

GFR abnormalities

Hyperfiltration, defined as an increase in GFR with more than 2 standard deviations than the mean GFR value, is related to an early increase in renal blood flow and high intraglomerular pressure (Tonneijck, 2017). In the first phases of DKD, hyperfiltration is observed in up to 40% of diabetic patients (Bjornstad, 2018).

In both T1DM and T2DM, hyperfiltration has been linked to GFR loss (Bjornstad, 2015, Ruggenenti, 2012). Hyperfiltration was noticed more frequently in females vs males in both T1DM and T2DM (Bjornstad, 2018, Lovshin, 2018).

The eGFR in children and adolescents with T1DM or T2DM should be screened at diagnosis and then annually (Lopez, 2021).

These ongoing changes help us to assess DKD stages, which are presented in Table 1.34 (Uwaezuoke, 2020, Salem, 2020, Zabeen, 2018). Normal GFR values according to child age are listed in Table 1.35.

Table 1.34 *Diabetic kidney disease stages*

Stage	Estimated period	Characteristics	GFR	BP	Biomarker – albuminuria	Biomarker UACR mg/mmoL
1 = hyperfiltration	From diabetes onset to 5 yr	Glomerular hyperfiltration and hypertrophy. No ultrastructure abnormality. A 20% increase in renal size. ↑Renal plasma flow	N/ increased	N	Normoalbuminuria < 30 mg/g	< 2
2 = silent	From 2 yr after onset	Mild GBM thickening and interstitial expansion	N	N	Normoalbuminuria < 30 mg/g	< 3
3 = incipient	5-10 yr after ibset	More significant changes vs stage 2. Moderate tubular and GBM thickening and variable focal mesangial sclerosis	GFR-N or mild decreased	Incresing BP; +/- hypertension	Microalbuminuria appears Albuminuria 30 – 300 mg/g	2-20
4 = overt	10-15 yr after onset	Marked GBM thickening and variable focal mesangial sclerosis	GFR-decreased < 60 ml/min/1.73 m^2	↑BP	Macroalbuminuria > 200 mg/g	> 20
5 – uremic		Diffuse glomerulosclerosis, ESRD	GFR-marked decreased < 15 ml/min/1.73 m^2	↑BP	Decreasing albuminuria	

UACR: Urinary albumin to creatinine ratio; GBM: Glomerular basement membrane; GFR: Glomerular filtration rate; BP: Blood pressure; ESRD: End-stage renal disease; ↑: Increase; N: Normal.

Table 1.35 *Normal GFR limit at different ages according to KDOQI Guidelines (Hogg, 2003)*

Age	Gender	Normal GFR
1 wk	Males and females	41± 15 ml/min/1.73 m^2
2-8 wk	Males and females	66± 25 ml/min/1.73 m^2
>8 wk	Males and females	96± 22 ml/min/1.73 m^2
2-12 yr	Males and females	133± 27 ml/min/1.73 m^2
13-21 yr	Males	140± 30 ml/min/1.73 m^2
13-21 yr	Females	126± 22 ml/min/1.73 m^2

KDOQI - Kidney Disease Outcomes Quality Initiative; GFR - Glomerular filtration rate; wk – week; yr - years.

Seric and urinary biomarkers for DKD

Common markers for kidney injury are creatinine, albuminuria, cystatin C, neutrophil gelatinase- associated lipocalin and alfa-1-microglobulin in plasma and urine. In a recent study, 11.5% of Romanian children with T1DM had DKD, manifested as transitory microalbuminuria (7.7%) and incipient diabetic nephropathy (3.8%) (Szabo, 2020). In another research study, T1DM patients were found to have microalbuminuria in 30% of cases, representing the most common microvascular complication.

In T1DM children the occurrence of microvascular complications was correlated with metabolic control, higher glycated Hb, albuminuria, systolic blood pressure (SBP), triglycerides and total cholesterol (El-Samahy, 2015). Microvascular as well as macrovascular complications can lead to serious morbidity and mortality.

Nephropathy (which is preceded by microalbuminuria), retinopathy and neuropathy represent diabetic microvascular complications (Stoian, 2014, International Diabetes Federation, 2011). According to the International Society for Pediatric and Adolescent Diabetes guidelines, annual microalbuminuria or urinary protein screening should start from the age of 11 years and after 2 years of diabetes evolution and then annually. It was demonstrated that persistent microalbuminuria predicts the progression to ESRD and is linked with an increased risk of macrovascular complications occurrence (International Diabetes Federation, 2011).

In T1DM pediatric patients, urine microalbumin to creatinine ratio (UACR) monitoring should start at puberty or 10 years of age (whichever is earlier), and when the child has had DM for 5 years this parameter should be checked annually.

In T2DM the UACR should be checked at diagnosis and every year thereafter (Lopez, 2021). In medical practice, the common and still the “gold standard” marker for prediction and detection of diabetic kidney involvement in pediatric diabetes is represented by the microalbuminuria screening (Salem, 2020), even if it has a low specificity and sensitivity to detect early stages of DKD.

Microalbuminuria screening should be done annually by timed overnight or 24-h urine collections (albumin excretion rate) or first-morning UACR (International Diabetes Federation, 2011).

BP in diabetic children

Another important sign of diabetes-related nephropathy is BP measurement. In pediatric T2DM the guidelines recommend BP and UACR evaluation at diagnosis and annually thereafter (Rohani, 2014).

An important and modifiable risk factor for the development of DKD is HTN (Shalaby, 2015). Arterial HTN is an important and frequent risk factor for the appearance of cardiovascular disease in T1DM patients.

High BP triggers the development and progression of microvascular complications, namely nephropathy, and retinopathy. Ambulatory blood pressure measurement is superior to office BP measurements in predicting future cardiovascular events and targeting organ damage (Dost, 2017). I

n their study, Shalaby and Shalaby (Shalaby, 2015) showed an abnormal BP profile for systolic and diastolic BP, with significant loss of nocturnal dipping.

Prophylactic and therapeutic strategies for DKD

The well-known strategies, namely rigorous glycemic control, strict BP control and modulation of obesity, still represent the most important tools to prevent and slow down the progression of diabetic nephropathy/the deterioration of renal function.

These therapies (listed in Table 1.36) proved to be effective mainly by targeting the modifiable risk factors for diabetic nephropathy.

Table 1.36 *Common and new therapeutic strategies in diabetic kidney disease*

Therapy	Drug class	Aim	Mechanism of action	DKD result/effect	Dose adjustment to eGFR (ml/min/1.73 m^2)
Conventional therapies					
Strict glycemic control (Insulin)	-	HbA1c < 7%	(1) Reduces the risk of microalbuminuria; and (2) Reduces progression of microalbuminuria to macroalbuminuria	Delay DKD progression/ risk	GFR = 10–50: Reduce the dose to 75%; GFR < 10: Reduce dose to 50%
Dietary protein/phosphate restriction	-	↓High protein intake	(1) Reduces hyperfiltration; and (2) Slows down/delays the loss of function or progression of diabetic nephropathy in T1DM and T2DM	Lower DKD risk	No restriction. CKD stage 3: 100%-140% of the DRI. CKD stage 4-5: 100%-120% of the DRI
Weight loss, increased physical activity	-		(1) Reduces hyperfiltration; and (2) Reduces albuminuria, especially in moderate/severe obesity	Lower DKD risk	No

Anti-hypertensive therapy	(1) ACEI/ARB/calcium-channel blockers; and (2) ACEI/ARB + calcium-channel blockers	Control of BP	(1) Reduces albuminuria and delays the onset of DN; (2) Prevents progression of DN in microalbuminuric patients; and (3) Reduces the frequency of microalbu-minuria in hypertensive normoalbuminuric cases	Delay DKD progression	ARB, calcium channel blockers: No adjustment ACEI: GFR 30-60: Reduce dose to 50%; GFR < 30: Stop
Treatment of Dyslip-idaemia	(1) Atorvastatin; (2) Fluvastatin; and (3) Osuvastatin	Reduce LDL-C	Reduce albuminuria in patients with DKD receiving RAAS blockers	Reduces CV disease/risk	No
Psychological Intervention	(1) Family therapy; (2) Cognitive behavioral therapy; (3) Motivational interviewing; (4) Counselling; (5) Mentoring; and (6) Peer support	Reduce depression	Follow lifestyle adjustment regimens and achieve optimal glucose levels	Delay DKD progression	No
Novel therapies					
Vitamin D analogues	Paricalcitol. Calcitriol		(1) Ameliorates nephropathy by reducing the albuminuria; and (2) Prevent glomerulosclerosis	Delay DKD progression	No
Vitamin D metabolites	-		Inhibit RAAS and prevent glomerulosclerosis	Delay DKD progression/risk	No
Uric acid antagonist	Allopurinol	Uric acid antagonist/xanthine oxidase inhibitor	(1) Reduces urinary TGF-β1 in diabetic nephropathy; (2) Reduces albuminuria in T2DM; and (3) Improves endothelial dysfunction	Delay DKD risk/progression	GFR > 50: No adjustment. GFR 30-50: Reduce dose by 50%. GFR < 10: Reduce dose to 30%, longer interval
Renin inhibitor	Aliskiren	Block RAAS cascade	Reduces albuminuria and serves as an antihyper-tensive in T2DM	Delay DKD progression	No

Endothelin antagonist or I inhibitor ETA receptor antagonist	Atransetan, avosentan, sparsentan (irbesartan + ETA)		(1) Reduces residual albuminuria in type 2 diabetic nephropathy; (2) Reduces proteinuria in T2DM patients and nephropathy; and (3) Significant proteinuria reduction	Delay/slow DKD progression	Yes
MRA Mineralocor-ticoid Receptor Antagonists	Spironolactone = nonselective MRA. Eplerenone	↑Natriuresis	Reduce albuminuria and blood pressure in patients with DN when added to a RAAS inhibitor	Delay DKD risk/progress ion	GFR > 50: No dose adjustment. GFR 30-50: Reduce dose to 25%, once daily. GFR < 10: no use
SGLT2 inhibitors	Empaglifozi, canaglifozin	Glucose-lowering	(1) Improves glycemic control, reduces fasting blood glucose and HbA1c by increasing urinary glucose excretion; and (2) Reduces the reabsorption of sodium	Delay DKD progression, reduces blood pressure	No
GLP-1 agonist	Liraglutide, semaglutide	Stimulates insulin secretion, ↑ satiety	Improves glycemic control	Delay DKD risk/progress ion	No
	Exenatide, lixisenatide	Stimulates insulin secretion	Improves glycemic control	Delay DKD risk/progress ion	Caution in CrCl< 50 ml/min
DDP-4 inhibitors	Linagliptin, saxagliptin, vildagliptin	Glucose-lowering-preserve the glucagon-like peptide effect	Reduce albuminuria in macroalbuminuric T2DM patients	Delay DKD risk/progress ion	eGFR < 50 ml/min: Reduce dose by 50%; eGFR < 30 ml/min: Reduce dose by 75%
TZD Thiazolidinedi ones	Rosiglitazone. Pioglitazone	↓Hepatic glucose production activate peroxisome proliferato-activated receptor-*y* to increase tissue insulin sensitivity	(1) Reduce albuminuria in macroalbuminuric T2DM patients; and (2) Lower microalbuminuria and proteinuria	Delay DKD RISK/PRO GRESSION	No

Aldosterone synthase (CYP11B2) inhibition		Decrease in plasma aldosterone levels		Delay DKD risk/progression	NL
Anti-inflammatory compounds					
CCR3 Antagonists	-	Emapticap pregol (NOX-E36), CCX-140	Reduces UACR and HbA1c	In T2DM-delay DKD, DN risk/progression	NL
VAP-1 inhibitors	An adhesion molecule for lymphocytes, regulating leukocyte migration into inflamed tissue	ASP-8232	Reduces albuminuria in T2DM in CKD	Delay DKD risk/progression	NL

ETA: Endothelin type A; T2DM: Type 2 diabetes mellitus; DKD: Diabetic kidney disease; UACR: Urine microalbumin to creatinine ratio; HbA1c: Glycated hemoglobin; GFR: Glomerular filtration rate; RAAS: Renin-angiotensin-aldosterone system; eGFR: Estimated glomerular filtration rate; ↓: Decreased; T1DM: Type 1 diabetes mellitus; CKD: Chronic kidney disease; DRI: Dietary reference intake; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; BP: Blood pressure; DN: Diabetic nephropathy; LDL-C: Low-density lipoprotein cholesterol; CV: Cardiovascular; TGF-1: Transforming growth factor 1; MRA: Mineralocorticoid receptor antagonists; SGLT-2: Sodium-glucose cotransporter-2; GLP-1: Glucagon-like peptide 1; CrCl: Creatinine clearance; DPP-4: Dipeptidyl peptidase 4; TZD: Thiazolidinediones; NL: Not listed; CCR2: Chemokine receptor 2; VAP-1: Vascular adhesion protein 1.

I.5.3.4 Conclusion

DKD, the most significant and frequent burden of this metabolic disorder, is still discovered late as microalbuminuria is the most used biomarker for predicting kidney involvement. Novel biomarkers are valuable tools in the detection of kidney damage in the early phases as well as reliable predictors for DKD progression.

Therefore, effective therapies may be proposed. Early-stage prediction and recognition of DKD in children and adolescents before microalbuminuria occurrence have a pivotal role in preventing the development of and/or progression to irreversible kidney damage and to provide timely management and appropriate treatment by using conventional and novel therapies that may slow the onset or progression of DKD.

I.5.4 Pediatric calciphylaxis - a rare and potentially fatal condition

I.5.4.1 Material and methods

Calcific uremic arteriolopathy (CUA) is a rare disease, with an incidence that does not exceed 5% in the adult population with end stage renal disease (ESRD). Histologic studies describe specific lesions of proliferative and calcifying endarteritis, associated with wide spread calcifications nodules in patients with end stage kidney disease (Sowers, 2010). Up to 90% of the calciphylaxis lesions occur at the lower limbs, with proximal lesions in 44% to 68% of patients (Imam, 2005). In the pediatric population, an increased risk in males with ESRD and secondary hyperparathyroidism, with frequent distal extremity and visceral organ involvement, as well as an increased resistance to medical treatment has been noticed

(Sowers, 2010). I report a pediatric patient with ESRD who developed systemic CUA after 2 years of peritoneal dialysis, a co-morbidity eventually leading to his death.

I.5.4.2 Results

A 4-year and 8-month-old Caucasian boy was admitted with pulmonary distress associated with dry cough, malaise, and irritability. The child was diagnosed with ESRD at age 2, due to untreated posterior urethral valve and subsequent urinary tract infections. Peritoneal dialysis has been initiated along with standard drug treatment (calcium carbonate 1000 mg 3 times a day, erythropoietin 1000 UI, 3 time weekly, calcitriol 0.5 mcg once a day, iron 20 mg daily, renal multivitamins with 5 mg of folic acid once daily). Despite the 2 years of an uneventful schedule of peritoneal dialysis the disease outcome was negative, due to development of secondary hyperparathyroidism and renal osteodystrophy (Table 1.37).

Table 1.37. *Average serum calcium (Ca), serum phosphorus (PO4), calcium–phosphate product (Ca PO4), parathyroid hormone (PTH), obtained throughout age 2 to 3.*

Year/age	**Serum calcium, mg/dL**	**Serum PO_4, mg/dL**	**Ca × PO_4, mg^2/dL^2**	**Alkaline phosphatase, UI/L**	**PTH, pg/mL**
2012 (2 years)	9,45	7,34	71,56	722	567
2013/ 01 (2 years and 6 months)	11.22	10.88	118,76	1230	650
2013 /08 (3 years)	12,18	7,01	85,38	890	757
2014 /01 (3 years and 6 months)	10,81	8,56	92,53	870	620
2014 /08 (4 years)	12,15	9,29	112,87	1320	765
2014 / 11 (3 years and 3 months)	11,22	10,88	112,07	1860	940

PTH - parathormone

This ended up in limping and difficulty to walk despite the continuous calcium carbonate supplementation (as phosphate binder) and calcitriol. The proposal to replace calcium carbonate therapy with other phosphate binder (lanthanum carbonate, in association with calcitriol) was refused by the family. He always had an elevated calcium–phosphorus product, the highest being 118, 76 mg2/dL2 with a co-responding PTH level of 650 pg/mL (n = 10–65 pg/mL). At 4 years and 6 months old, he presented with asthma like symptoms, (chest tightness, shortness of breath, dry cough, and wheezing) predominantly at night. An elevated IgE (1665 UI/mL) have been noted. Specific treatment with leukotriene inhibitors was added, with poor an outcome: as persistent dry cough. In the following 2 months, he experienced a progressive deterioration of his nutritional status (with weight loss of 3 kg in 2 months), anemia, hypoproteinemia, and low cholesterol. The physical examination revealed: irritability, very painful, hard, purple subcutaneous nodules, located at the level of

the nasal pyramid, thorax, and abdomen (Fig. 1.55 B). He also had tachypnea, dry spasmodic cough, respiratory rate 45/min, heart rate 110/min, blood pressure 100/60 mm Hg, with normal heart sounds, no murmurs, hepatomegaly with hepato-jugular reflux. The chest radiograph revealed bilateral interstitial and alveolar infiltration, with peripheral disposition and cotton-wool like distribution that did not improve following ultrafiltration. Apart from the ESRD, the provisional diagnosis for this moment was bronchopneumonia, respiratory and cardiac failure. His respiratory distress rapidly deteriorated within 50 minutes from the moment of hospital admission, up to severe hypoxemia (PaO2 74%), seizures and cardio-respiratory arrest, despite the initiation of intensive care measures. Post-mortem examination revealed: diffuse calcifications in the skin, skull, brain (cerebellar tentorium and dura mater), lungs and heart (subendocardial, within the myocardium and large vessels walls) (Fig. 1.55). Both kidneys had severe hydronephrosis with bilateral renal cortical atrophy and calcifications in the remaining renal parenchyma (Fig. 1.55F). The histopathological examination with hematoxylin eosin staining, confirmed the microscopic diffuse calcifications in the skin, brain, heart, lung, kidney, stomach, and pancreas (Fig. 1.56). All these are consistent with the diagnostic of calcific uremic arteriolopathy.

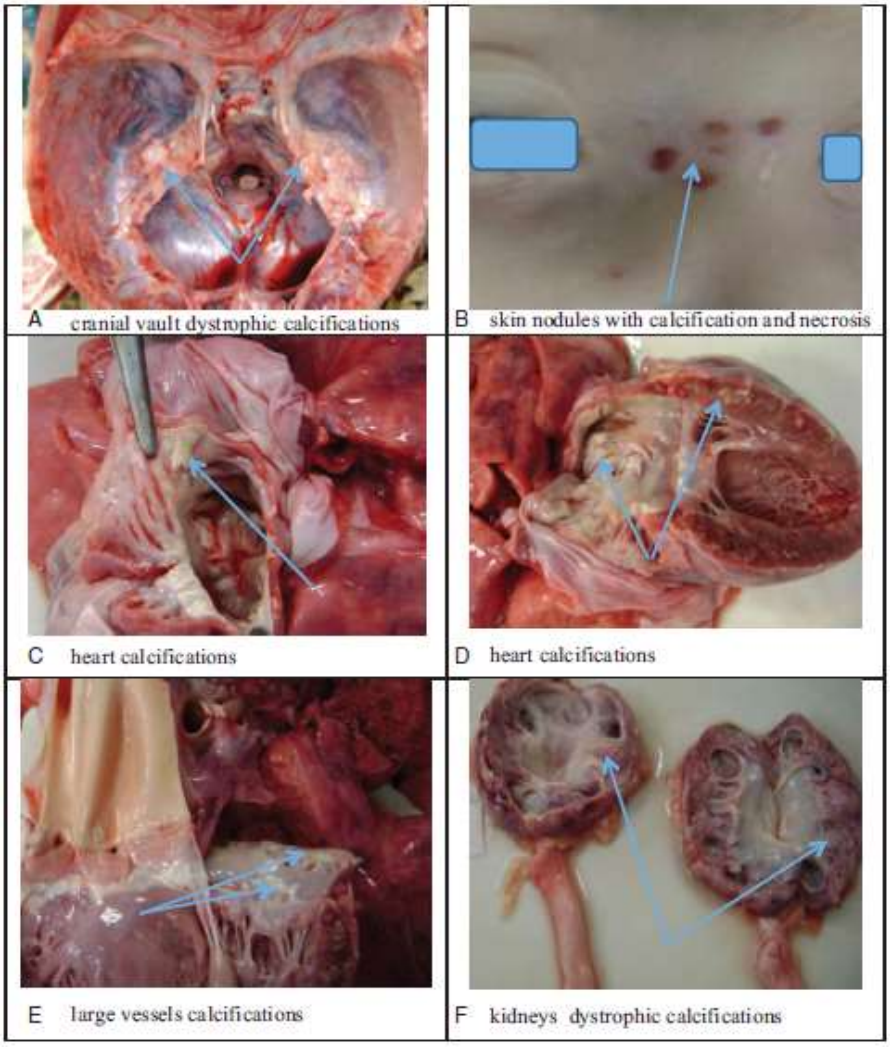

Fig. 1.55 *Dystrophic calcifications.*

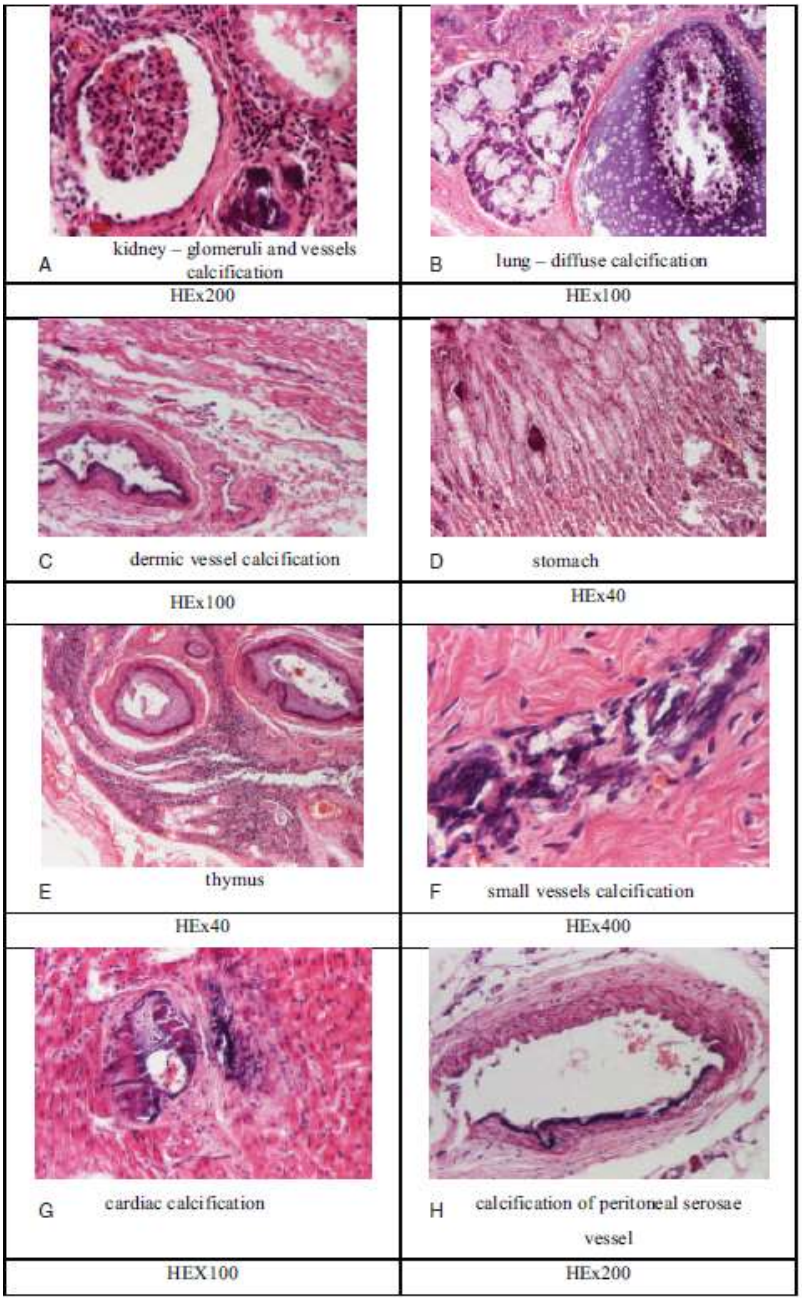

Fig. 1.56 *Calcifications—microscopic aspects (hematoxylin-eosin staining)*

I.5.4.3 Discussion

Calcific uremic arteriolopathy (CUA), previously known as calciphylaxis, has been reported to occur in 1% to 5% of adult patients with ESRD and has a mortality rate of more than 80% (Sowers, 2010, Imam, 2005, Araya, 2006). Although calciphylaxis predominantly affects patients with chronic kidney failure and secondary hyperparathyroidism, it is not limited to this group, but also occurs in patients with normal kidney function and those with earlier stages of chronic kidney disease (nonuremic calciphylaxis) (Nigwekar, 2015, Bakkaloglu, 2007).

Occasionally, it may occur before the initiation of the renal replacement treatment, or in individuals with no history of chronic renal impairment. It has also been discovered in patients with renal allograft transplantation who are noncompliant with diet, medication and /or dialysis instructions (Nigwekar, 2015). It is considered a life-threatening small-vessel vasculopathy characterized by intimal proliferation, endovascular fibrosis, and medial wall calcification, which result in ischemia and painful necrosis most commonly in the skin and subcutaneous tissues (Araya, 2006). It was considered that the ischemic necrosis evolves in a rapidly progressive manner, covering large areas of the skin and muscle due to extensive vascular calcifications (Imam, 2005). These areas may become ulcerated and infected, sometimes resulting in limb amputation (Amin, 2010).

Metastatic calcinosis subsequent to renal insufficiency was first described by Virchow (Virchow, 1885). Although soft tissue calcification is a recognized complication of uremia in adult patients treated by dialysis (occurring in up to 40% to 76% of adults on maintenance dialysis), it has been considered as rare in pediatric renal patients (Milliner, 1990).

The first pediatric CUA case was reported in 1898, by Bryant and White who described a 6-month-old boy with severe calcification of the large arteries and occlusion of peripheral arteries and arterioles associated with hydronephrosis, which led to gangrene of the right foot with a lethal outcome (Bryant, 1898) It occurs rarely in children, where the reported incidence is 3.5 new cases/1000 patients/year in chronic hemodialysed pediatric patients (Nigwekar, 2017). An increased incidence was found in boys with chronic renal disease and secondary hyperparathyroidism, with acral necrosis (tip of the fingers or toes). This was associated with a poor prognosis (Brandenburg, 2014). Hyperphosphatemia and concomitant calcium–phosphorus product are the strongest risk factors for the development of CUA.

Our case presented an unusual, diffuse, and extensive calcifying uremic arteriolopathy syndrome with diffuse calcifications in the dermis, brain, thymus, heart, lung, kidney, stomach, and pancreas. From all these locations, pulmonary calcification is one of the most severe complications in patients on dialysis. Furthermore, the clinical and radiographic manifestations of this lesion may be mistakenly diagnosed as pulmonary oedema or pneumonia. Pulmonary calcification, when extensive, can be the cause of death in uremic patients (Hossein, 1977). We appreciate that this was also the case in this current case study.

Our patient developed rapidly progressive respiratory failure. Multiple calcifications in the lungs and skin have been reported by Zouboulis et al (Zouboulis, 1996), who described a 6-year-old boy undergoing peritoneal dialysis for chronic renal failure due to bilateral renal hypoplasia. Pulmonary calcinosis can be responsible even for sudden death, as it has been reported by Milliner et al (Milliner, 1986) in an adolescent following renal transplantation. The same author has reviewed 120 pediatric patients with uremia, on dialysis or following renal transplantation who died. During these autopsies soft tissue calcifications in 72 cases, out of which 29 had pulmonary calcinosis were discovered (Milliner, 1990).

I.5.4.4 Conclusion

CUA is an under recognized, understudied, and undertreated rare cause of major morbidity and mortality in patients with chronic renal insufficiency regardless of etiology. The available, though heterogenous, case reports on this topic suggest an increased incidence in pediatric males and adult females. The reported pediatric patients are usually already on peritoneal dialysis at the time of diagnosis. Adult treatments have not yet been applied consistently to pediatric patients with CUA, although initial results seem promising. Prophylaxis of hyperphosphatemia and secondary hyperparathyroidism, patient compliance with doctor recommendations, and early diagnosis of calciphylaxis are believed to improve survival in these cases. Calciphylaxis remains a subject of relevance for current medical

research, because the pathogenesis is not yet clarified and data on diagnosis and therapeutic approach are still under debate.

I.5.5 Oral manifestation of renal osteodystrophy in children

I.5.5.1 Material and methods

Very rare in children, the brown tumor, or osteoclastoma, is an understudied ectopic entity that causes severe debilitation in patients with chronic renal insufficiency. I report two cases who developed particular forms with different evolutions of severe renal osteodystrophy. The management of CKD must prevent the development of serious forms of renal osteodystrophy. Treatment noncompliance may give rise to severe manifestations of bone involvement in uremic children with active osseus metabolism (Orejas, 1993).

I.5.5.2 Results

Patient 1 is a 13-year-old boy with ESRD due to hemolytic uremic syndrome, who was on continuous ambulatory peritoneal dialysis (CAPD) for 5 years, the switched to HD (because of recurrence of peritonitis) for another 2 years. Since the first presentation he showed short stature in context of ESRD and severe renal osteodystrophy, clinically manifested by important bones deformities (Fig. 1.57), with a typical radiological appearance.

The clinical examination at presentation reveals the presence of severe changes in context of severe renal osteodystrophy (dissociation with superior jaw protrusion, nasal pyramid collapse, costal mantle, metaphysis bracelet, genus valgum, 1/3 left femur left fracture).

The biological parameters of the child confirm the renal osteodystrophy: high intact parathormone (iPTH) of 1602 pg/mL, serum calcium of 9.7 mg/dL and phosphorus of 8,5 mg/dL, high serum concentrations of alkaline phosphatase (2644 IU/l), low level of vitamin D 23 ng/mL. The recommended treatment for these complications of ESRD was poor diet in phosphorus, oral administration of calcium carbonate, like phosphorus binder therapy, calcitriol, corrections of metabolic acidosis, multivitamin supplements. The biochemical control of hyperparathyroidism was poor, because of the family ‘s noncompliance at the diet and therapy.

The patient developed a swelling of the hard palate that increased in size gradually. In timethis tumoral formation resulted in tooth loss, swallowing and phonation disorders.
The swelling was soft, painless, but tender at palpation, with elastic in consistency (Fig. 1.58).

A diagnosis of brown tumor of the hard palatewas made. CT performed to exclude a possible expansive process concluded: fibrousdysplasia with the interest of the mandible, jaw and anterior floor of the lip, skull and calotte, without any intracranial expansive process.

The tumor biopsy demonstrated lesions with giant cells that were fibroblasts with a rich vascular network, highly suggestive of a brown tumor. In the sametime, we discussed with the surgical staff, because the neck ultrasound showed the adenomatous development of parathyroids glands.

After three months of parenteral therapy with activated vitamin D the resuls were poor: iPTH was reduced to 1852 pg/mL, but the oral mass increased in size. We proposed

parathyroidectomy for control of severe osteodystrophy, but the family refused. Unfortunately, the boy died suddenly a few weeks later, at home, because of an odontoid fracture in context of severe osteodystrophy.

Fig. 1.57 *Bones deformities in patient no.1*

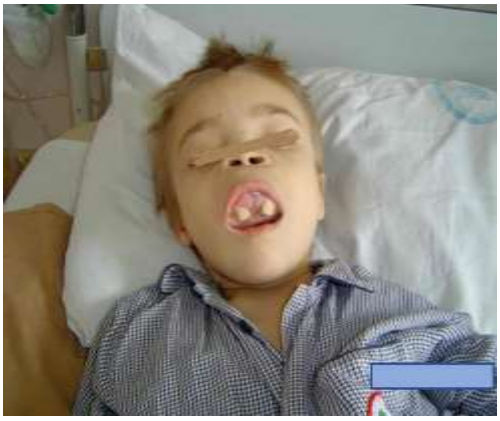

Fig. 1.58 *Patient 1 – brown tumor of hard palate*

Patient 2 is a girl, 16-yers-old at diagnosis, inour clinic evidence since December 2000 (6 years of age) with chronic end-stage renal failure, caused by a chronic glomerulonephritis in the context of an immune vasculitis. She required hemodialysisin an emergency, then, from April 2001 she has been introduced into a chronic hemodialysis program on arteriovenous fistula.

The clinical examination at presentation reveals the presence of severechanges in context of severe renal osteodystrophy (sinistroconvex scoliosis,walked licked, shortening of the inferior right member) (Fig. 1.59, 1.60).

She had a history of aseptic necrosis of the right femoral head at the age of 13 in the context of the brown tumor developed at that level. She benefited from orthopedic therapy through osteosynthesis with brooches, then right femoral head prosthesis.

For several weeks, she has been accusing major headache, headquartered at the level of the tall central palate, and vertex irradiation, no influenced by the usual antalgic medication. A tumor was protruding through her oral cavity, in the right side of hard palate (Fig. 1.61, 1.62), it had appeared insidiously 3 years ago and had increased gradually in size. The lesion was tender to palpate, painless.

Some bleeding areas were observed on the fragile mucosa. The girl had functional problems with swallowing, chewing and speech. Serum chemistry revealed an elevated intact parathyroid hormone (iPTH) level of 3753 pg/dl, serum calcium 9.08 mg/dl, phosphorus 5.2 mg/dl, and alkaline phosphatase 2740 IU/l.

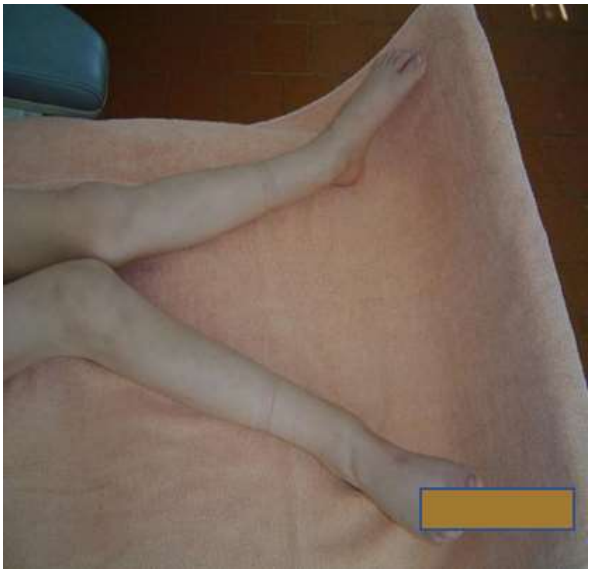

Fig. 1.59 *Patient 2 – legs deformities – clinical aspect*

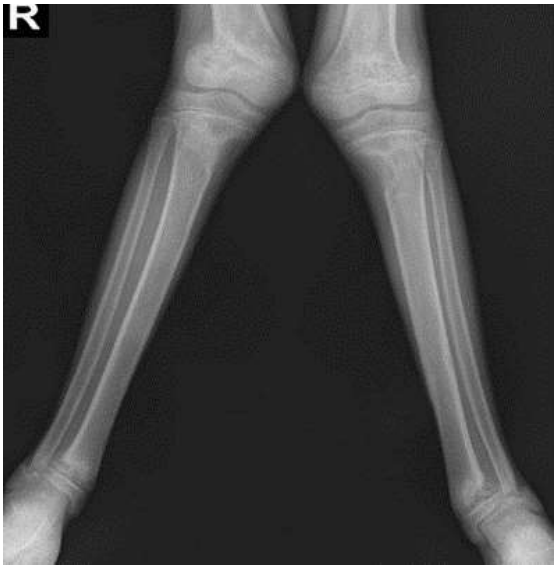

Fig. 1.60 *Patient 2 – legs deformities - radiological aspect*

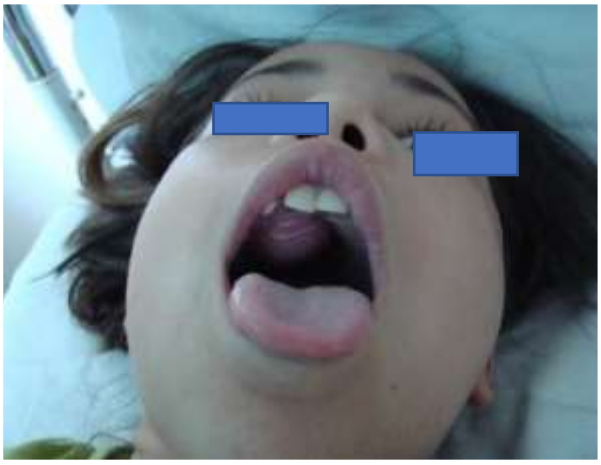

Fig. 1.61 *Patient 2 – brown tumor of hard palate*

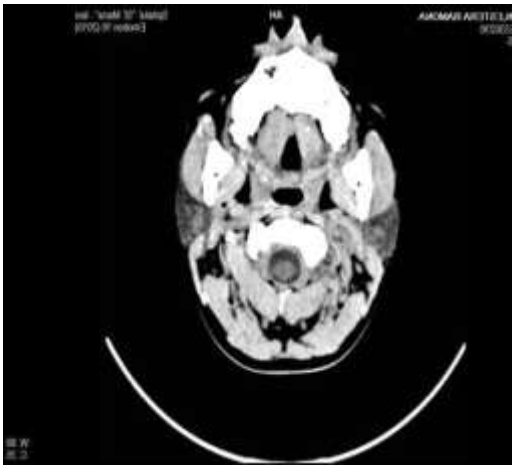

Fig. 1.62 *Patient 2 – Brown tumour of hard palate/CT*

I.5.5.3 Discussion

Brown tumors are unifocal or multifocal bone lesions that are characterized by increased osteoclast activity and fibroblast proliferation. They are found in patients with uncontrolled hyperparathyroidism (Goyal, 2018).

Actually, the term brown tumor is a misnomer, as these lesions are benign. Histologically, the lesion resembles a giant cell tumor, consisting of multinucleated giant cells in a background of spindle cell proliferation with abundant hemosiderin that gives the lesion its brown color. In the majority of series, brown tumors have been reported at a rate

of 3–4% in primary hyperparathyroidism and 1-2% in secondary hyperparathyroidism (Silverber, 2016).

Brown tumors that occur in patients with ESRD represent an extreme form of osteodystrophy. They occur most often in the long bones, ribs and pelvis, but can be found in any bone (Doaa, 2016). Clinically significant lesions in the pediatric population are rare, especially due to the short time spent in chronic dialysis, pending a kidney transplant. The diagnosis must to be as earlier as possible, and the treatment with activated vitamin D and/or surgery should be administered or performed rapidly.

Due to the reversible nature, excision of brown tumor is not recommended unless the lesion causes compressive symptoms, significant cosmetic disfigurement or fails to regress on follow up. In our patient, the lesion healed completely with correction of secondary hyperparathyroidism.

Orejas described in 1993 the smallest case of brown tumor (a 3-year-old girl with peritoneal dialysis) in which family noncompliance with therapy and diet determines the death of the patient (Orejas, 1993). The similar aspect was in our first case.

In order to develop an accurate management plan and to achieve a good prognosis we need to consider early diagnosis, effective communication with stakeholders, as well as reflection upon the moral values (Gavrilovici, 2014).

Decision to determine what is best or not for the child can be very difficult, the respect for the child‘s interest supposes sometimes ignoring the child‘s disagreement when for example, a surgical act is essential for saving his life (Miron, 2009).

Clinical manifestations of abnormal bone metabolism in secondary hyperparathyroidism in ESRD are nonspecific, with majority being asymptomatic for long time. The definitive treatment of brown tumor is parathyroidectomy as studies have shown that 80% of brown tumors result from parathyroid adenoma while parathyroid hyperplasia and co-existence of hyperplasia and adenoma account for the rest (Makusidi, 2014, Hiramitsu, 2015, Li, 2017).

In our second case the rapid surgical intervention with subtotal excision of parathyroid glands saved the child. Despite the parathyroidectomy and optimal control of calcium/phosphate metabolism, some brown tumor did not decrease in size during follow-up (Özgür, 2016). In our second patient residual hyperostosis was described in CT scan after 6 months after parathyroid surgery. In this case the renal transplant remains the unique chance for bones rehabilitation.

Finally, the entire patient approach should be part of the internal ethics audit, meaning the process aimed to improve the organization's performance (Agheorghiesei, 2013).

I.5.5.4 Conclusion

The brown tumor remains a striking complication of osteodystrophy in the ESRD. The diagnosis should be suspected when we have uncontrolled hyper-parathyroidism, and must to confirmed by CT scan, biopsy and specific serological changes. The parathyroidectomy seems to be the most appropriate treatment for this pathological entity. The renal transplant must to be the final decision making in cases resistant to parathyroidectomy and optimal control of calcium/phosphate metabolism.

CHAPTER II. URINARY TRACT INFECTIONS (UTIS) AND URINARY TRACT MALFORMATIONS - TWO DISTINCT YET RELATED CONDITIONS OF URINARY SYSTEM

State of art in Urinary Tract Infections and Urinary Tract Malformations

Urinary Tract Infections (UTI) is defined by the presence of organisms in the normally sterile urinary tract. Due to the possibility of colonization of the urinary tract without symptoms, it may be necessary to look for other signs, such as the presence of inflammatory markers or follow-up cultures, to be sure that someone has a UTI. Typically, bacteria cause clinically significant infections, although viruses, fungi, and parasites can also cause infections. Urinary tract infections are one of the most prevalent childhood infections (Leung, 2019). In the first year of life, it is significantly more prevalent in boys than in girls (3.7% versus 2%), but after infancy, it is significantly more prevalent in girls. Within the first 6 months of life, boys who haven't undergone circumcision face a 10 to 12 times higher likelihood of developing a urinary tract infection (Balighian, 2018). Compared to circumcised males (0.22%) and females of the same age (2.0%), the incidence of UTI is significantly higher among uncircumcised neonates (2.15%) (Mattoo, 2021). During the neonatal period, urinary tract infections (UTIs) are more prevalent among premature infants compared to full-term infants (Schlager, 2016). In prepubescent girls, the incidence is 3%, compared to 1% in prepubescent boys (Mattoo, 2021). In the six to twelve months following the initial UTI, the risk of recurrence is between 12% and 30% (Conway, 2007; Dai, 2010). Hispanic and white children exhibit a two- to fourfold higher prevalence of UTIs compared to black children (Shaikh, UpToDate). Generally, the recurrence rates for UTIs fall within the range of 30% to 50% (Korbel, 2017). The likelihood of recurring UTIs is notably higher in girls (Leung, 2019). About 75% of Caucasian and about 50% of African American school-aged girls in the United States who have had a UTI will experience at least one more recurrence (Leung, 2019). In addition to sexual activity, other significant risk factors for UTI include bladder-bowel dysfunction (BBD), CAKUT, including vesicoureteral reflux (VUR), and circumcision in young boys (Mattoo, 2021).

Approximately 85 to 90 percent of urinary tract infections are caused by Escherichia coli. Klebsiella, Proteus, Enterococcus, and Enterobacter species are also widespread (Akram, 2007). Organisms such as Pseudomonas, group B Streptococcus, and Staphylococcus aureus are typically associated with CAKUT, genitourinary surgery, a foreign body (e.g., a catheter), or recent antibiotic treatment, whereas infection with urea-splitting organisms (e.g., Proteus) is linked to stone formation (Mattoo, 2021).

The infection can impact either the upper urinary tract (known as pyelonephritis) or the lower urinary tract (known as cystitis). Regrettably, telling pyelonephritis apart from cystitis based on clinical symptoms and signs might be tough, if not impossible, especially in infants and young children younger than 2 years (Balighian, 2018).

In practical terms, these two conditions are grouped together as UTI. The high occurrence, likelihood of recurrence, linked morbidity, and difficulties in obtaining an uncontaminated urine sample pose substantial challenges for medical practitioners (Leung, 2019). Recurrent UTI is defined as the occurrence of two or more infections within six months, or at least three UTIs in a year.

Two risk factors are associated with the highest recurrence rate: vesicoureteral reflux (VUR) and BBD, with their combination doubling the risk (56%) (Mattoo, 2021). Children with high-grade reflux, whose initiation of antibiotics was delayed after 72 hours, with recurrent urinary infections, with annoying bacteria other than E. coli, and older than 2 years are risk factors for kidney scars in the case of fever UTI (Snodgrass, 2013, Karavanaki, 2017, Shaikh, 2019).

Laboratory results associated with kidney scars include fever (> 39 °C), polymorphonuclear number > 60%, CRP > 40 mg/L, and abnormal ultrasound of the kidneys and bladder (RBUS) (Shaikh, 2014).

Rapid diagnosis and treatment are essential for preventing both acute complications and renal scarring. In the past two decades, a substantial amount of research has been conducted on UTIs in children, specifically on renal imaging and long-term antibiotic prophylaxis after UTIs. The recent introduction of UTI risk calculators for febrile infants has enhanced detection in this population.

In comparison to the AAP algorithm and dipstick urinalysis, the University of Pittsburgh's risk calculator decreased UTI testing rates by 8.1%, increased testing accuracy, and decreased treatment delays by 10.6% (Shaikh, 2018). 5% of children aged 2 to 24 months with a fever of unknown origin have an infection of the urinary tract (Finnell, 2011).

Urine testing is a crucial diagnostic tool. In toilet-trained children, a sample of urine from the middle stream is collected following the use of a clean local toilet. Recent studies (Marzuillo, 2018) have demonstrated a significant rate of urine culture contamination among children who did not perform perineal washing (23.9%) compared to those who did so (7.8%) prior to midstream urine collection. For diapered children, there are three options: collecting the perineal bag, catheterizing the bladder, and suprapubic aspiration. Up to 85% of specimens obtained from bags with a positive culture are false positives (Finnell, 2011). The collection of bags should serve only as a preliminary screening measure; a negative result confirms the absence of a urinary tract infection (SUBCOMMITTEE ON URINARY TRACT INFECTION, 2016).

Compared to suprapubic aspiration, catheterization of the blader is more sensitive (95%) and specific (99%), less technically challenging, and more accepted by parents (Finnell, 2011). While some studies claim that suprapubic aspiration is more painful and has a higher rate of collection failure, it has also been shown (Eliacik, 2016,Mattoo, 2021) to have a lower rate of false-positive results. For a positive result of UTI, the criteria are > 100,000 CFU/mL for a midstream specimen, > 50,000 CFU/mL for catheterization, and > 1000 CFU/mL for suprapubic aspiration (Olson, 2022, Mattoo, 2021).

Antibiotics should be administered to a child diagnosed with UTI within the first 48 hours to reduce the risk of kidney scarring (Karavanaki, 2019, Olson, 2022). There is a linear relationship between the prevalence of renal scar formation and the duration of treatment delay (Oh, 2012). With the rise of multidrug-resistant pathogens, antimicrobial administration is more crucial than ever. These include organisms that produce extended-spectrum beta-lactamases (ESBLs), which are increasingly identified in community-acquired UTIs (Erol, 2018, Patwardhan, 2017, Konca, 2017). A 2- to 4-day course of oral antibiotics is just as effective as a 7- to 14-day course in treating cystitis in children, according to multiple studies (Strohmeier, 2014, Olson, 2022). Acute pyelonephritis can also be treated with oral antibiotics for 10–14 days or with intravenous antibiotics for 2–4 days followed by oral therapy (Olson, 2022).

The purpose of medical imaging is to identify abnormalities in the genital and urinary systems that could lead to an increased risk of recurring urinary tract infections and subsequent scarring. For infants aged 2 to 24 months who experience their first fever-related UTI, a renal-bladder ultrasound (RBUS) is recommended (SUBCOMMITTEE ON URINARY TRACT INFECTION, 2016). Older children who have recurrent febrile UTIs should also be evaluated, although RBUS might not effectively detect mild to moderate vesicoureteral reflux (VUR) [18]. If an abnormality is detected during RBUS or in cases of

recurrent febrile UTIs, a voiding cystourethrogram (VCUG) is recommended (SUBCOMMITTEE ON URINARY TRACT INFECTION, 2016, Olson, 2022). VCUG is used to identify high-grade (IV-V) reflux in children, which poses a risk of kidney damage, but its use should be selective due to the need for catheterization and exposure to radiation (SUBCOMMITTEE ON URINARY TRACT INFECTION, 2016).

Research has indicated that low-grade VUR often does not contribute to kidney damage and tends to resolve on its own. Less than 40% of children with their first fever-related UTI are diagnosed with VUR, and within this group, fewer than 10% have severe (IV, V) VUR (Juliano, 2013, Mattoo, 2019).

A radiation-free approach for assessing VUR in children has emerged known as contrast-enhanced voiding urosonography (CEVUS). This method involves using contrast-filled microbubbles that are visible through low-intensity ultrasound. Recent studies have demonstrated CEVUS's excellent diagnostic accuracy for VUR, with sensitivity ranging from 90.4% to 92% and specificity from 92.8% to 98% (Chua, 2019, Ntoulia, 2018). However, this technique has yet to become standard practice in pediatric nephrology centers in Romania due to its relatively high cost and limited specialization in the field.

Another method, dimercaptosuccinate (DMSA) scans, can identify patients with kidney scarring. These scans are also sensitive in detecting other renal anomalies such as small or absent kidneys, ectopic kidneys, and duplex systems. DMSA scans have higher sensitivity than RBUS for detecting kidney parenchymal damage.

It's important to note that inflammatory changes in the kidney following an infection can laed to false-positive results if the scan is conducted within the first 4 to 6 months after the infection (Olson, 2022). The use of continuous antibiotic prophylaxis (CAP) can be prescribed to prevent kidney damage in children who suffer from recurrent febrile UTIs. Guidelines regarding the use of prophylaxis can be a subject of debate.

The American Urologic Association and our own clinical practice align in recommending CAP for children below the age of 1 with vesicoureteral reflux and a history of febrile UTI (Management and Screening of Primary Vesicoureteral Reflux in Children, 2010, amended 2017). It's advised to consider prophylaxis for all patients with high-grade VUR (III-V). Additionally, CAP is suggested for children above the age of 1 who have both bladder and bowel dysfunction and VUR (Management and Screening of Primary Vesicoureteral Reflux in Children, 2010, amended 2017). In cases of VUR or renal cortical anomalies without BBD, the decision to use CAP is discretionary and should be deliberated through shared decision-making (Olson, 2022).

Pediatric urinary tract infections (UTIs) continue to pose a considerable health concern for children, particularly in uncircumcised males during their first year and females across their lifetimes. The use of UTI risk calculators, algorithms, and improved collection methods can contribute to reducing the occurrence of incorrect positive diagnoses and unnecessary antibiotic treatments.

Ongoing research into areas like urinary microbiomes, and UTI vaccinations has the potential to revolutionize UTI management, altering how we approach treatment and preventing chronic kidney issues in patients at elevated risk.

II.1 UTI and Urinary tract malformations in children

Vesicoureteral reflux is the most frequent congenital renal malformation and is defined as a backward flow of urine from the bladder into the ureter (Parmaksız, 2018). It is considered the most important congenital risk factor for the development of urinary tract infections in the pediatric population (Amiri, 2020, Forster, 2017).

My relevant papers and research on this topic are listed below.

Articles ISI – principal author

Gavrilovici C, Dusa CP, Iliescu Halitchi C, Lupu VV, Spoiala EL, Bogos RA, Mocanu A, Gafencu M, Lupu A, Stoica C, **Starcea IM**. The Role of Urinary NGAL in the Management of Primary Vesicoureteral Reflux in Children. International Journal of Molecular Sciences. 2023; 24(9):7904, IF= 5.6/2022, **Q1**, https://doi.org/10.3390/ijms24097904

Aldea C., Duicu C, Delean D, Bulata B**, Starcea M**., Long term follow-up in a patient with prune-belly syndrome - a care compliant case report. Medicine (Baltimore). 2019;98(33):e16745, IF= 1.552/2019, **Q3**,https://journals.lww.com/mdjournal/Fulltext/2019/08160/Long_term_follow_up_in_a_patient_with_prune_belly.24.aspx

Article BDI – principal author

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R. Russu, Nedelcu D., Munteanu M., **Starcea M**., Primary vesico-ureteral reflux prenatally diagnosed,with particular evolution**,** Romanian Journal of Pediatrics Volumul LXII, 2013, Nr. 1, 101 – 103, (Autor principal), https://view.publitas.com/amph/rjp_2013_1_art-12/page/1

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Book chapter

Stârcea M., Iliescu Haliţchi C., Munteanu M., Russu R., INFECŢIA DE TRACT URINAR LA COPIL, în Pediatrie, tratat, Editura Gr.T.Popa, Iași 2016 (ISBN 978-606-544-429-4), capitolul VI, pag. 231 – 237;

II.1.1 The Role of Urinary NGAL in the Management of Primary Vesicoureteral Reflux in Children and a particular evolution in a Primary vesicoureteral reflux prenatally diagnosed

II.1.1.1 Introduction

Primary VUR is considered to be the most common type of CAKUT (Amiri, 2020, Anand, 2021). It accounts for up to 44% of cases of CKD in children and is the main cause of ESRD in children younger than 5 years (Kovacevic, 2020).

Primary VUR occurs in 1% of individuals in a healthy population, 20% of individuals with UTIs, and up to 50% of individuals with recurrent cases of UTIs (Mattoo, 2021). Half of children with VUR may develop RN. VUR is asymptomatic and is usually diagnosed during a urinary tract infection (Parmaksız, 2018, Amiri, 2020).

VUR is diagnosed in 40% of children presenting febrile UTIs and in 15–20% of children with a history of antenatal hydronephrosis (Mattoo, 2021). Consequently, there is a bimodal distribution in the age of presentation of VUR, with one mode occurring at less than 3 months of age and the other at approximately 2–4 years of age (Mattoo, 2021, Kovacevic, 2020).

There appears to be a gender difference in those affected by VUR; infants with reflux detected during the antenatal period are more likely to be boys, while children with reflux diagnosed following a febrile UTI are more likely to be girls. Additionally, there appears to be a racial difference in those affected with VUR. Caucasian girls are 10 times more likely to have reflux than their African-American counterparts (Kovacevic, 2020). There are controversies regarding systematic screening for VUR in children with UTIs.

According to American Academy of Pediatrics, voiding cystourethrograms (VCUGs) are not routinely recommended in children aged between 2 and 24 months old with a first episode of febrile UTI (Briggs, 2010). There are two reasons: First, they are invasive due to bladder catheterization; in addition, this exposure to the X-rays risks potential urethral damage and iatrogenic infections, and it is not always associated with good parental adherence (Kopiczko, 2017).

Second, there is a lack of effective therapeutic strategies for the lower grades of VUR. On the other hand, those who promote the routine use of VCUGs underline that the potential significant morbidities associated with RN (growth retardation, HTN, and CKD (Sepahi, 2017) as well as the risk of delayed surgical procedures for high-grade VUR) are important justifications for their position (Jonhson, 2015).

The routine laboratory tests that are often used as markers for renal injuries include blood urea nitrogen, creatinine, creatinine clearance, and urine sediment, whereas the diagnosis of RN is frequently based on imaging studies such as 99 mTc-dimercaptosuccinic acid (DMSA) renal scintigraphy, an invasive and costly procedure (Juliano, 2013).

Thus, urinary biomarkers that are able to predict the association of VUR as well as detect the early progression of renal scars are needed. Therefore, newer, non-invasive, and more precise tools are needed for a better prediction of the risk of kidney damage.

Neutrophil gelatinase-associated lipocalin (NGAL) is included in the lipocalin family (Arlene, 2015). NGAL is secreted by the thick limb of the Henle loop and collecting renal ducts (Amiri, 2020) and normally accumulates at low levels in different organs (such as the stomach, colon, trachea, kidneys, and lungs) in the healthy population.

It increases to high levels in the kidney serum and urine after an ischemic or nephrotoxic injury (Parmaksız, 2018, Filho, 2017).

II.1.1.2 Aim of study

Our aim is to review the predictive value of this non-invasive biomarker for RN in children with primary VUR, as well as its ability to predict the evolution of CKD in these children. CKD in children contributes to an additional burden on the global health system.

The use of new biomarkers to predict disease onset and progression has grown tremendously over the past decade. The discovery of biomarkers offers insights for the early anticipation of renal degradation towards the advanced stages of CKD, thus contributing to decreasing the rate of disease progression.

I will also present a clinical case with this pathology, with the aim of evaluating a case of severe vesicoureteral reflux, hospitalized at the age of 6 weeks with urinary infection and nitrate retention, with antenatal ultrasound suspicion of bilateral hydronephrosis.

II.1.1.3 Material and method

We performed an electronic search in the PubMed and Embase databases using the following search terms: primary vesicoureteral reflux AND NGAL OR (Neutrophil Gelatinase- associated Lipocalin)) AND children (OR pediatric OR paediatric). The databases were searched from the date of inception until March 2023. Articles were screened by titles and abstracts.

Full texts of relevant articles were retrieved and independently assessed. We limited our search to the English language, humans, and original studies. Review articles, case reports, and letters were excluded. All of the significant articles were manually searched to further identify any additional eligible studies.

Among these, it was evident that uNGAL was used with two main purposes:

(1) as a diagnostic tool in children with primary VUR and

(2) as a predictive tool for RN.

Eight original articles were included for a deep analysis in this review. A summary of the main results of these studies is presented in Table 2.1. Another 58 selected articles were used to discuss the topic.

In the second part of this section, I want to present T.C., boy of 6 weeks of age, was admitted in our clinic for fever, vomiting, oliguria. He is the first child of a young healthy couple without pathological familial history. Pregnancy was normal, but at 32 weeks the fetal ultrasound describes bilateral hydronephrosis. He was normally delivered, with birth weight 3000 gr and Apgar score of 9. He was diagnosed with acute pyelonephritis with E.coli and acute renal failure (creatinine clearance 20 ml/ min/1,73 mp). After rehydration and antibiotic treatment with ceftriaxone the clinical evolution was favorable, the urine culture was negative and the renal function normalized after 10 days. The renal ultrasound revealed ureterohydronephrosis grade III on the right side and grade I on the left.

Table 2.1. *Studies depicting the role of NGAL in VUR management in children.*

Authors, Year of Publication	Study Design and Study Population	Aims	Sample Size and Age	Main Results	Limitation of uNGAL Determination	Conclusions
Amiri, 2020	Prospective case-control study	uNGAL in primary VUR	63 children with primary VUR 72 healthy controls 2 months–12 years old	No significant difference in uNGAL between mild/moderate and severe VUR Significant differences in uNGAL/uCr between study groups	None	Higher uNGAL/uCr ratio in severe vs. mild/moderate VUR
Ichino, 2010	Prospective case-control study	uNGAL—biomarker of renal scars in VUR	34 children with primary VUR 28 healthy controls 5 months–11 years old	Significantly higher uNGAL in the VUR group No significant differences in uNGAL between the lower and higher grades of VUR Significantly higher uNGAL in patients with renal scars	No correlation with VUR grade	uNGAL—non-invasive diagnostic and predictive biomarker for renal scars uNGAL is biologically stable and resistant to protein degradation. The parents collected urine samples from small children (less than 3 years) at home for transport to the hospital.
Nickavar, 2020	Prospective case-control study	uNGAL in primary VUR	32 children with primary VUR 37 children without VUR 36.84 ± 28.16 months for children with VUR-32.32 ± 29.08 months for children without VUR	Significantly higher uNGAL and uNGAL/uCr ratio in patients with VUR Significantly higher uNGAL in patients with renal scars	None	uNGAL/uCr ratio—good accuracy, high specificity, and high sensitivity as a non-invasive biomarker of primary VUR Children with decreased uNGAL did not need further imaging studies.
Eskandarifar, 2021	Prospective cohort study	uNGAL in primary VUR	34 children with VUR 37 children without VUR 1–5 years old	Significantly higher uNGAL and uNGAL/uCr ratio in patients with VUR	uNGAL cannot replace VCUG, the gold standard for VUR diagnosis.	uNGAL and uNGAL/Cr ratio—biomarkers for renal scars in VUR patients

Parmaksız, 2016	Prospective case-control study Patients with VUR were divided as follows: A: VUR with renal scarring; B: VUR without renal scarring; C: renal scarring and remitted VUR; D: without renal scarring or remitted VUR; E healthy patients.	uNGAL, KIM-1, and L-FABP in RN	123 children with primary VUR 30 healthy controls Group A: 8.3 ± 2.6 years old Group B: 9.2 ± 3.2 years old Group C: 9.7 ± 3.2 years old Group D: 10.6 ± 2.9 years old Group E: 9.5 ± 2.9 years old	Significantly higher uNGAL and uNGAL/Cr ratio in patients with renal scars KIM-1/uCr ratio similar in all five study groups No significant differences in KIM-1 or L-FABP between mild/moderate and severe VUR	The kidneys of small children have the capacity to produce high levels of NGAL. There was lower specificity and sensitivity in children.	uNGAL—non-invasive predictive biomarker for renal scars in RN uNGAL is more sensitive than uKIM-1 and uL-FABP in predicting renal scars.
Naik, 2022	Cross-sectional observational study	uNGAL and KIM-1 in VUR and renal scars	94 patients with VUR 0–16 years old	Significantly higher uNGAL in patients with renal scars Low prognostic value of uKIM-1 and uKIM-1/uCr in patients with renal scars	None	uNGAL predicts renal scars in primary VUR.
Anand, 2021	Prospective case control study	TFFs, uNGAL, and microalbuminuria in CAKUT patients	18 children with VUR 20 age-matched healthy controls 0–14 years old	Significantly higher TFFs, uNGAL, and microalbumin in patients with CAKUT	None	uNGAL—the strongest predictor of functional deterioration in RN
Eskandarifar, 2023	Prospective cohort study	uNGAL in VUR and renal scars	92 children with VUR (grades 2 to 5) 40 with renal scars 52 without renal scars 3–60 months old	Significantly higher uNGAL in patients with renal scars	Not a good test for screening or early diagnosis due to its low sensitivity	uNGAL—strong predictor of renal scars in primary VUR

VCUG—voiding cystourethrograms; VUR—vesicoureteral reflux; UTI—urinary tract infection; CKD—chronic kidney disease; uNGAL—urine neutrophil gelatinase-associated lipocalin; uCr—urinary creatinine; uNGAL/uCr ratio—urine neutrophil gelatinase-associated lipocalin/urinary creatinine ratio; TFFs—trefoil family factor, small children (less than 3 years); uL-FABP—liver-type fatty-acid-binding protein; uKIM-1—urinary kidney injury molecule 1; CAKUT—congenital anomalies of kidney and urinary tract; KIM-1/uCr ratio—urinary kidney injury molecule 1/urinary creatinine ratio.

II.1.1.4 Results

The voiding urethrocistography (VUCG) performed after the urine became sterile discovered a urinary bladder with a discrete abnormal shape and VUR grade V on the right kidney and grade III in the left, with an apparently normal urethra (Fig. 2.1).

Cystoscopy was performed to exclude a posterior urethral valve, but it revealed normal detrusor and trigone, large ureteral orifices, a reflux site, and a normal posterior urethra.

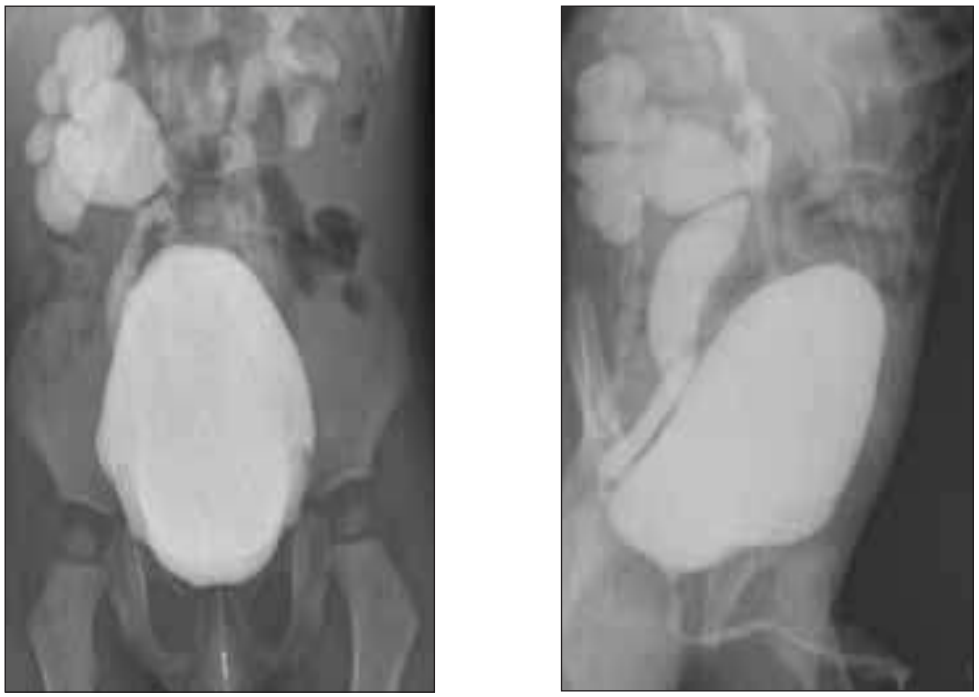


Fig. 2.1 *Uretrocistography: VUR grade V right kidney and III left kidney*

In these circumstances, we established the diagnosis of acute pyelonephritis on a severe bilateral primary VUR with the onset of acute renal failure. The small age initially imposed a conservative treatment with continuous antibiotic prophylaxis and follow-up, according to the inter-national protocols (1). Relapses of UTI despite antibiotic prophylaxis and the persistence of high-degree VUR (control VUCG) determined the surgical correction at 1 year of age (bilateral uretero-vesical reimplantation Cohen). After surgery, he developed a new episode of acute renal failure, possibly caused by postop edema and an UTI. After the antibiotic treatment and hydration, the renal function normalized in 2 weeks. The prophylactic anti-biotherapy was restarted with nitrofurantoin, and the infection did not relapse. The VUCG performed six months after surgery revealed remission of VUR, and the antibiotic prophylaxis was stopped. The follow-up did not detect a UTI relapse. A technetium-99m-labeled dimercaptosuccinic acid (DMSA) scan revealed the right kidney with deformed outlines at the upper pole and multiple hypoactive areas (6.7/4.5/3.4 cm), split function 62.5%, and the left kidney with global volume contraction (5.5/3.7/3.1 cm), differential renal function 37.5% (Fig. 2.2). These data suggest pyelonephritic scarring on the right side and possible congenital scarring (vo-lumen contraction) at the left kidney. At the last control at 4 years of age, the blood pressure was normal, the urine culture was negative, and the creatinine clearance was 66 ml/min/1.73 m2. Renal ultrasound revealed ureterohydronephrosis grade III on the right side. We consider these to be residual aspects. The child was discharged with the recommendation of constant follow-up in our clinic at a 6-month interval (blood pressure, serum creatinine level, urinalysis) or immediate if fever or urinary symptoms occur.

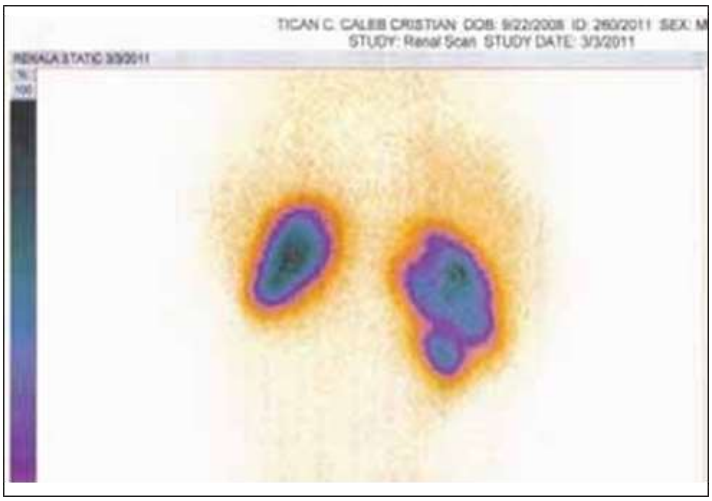


Fig. 2.2. *DMSA scan*

II.1.1.5 Discussion

Both plasma NGAL (pNGAL) and uNGAL are markers of kidney injury. While raised levels of pNGAL are indicative of systemic inflammation, significant increases in uNGAL are seen in conditions involving the urinary tract (Kovacevic, 2020).

Nishida et al. (Nishida, 2010) also demonstrated the superiority of uNGAL over pNGAL as a biomarker of the progression to CKD. The etiological factors recognized in CKD in children are dominated by CAKUT and hereditary nephropathies, which are responsible for two thirds of all cases of CKD in developed countries, as shown by current reports from the United States (Chua, 2019), Italy (Ardissino, 2003), Belgium (Hiep, 2010), France (Deleau, 1994), and Sweden (Esbjörner, 1997).

A reduction in the number of nephrons associated with intrauterine growth restriction and pediatric obesity are additional risk factors for the evolution of CKD in children. Uwaezuoke reported the role of biomarkers as predictors of the onset of CKD and the risk of progression, such as in NS, chronic pyelonephritis, congenital obstructive nephropathy, and diabetic nephropathy (Uwaezuoke, 2018).

Primary Vesicoureteral Reflux in Children—Focus on Genetics

VUR is the most common congenital anomaly of the kidney and urinary tract and is a major risk factor for pyelonephritic scars and CKD in children. The global incidence of VUR is estimated to be 10% in the general population. Since the 2000s, Feather has published the results of the first genome-wide search for VUR and RN using the GENEHUNTER program. VUR maps to a locus on chromosome 1p13 and 2q37 under autosomal dominant inheritance (Feather, 2000). VUR has been described with a prevalence of 27–51% in siblings of patients with VUR, and a 66% rate of VUR has been observed in children whose parents had reflux (Soni, 2010). However, it is known that VUR can resolve spontaneously in the first 3 years of life; therefore, the exact prevalence in family members could be underestimated.

Neutrophil Gelatinase-Associated Lipocalin—Current Knowledge

NGAL is a 25 kDa protein belonging to the lipocalin superfamily. Initially found in activated neutrophils, it can be produced in kidney tubular cells in response to various injuries. uNGAL has been proposed to be an early predictor of AKI. Both pNGAL and uNGAL have been studied in relation to kidney injury. Nickolas et al. reported the first study of urinary NGAL in adults admitted to emergency departments and demonstrated that uNGAL has a good predictive capability for intrinsic AKI. This study also suggested that NGAL could be useful as a predictive marker for adverse clinical outcomes such as the need for dialysis and admission to the ICU (Nickolas, 2008). There is a distinct difference between uNGAL, which is specific to injured epithelial cells of the distal nephron, and pNGAL, which results from tubular reabsorption from the injured kidney as well as from organs that ultimately crosstalk with the kidney (Shapiro, 2010). Urinary tract infections are one of the trademarks of subjacent malformations. In this sense, the role of NGAL in pediatric UTIs had to be determined.

The Diagnostic Value of uNGAL in Children with Primary VUR

Depending on the severity of a kidney injury, increased NGAL production and de- creased NGAL reabsorption may occur in patients with renal tubular damage. uNGAL has already proven its validity as a biomarker for the diagnosis of children with acute UTI and for steroid responses in idiopathic NS or in children with different urologic conditions (Amiri, 2021, Ichino, 2010). Nickavar et al. (Nickavar, 2020) recognized the diagnostic role of uNGAL in patients with primary VUR and demonstrated in a prospective case control study of 69 small children (2–3 years old) the accuracy of uNGAL/uCr for VUR diagnosis, demonstrating high specificity, sensitivity, and accuracy. Therefore, imaging exploration (e.g., scintigraphy) might not be compulsory for VUR management in children with low uNGAL. However, there was no correlation between uNGAL and the severity of VUR. In a recent study, Amiri et al. (Amiri, 2020) also found higher levels of uNGAL in VUR patients vs. control and higher but not significant levels of uNGAL in the severe compared to mild/moderate forms of VUR as well as in bilateral vs. unilateral involvement. However, when adjusting for uCr, significant differences in the uNGAL/uCr ratio between study groups (patients and controls) and between the patient subgroups, according to the severity of the disease, have been found. No significant differences were found for uNGAL and the uNGAL/uCr ratios between the patients with and without renal scars. This means that uNGAL could not predict RN and could only predict the severity of VUR. In a similar sample (71 children aged 1–5 years), Eskandarifar et al. (Eskandarifar, 2021) confirmed significant differences between the uN- GAL levels and the uNGAL/uCr ratios in the VUR group compared with a healthy group. Furthermore, contrary to Nickavar(Nickavar, 2020) and Amiri (Amiri, 2020) they detected a significant correlation between uNGAL and the VUR grade. Thus, these authors, referring specifically to the diagnostic role of NGAL in VUR (with no attempt to describe the predictive value for renal scars), reinforced that VCUGs should not be routinely performed in small children after a first febrile UTI, as long as the NGAL/Cr ratio can help, at least in the preliminary stages of VUR management. As there are disagreements regarding the relation to the severity of VUR, the role of uNGAL in predicting the severity of reflux is not well established.

NGAL as a Predictive Tool for Renal Scarring and RN

Four original studies aimed specifically to assess the predictive value of uNGAL for the development of RN after they had already demonstrated the significant relationship between increased uNGAL and VUR (Anand, 2021, Parmaksız, 2016, Naik, 2022, Eskandarifar, 2023). Unlike uNGAL, uKIM-1 and uKIM-1/Cr were not able to predict renal scar formation. Anand et al. (Anand, 2021) underlined the importance of NGAL in predicting the functional deterioration associated with VUR. They studied uNGAL (among three other biomarkers: trefoil family factors (TFF 1 and 3) and microalbuminuria), in a sample of 50 children with congenital anomalies of the kidney and urinary tract (of which 18 had primary VUR). Their main outcome was a progressive decline in renal function (a decrease in GFR from 60 to <60 mL/min/1.73 m^2 and/or new-onset kidney scars or the growth of previous scars on DMSA scans. uNGAL proved to be an accurate biomarker for the progression of CKD: the median concentrations of NGAL were significantly higher in children with the progressive deterioration of kidney function.

NGAL—Predictive Tool for CKD Progression in Children

CKD involves irreversible structural and/or functional damage to the kidneys, with evolutionary potential and an evolution longer than 3 months. It is usually accompanied by albuminuria and histopathological and imaging changes characteristic of its etiological type (Kovesdy, 2022). Currently, the traditional markers used for the diagnosis of CKD, i.e., creatinine, urea, GFR, albuminuria, and proteinuria, do not have a high sensitivity (Acute Kidney Injury Work Group, 2012). Although albuminuria and proteinuria are important parameters for the assessment of the CKD status in adults, they are not always applicable in pediatric practice. In accordance with the 2012 KDIGO guideline (Furth, 2018) the range of values for albuminuria in children is the same as in adults, but these criteria are not useful in children under 2 years of age due to renal immaturity and protein reabsorption in the proximal convoluted tubule compared to adults (Bolignano, 2009). In addition, CKD in children is often due to congenital abnormalities associated with the tubular loss of albumin; therefore, albuminuria is a less sensitive renal marker in this category of patients (Alderson, 2016). Individual biological variations in urinary NGAL have a wide range of values. However, more attention should be paid to the biological variations in both urinary and systemic NGAL. These practical issues pose great challenges for the standardization of NGAL testing (Ning, 2018). These results illustrate that urinary NGAL is a useful biomarker for risk classification and the prediction of clinical outcomes in CKD patients. In this context, uNGAL may be the promising marker of renal function in this patient population. We tried to summarize the advantages and limitations of using uNGAL in primary VUR in children in Table 2.2. The next years of cost-effectiveness research in the use of biomarkers in the early diagnosis of kidney diseases are likely decisive. There are already studies evaluating the usefulness of new biomarkers since 2012, when KDIGO recommended them for the early diagnosis, differential diagnosis, and prognosis of kidney diseases, especially AKI. As such, more detailed models that closely reproduce the progression of AKI and/or CKD would greatly help to evaluate the profitability of new diagnostic and surveillance technologies in the field of renal pathology.

Table 2.2*.The advantages and limitations of the assay of uNGAL in primary VUR in children.*

	The Advantages	**The Limitations**
uNGAL	Biologically stable, resistant to degradation, and useful for collecting urine samples from small children Non-invasive predictive biomarker for renal scars in RN More sensitive than uKIM-1 and uL-FABP in predicting renal scars The strongest predictor of the functional deterioration of the kidney in RN Useful marker for the diagnosis of early CKD (stages 1–3) uNGAL/uCr ratio—better accuracy, high specificity, and high sensitivity compared to uNGAL alone in primary VUR Further imaging studies are not necessary if uNGAL is decreased.	Cannot replace VCUG for VUR diagnosis Small kidneys lack sufficient renal tubular cells with the residual regenerative capacity to produce high levels of NGAL, so specificity and sensitivity are lower in small children. A wide range of values due to individual biological variations No significant differences in uNGAL between the lower and higher grades of VUR The high cost

VCUG—voiding cystourethrograms; VUR—vesicoureteral reflux; CKD—chronic kidney disease; uNGAL—urine neutrophil gelatinase-associated lipocalin; uNGAL/uCr ratio—urine neutrophil gelatinase-associated lipocalin/urinary creatinine ratio; uL-FABP—liver-type fatty-acid-binding protein; uKIM-1—urinary kidney injury molecule 1.

II.1.1.6 Conclusions

There have been some studies dedicated to the role of uNGAL in primary VUR management in children, outside the association with a concomitant UTI. From our analysis of the available original studies, there is no doubt that uNGAL is an accurate and reliable biomarker, not only for UTIs but also for primary VUR. It also shows a good predictive ability for RN and its progression to CKD, as it was proven to be associated with renal scars. The severity of VUR was not clearly demonstrated to be linked with increased uNGAL, as the results were contradictory. uNGAL is better than uKIM in predicting renal scarring when assessed alone. The NGAL concentration reflects the progressive activity of kidney damage during CKD. In several studies, by demonstrating a correlation between uNGAL and VUR, irrespective of the severity of the reflux, it was suggested that the monitoring of uNGAL will help to establish the opportunity for surgical management. Consequently, imaging studies might become unnecessary for the diagnosis of VUR in children with low uNGAL excretion. uNGAL/uCr is superior to other biomarkers such as uKIM-1/uCr in predicting renal scars and VUR. However, additional multi-center studies in larger pediatric populations are

needed in order to confirm the potential application of uNGAL for the diagnosis and management of patients with VUR and kidney damage.

II.2 Malformative uropathies - major cause of CKD

Antenatal ultrasound is one of the main modern methods of screening of renal and urinary malformations and ap-propriate use in our country as a method of screening all pregnant women. Malformative uropathies represent a major cause of CKD in children. The genitourinary system is the most frequently and severely affected in Prune-Belly syndrome and in posterior urethral valve. That is why the findings of early diagnosis and vigilant monitoring in these situations remain a major challenge for the medical team.

II.2 Long term follow-up in a patient with Prune-Belly syndrome

Posterior Urethral Valve, Part Of Congenital Obstructive Uropathies; Prognostic Factors In Long Term Follow Up.

Protocol For Postnatal Management of Antenatal Hydronephrosis Diagnosed Children

Prune-Belly Syndrome (PBS), also known as Eagle-Barrett syndrome or triad syndrome, is a rare congenital disorder with a wide spectrum of severity consisting of abdominal wall defects, urinary tract malformations and bilateral intra-abdominal testes, associated with pulmonary, cardiovascular and musculoskeletal malformations (Seidel, 2015, Gupta, 2016, Yalcinkaya, 2017). Nearly 10% to 25% of newborn infants die in the perinatal period (Zugor, 2012). The male predominance is overwhelming (95%) and unexplained (Duicu, 2018). Diagnosis is performed through prenatal ultrasound, in the second trimester sometimes as early as 12 weeks, depending on the severity of the urinary tract obstruction and oligohydramnios and last but not least influenced by other factors like examiner experience (Yalcinkaya, 2017). Skeletal involvement is less common (30–40%) (mainly vertebral defects and dysplastic hip), while anomalies of the gastrointestinal tract (20–30%) and, more rarely, heart malformations (10%) can be seen (Seidel, 2015, Yalcinkaya, 2017, Duicu, 2018). The mainstay therapy is surgical decompression of the upper urinary tract through ureterostomies or vesicostomy (Seidel, 2015, Gupta, 2016).

The posterior urethral valves (PUV) are the leading cause of lower urinary tract obstruction in male children as a 1 in 8000 – 25000 live births (Nasir, 2011). The severity spectrum and the clinical presentation are variable. Severe forms are presented with urinary tract abnormalities; a few are life- threatening condition in neonatal period. Many of these patients have long-term complications regarding urinary continence and impaired kidney function even under a correct and continuous management. It is known that 25- 40% of cases develop CKD at different ages (El-Ghoneimi, 1999). The causes of renal injury in PUV are: associated irreversible dysplasia, respectively persistent obstructive aeropathy, scars after repeated/recurrent UTI and detrusor dysfunction that can be influenced by early and correct medical-surgical treatment.

Hydronephrosis is the most common urinary abnormality detected antenatally. Management strategy in children with urinary tract abnormalities has changed considerably, as a result of the development of equipment and techniques for the assessment of fetal details (Nguyen, 2015). Post- natal management goal is to identify early and treat patients whose renal function is endangered, while patients with low risk of renal damage will be followed conservatively (Barbosa, 2012). This management involves a spectrum of radio- logical interventions, medical and surgical diagnosis, monitoring and treatment.

Aim

I present the clinical course of a 10-year-old child with the diagnosis of Prune-Belly syndrome. A urinary tract abnormality was suspected at 25 weeks of gestation when a routine ultrasound showed oligohydramnios, an increased urinary bladder size, bilateral hydronephrosis, megaureters, and a thin abdominal wall. I also want to present the evolution of children operated on for the posterior urethral valve and their follow-up in our department. In the last part of this section, I want to demonstrate the importance of antenatal diagnosis of urinary tract malformations for the future of the child affected, with an emphasis on hydronephrosis.

II.2.1 Material and method

Case presentation: 10 year old boy admitted in Pediatric Nephrology Department for the first time at age 3 days with suspicion of PBS. The baby came from healthy parents, without any known medical family history, like genetic disease or kidney abnormalities. A renal malformation was suspected starting 25 weeks of gestation, when a routine ultrasound showed oligohydramnios, increased size urinary bladder, bilateral hydro- nephrosis and megaureters, thin abdominal wall (Fig. 2.3A). Because of fetal distress, labor was induced at 32 weeks, APGAR scores were 5 at 1 minute and 8 at 5 minutes, birth weight 2200 grams. Clinical examination showed: mild respiratory distress syndrome, absence of anterior musculature of the abdominal wall, loose and crinkled skin while urine was expressed through an orifice below the umbilicus. The scrotum was hypoplastic and the testes were absent.

Based on these data a diagnosis of PBS was established. This was confirmed by a renal ultrasound showing bilateral grade III hydronephrosis and megaureters. The bladder was empty and the juxtaposed ureters were clearly visible suggesting an obstruction at this level. Due to the medium grade hydronephrosis and the persistence of a renal function (albeit decreased) we supposed the existence of a persistent urachus. We failed to catheterize the urethra but we succeeded to place a temporary catheter into the urachus in the 5th day of life, which expressed urine. Two weeks later, the catheter was used for a retrograde injection of an iodine-based contrast (Fig. 2.3B) that showed bilateral high grade reflux into the dilated ureters and hydronephrotic kidneys. A small amount of contrast entered the bladder suggesting that the ureteral obstruction was not complete. Antibiotic prophylaxis was started. The urachus drain was left in place until the age of 6 weeks, when a bilateral ureterostomy was performed. Soon after the surgical intervention, upon the placement of the ureteral catheters the left stomy yielded grossly cloudy urine and the child became febrile. The culture grew Pseudomonas maltophila.

The clinical examination also showed bilateral hip displacement, confirmed by ultrasonography. The renal ultrasound showed bilateral moderate hydronephrosis, left kidney of 32 mm in length, hyperechoic cortex, right kidney of 37 mm, normal cortex, and decreased 152arenchymal index on both sides. The ureters had a maximal diameter of 12 to 14 mm on both sides. The urinary bladder was empty.

Bloodwork showed leukocytosis (16.000/mm3) with neutrophilia predominance (70%), increased CRP (12 mg/dl – cut-off 0.8 mg/dl), elevated urea (78 mg/dl, cut-off 40 mg/dl) and creatinine (0.99 mg/dl, cut-off for age – 0.4 mg/dl), metabolic acidosis, severe normocytic, normochromic anemia (Hb= 6.8 g/dl, Ht= 20.4%). We interpreted the case as left kidney pyonephrosis with secondary anemia and Ceftriaxone treatment was started. Baby was transfused with packed red blood cells (RBCs) typed and cross-matched. He was later switched to Meropenem according to the antibiogram. The immediate outcome was favorable. The creatinine stabilized at 0.6 mg/dl, showing the development of CKD. The metabolic acidosis required constant NaHCO3 administration for appropriate correction. The child was put on chronic antibiotic prophylaxis.

Long-term 5 year follow-up revealed recurrent nonfebrile urinary tract infections (UTIs) and a decrease in the left ureter urine output. Clinical examination showed moderate dextroconvex dorsolumbar scoliosis, pectus excavatum, distended abdomen, with visible peristalsis and palpable kidney in the right flank. Ureterostomies looked normal, no signs of inflammation. Leg length asymmetry was observed. Blood work established a second degree CKD, without proteinuria. Chronic, intermittent erythropoietin (EPO) admin- istration had been necessary to maintain a normal level of Hb. Compensated metabolic acidosis persisted despite oral NaHCO3 therapy.

Renal ultrasound yielded a small left kidney (4 cm in length), with severely decreased parenchymal index; the right kidney was 5.8 cm in length with grade II hydronephrosis. Both ureters remained dilated, with diameters ranging between 8 and 12 mm. The reduced size of the left kidney and the decreased urine output on the same side led to the need to evaluate renal excretion. We used a dynamic renal scintigraphy with Tc-99m DTPA (diethylene-triamine-pentaacetate) (Fig. 2.3C). This showed no glomerular function on the left side. The right side showed no obstruction, but there was significant pooling in the right ureter. Pelvis and inferior limb X-rays showed asymmetrical femoral diaphysis secondary to bilateral hip arthroplasty, which had been performed at ages 1 and 3 years.

At the age of 10 years he is a well-adapted child. Ureterostomy is still in place (Fig. 2.3D); he had no corrective surgery for the abdominal wall defect. Unilateral left orchidopexy and right orchiectomy have been performed.

He has had fewer than 3 UTIs per year, all of them without fever while on antibiotic prophylaxis. Blood pressure is within the normal range. His renal function is stable (eGFR 62 ml/1.73m2/min). Hb levels have been stable for the last 6 months, but EPO analogues were needed. Renal ultrasound shows an 8.1 cm right kidney, with grade 2 hydro- nephrosis, normal parenchymal index, and a 4 cm left kidney with decreased parenchymal index. His current medication consist just of oral NaHCO3 8.4% 4 ml qid. We envisage a cystoscopy and ureteral reimplantation and a conservative management of his CKD.

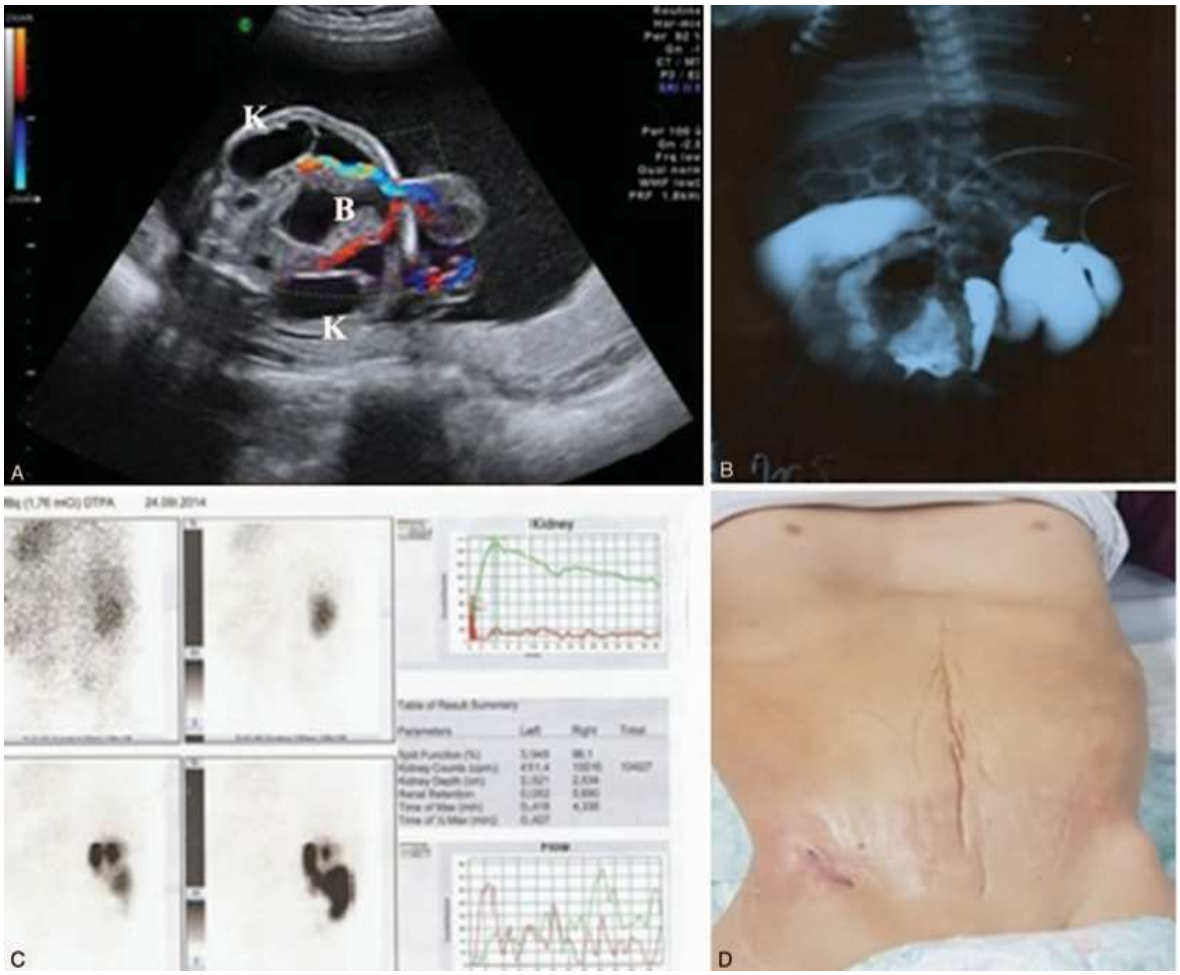


Fig. 2.3 *A. Prenatal ultrasonography showing an enlarged bladder (B), dilated ureters and hydronephrosis, kidneys with reduced parenchymal thickness (K); B. Voiding cystography: contrast agent introduced trough the uracha into the bladder showing high degree bilateral vesicoureteral reflux (IV grade); C. Dynamic renal scintigraphy 99mTc-DTPA showing no glomerular function on the left side, the right side: no obstruction but with significant pooling in the right ureter; D. Photo of the patient at age of 10 showing the abdominal wall defect and right iliac fossa ureterostomy opening.*

PUV: Retrospective analysis of observation records of 18 children who were diagnosed and treated for the posterior urethral valve at Pediatric Nephrology and the Pediatric Surgery Division "St. Mary" Children's Hospital Iasi during 2004-2014. We followed: the clinical presentation; main complain at diagnosis, age at diagnosis, recurrences of urinary tract infection (UTI), association with vesicoureteral reflux (VUR), association with dysuria, serum creatinine level (at diagnosis, the minimum value in the first year after surgery and at the end of follow-up). We studied the association of above mentioned parameters with the level of impairment of renal function. The patients were classified based on the creatinine clearance calculated by the Schwarz formula, in stages III (GFR: 60-30 ml / min / 1.73 sqm), stage IV (GFR: 30-15 ml / min / 1, 73 sqm) and V (GFR < 15 ml / min / 1.73 sqm) of CKD at the end of follow-up.

Hydronephrosis: We conducted a retrospective study on 140 cases of children with antenatal hydronephro- sis hospitalized in the Pediatrics - Nephrology Department of Emergency Clinical Hospital for Children St. Mary, Iasi, in the period 2010 - 2014. We analyzed age, first presentation, postnatal diagnosis, sequences applied investigations, use of antibiotic prophylaxis, the need for surgery. Postnatal investigations were: ultrasonography, voiding cystourethrogram, Tc^{99}DTPA dynamic scintigraphy with furosemide test, URO - MRI, intravenous urography, cystoscopy.

II.2.2 Results

PUV: The series includes 18 boys aged between 4 days and 3 years at diagnosis, followed by 6 to 120 months. All patients received primary endoscopic resection of the valve except in one case where initially vesicostomy was performed and after 2 months the resection.

At diagnosis creatinine was increased > 1 mg% in all patient at diagnosis, except for one, and at the end of follow-up 5 patients (27.7%) had stage III CKD or greater, of whom 2 patients (11.1%) entered the extra renal dialysis and 1 (5%) before starting dialysis. Severe VUR was noted in 12 cases (66%) bilateral in 7 of 12 cases. Recurrent UTI were present in 13 of 18 cases (72%). Micturition dysfunction was identified clinically and by ultrasound in 9 of 18 cases (50%).

The age at diagnosis shows that 38.9% of patients were diagnosed in the neonatal and infant period, 27.8% were diagnosed between 1 and 2 years, and 33.3% after the age of 2 years, results that attest to a late diagnosis.

By analyzing the average age at diagnosis differentiated for the years of the studied period (Fig. 2.4) it is noted the improvement in diagnosis after 2010; so in 2014 the average age of diagnosis was 0.9 months. These data reflect the improvement the early diagnosis in the recent period. Age at presentation: in 61% of patients were diagnosed after having at least one episode of UTI and only 27.8% of cases by evaluation of antenatal hydronephrosis (ANH).

By analyzing the way of clinical presentation separately for the years studied (Fig. 2.5) there is a sharp increase in cases of PUV that are diagnosed after investigating newborns with ANH. This tendency towards early diagnosis is probably also due to the increase number of pregnancies that benefit from antenatal echographia with the more frequent detection of antenatal hydronephrosis. Results are close to literature data which reveals that in the last 20 years antenatal ultrasound identification has become predominant in developed countries (Roth, 2001).

Analysis of postoperative serum creatinine indicates a significant association of its increased value with the advanced stages of CKD at the end of follow-up. (Fig. 2.6). Multivariate analysis indicated that the prognostic factors for CKD severity were increased creatinine (HR = 5.1), post-diagnosis UTI number (HR = 4.8), VUR (HR = 4.5), urinary dysfunction (HR = 2.6), and old age at diagnosis (HR = 3.46) (Table 2.3).

The literature indicates as predictive factor the plasma renin activity, increased in children with obstructive nephropathy secondary PUV, but the assessment was not accessible to this series of patients (Bhadoo, 2014).

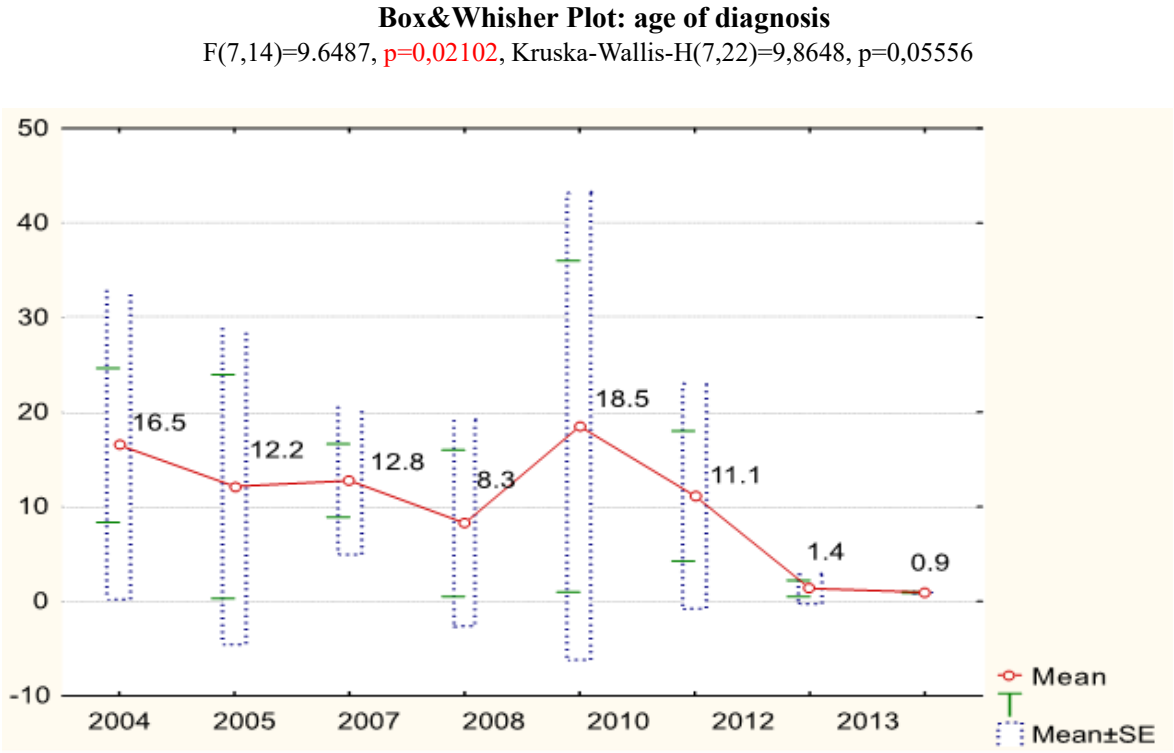


***Fig. 2.4. PUV**: Age at diagnosis in the studied period*

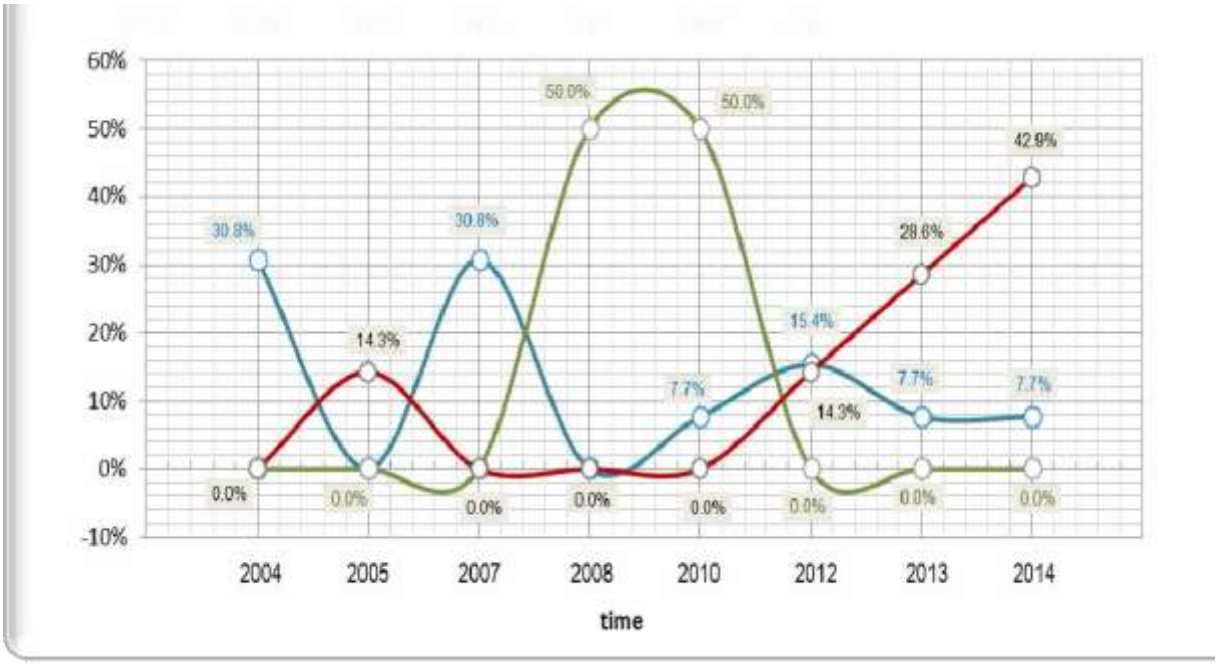


Fig. 2.5 Ways of presentation depending on the period studied Red – AHN, green – urinary ascites, blue – UTI

Box&Whisher Plot: age of diagnosis
F(4,13)=5,1755, p=0,0102, Kruska-Wallis H(4,18)=12,0699, p=0,0168

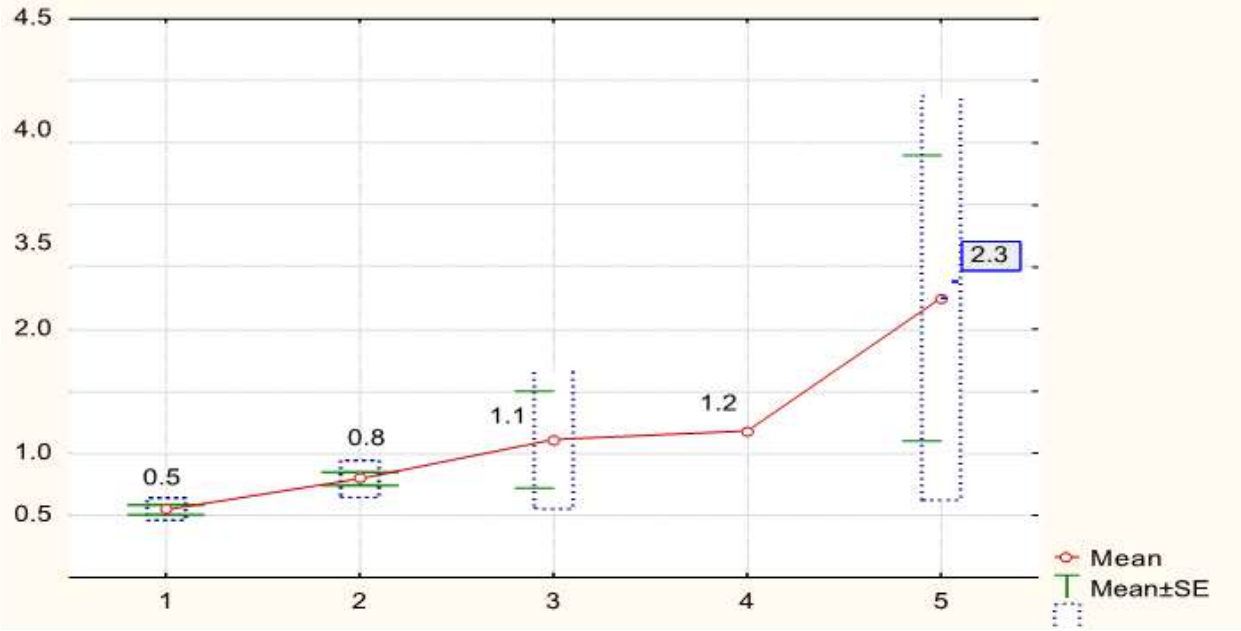


***Fig. 2.6**.PUV: Relationship between postoperative serum creatinine – CKD stage at the end follow-up*

***Table 2.3** Multivariate analysis*

MULTIVARIATE ANALYSIS	Beta	SE	Wald	Sig. p	Hazard Ratio Exp(β)	95% CI for Exp(B) Lower	Upper
Increased creatine	5.002	0.047	11.57	0.001	**5.147**	2.987	6.987
Post-diagnosis UTI number	4.871	0.024	9.846	0.002	**4.806**	2.241	5.091
VUR	4.969	0.256	7.817	0.034	**4.548**	1.946	6.724
urinary dysfunction	1.568	0.155	5.681	0.021	**2.645**	1.987	3.541
old age at diagnosis	5.871	0.241	6.884	0.037	**3.461**	1.764	5.975
ways of clinical presentation	1.664	0.367	1.578	0.069	1.576	0.579	2.564

χ^2 statistical test = 5.691 (the degree of fit of the model); df = 5; p = 0.0178; 95%CI.

CI – confidence interval, df- degrees of freedom , HR- hazard rate (risk ratio), SE- standard error

Hydronephrosis: This current study was done in our clinic in patients who was carried out for: evaluation in 85% of cases, and for first urinary tract infection in 15% of cases. The study group consisted of 2/3 boys and 1/3 girls, average age at first presentation in the clinic - 2 months (see Table 2.4). 38% of patients were diagnosed last year, 75% of who were from urban areas (higher pregnancy surveillance in the big cities).

Table 2.4 *Distribution of children with hydronephrosis ante- and posnatal diagnosed*

		Antenatal diagnosis group	Postnatal diagnosed group
Patients number		38	102
Boys:Girls		2:0.4	2:1
The mean follow		29.03 months	39.83 months
Hydronephrosis degree	I II III IV	2 patients 4 patients 11 patients 21 patients	5 patients 20 patients 26 patients 51 patients
Urinary tract infection at first presentation in clinic		12 patients	45 patients

Student's t-test showed no statistical differences between the two sub- groups of the postnatal initial ultrasound hydronephrosis grade (p = 0.4, CI 95%), the duration of follow-up (p = 0.5, 95% CI).

All children received ultrasound evaluation, 75% of them were evaluated by voiding cystography. In 80% of cases isolated malformations were noted, while the rest had presented complex abnormalities.

- *Ureteropelvic junction obstruction (UPJ) - the most frequent abnormality diagnosed (40% cases)*
- *Vesicoureteral reflux (30% cases)*
- *Ureterovesical junction (UVJ) obstruction (15% cases)*
- *Multicystic renal dysplasia (6% cases)*
- *Renal agenesis isolated or associated with multicystic dysplasis (4% cases)*
- *PUV in 3% of the cases,*
- *Ureterocele in 2% of cases.*

Dynamic scintigraphy with ^{99}Tc DTPA was practiced to 25% of patients. Indications was uropelvic junction obstruction, uretero-vesical junction obstruction, vesicoureteral reflux. In 55 patients (40%) was practiced intravenous urography, and in 6 cases was performed pyelography. 16% of patients required corrective surgery for lower urinary tract obstruction (10% cases) or Ureteropelvic junction obstruction (6% cases).

3 patients with V th degrees VUR who had many infections with prophylactic therapy required surgery. Of the 42 patients with primary VUR only 25 could perform voiding cystography control, and we proved reflux remission in 10 cases.

57 patients (40.7%) experienced at least one episode of UTI. The incidence of infectious recurrences with resistant germ was higher in patients with complex malformations and combined treatments, medical and surgical. Antibiotic prophylaxis was

recommended at half patients, and was taken correctly by 26% of them. Infectious recurrences at patients with antibiotiC prophylaxis were registered under the 5% of patients.

II.2.3 Discussion

PBS: Urinary tract abnormalities require multidisciplinary approach regarding the diagnosis, treatment and prognosis (Duicu, 2018, Sur, 2018, Fufezan, 2013). PBS can be a life-threatening disease, especially when the urethral atresia is not compensated by a patent urachus, thus leading to oligohydramnios and pulmonary hypoplasia. The latter variants the most severe (grade 1). Grade 2 comprises the classic triad and minimal unilateral renal dysplasia, whereas cases that do not meet the triad are considered grade 3. The increased abdominal wall pressure, due to the enlargement of the urinary tract is seen as a probable cause for the abdominal muscle hypoplasia (Hassett, 2012). This pathogenic theory also regards the massively distended bladder as a potential cause that hinders the descent of the testes, thus causing cryptorchidy. Another pathogenic theory suggests a developmental mesodermal defect between weeks 6 to 10 of gestation. This leads to aberrant formation of the urinary tract and anterior abdominal wall (Hassett, 2012). Diagnosis is usually made antenatally, through uterine ultrasound. Anatomical information regarding ureters and bladder can be obtained using a voiding cystourethrogram (VCUG), with contrast injected through any type of urine outlet or intravenous pyelogram or if possible, better with abdominal contrast MRI.

Kidney function can be monitored by estimating glomerular filtration rate (GFR) and renal Tc-99m DTPA excretion scintigraphy. Our case presents the classic triad of PBS and the common association of orthopedic malformations. Amnioinfusion may be a treatment option, but it should be performed just in centers specialized in invasive fetal medicine (Sarhan, 2013). Because of fetal distress labor was induced at 32 weeks, with mild respiratory distress syndrome. We regarded this as the best option for fetal distress management and for early decompression of the upper urinary tract through bilateral ureterostomy.

Literature data suggests in utero placement of a vesicoamniotic shunt as a possible decompression solution (Hassett, 2012, Galati, 2008). This was unavailable at the time in our center and the procedure is known to have an important infectious risk. Antenatal corticosteroid therapy was given for reducing well-known neonatal consequences associated with early birth, like respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis and perinatal death. PBS is a clinical entity with a broad spectrum of severity; around 25% of newborns die within the perinatal period, and nearly 25% to 30% of those affected by PBS go on to develop CKD of ranging grades outside the postnatal period (Seidel , 2015, Yalcinkaya, 2017). Long term follow-up showed a relatively slow decline in the eGFR in our child. According to recent data, in case of unfavorable evolution to ESRD KRT should be offered to all PBS patients until renal transplantation, which appears to be a treatment option in 15% of PBS children (Yalcinkaya, 2017). Transplanted patients necessitate a follow-up program in order to avoid severe complications like infections or limphoproliferative disorder (Isac, 2017). Due to the rarity of the condition, there are only a few publications that describe such cases, especially regarding the long-term follow-up. We did not find any publication regarding early induced labor as a viable alternative to slow CKD progression in PBS. Prenatal diagnosis of PBS plays a deciding role in renal disease

progression. Induced preterm labor could prove beneficial for early upper urinary tract decompression through faster access to surgery, especially when vesicoureteral shunt placement is not available. Our patient is one of the few follow-up cases reported in our country population. The long-term follow-up showed a well conserved GFR due to the interdisciplinary approach.

PUV: The literature indicates as predictive factor the plasma renin activity, increased in children with obstructive nephropathy secondary PUV, but the assessment was not accessible to this series of patients (Divya Bhadoo, 2014).

The literature reveals that the minimum value of creatinine in the first year after valve resection (≤0.8 mg / dL) correlates with good long-term renal function (Deshpande, 2018). Other studies have found creatinine threshold value of ≤ 1 mg / dL (Sarhan, 2010). In patients who presented more than 3 recurrent UTIs, it was noted a significant association with the evolution to CKD stages III-V ($p = 0.00224$ - Spearman Rank R). The presence of severe bilateral VUR was significantly associated with CKD stages III-V (Chi-square = 19.25, $p = 0.032103$). The role of reflux in PUV is debatable. Some authors consider that bilateral IV-th and V-th grade VUR correlates significantly with the prognosis (Bingham, 2021). Analysis of the presence of micturition dysfunction showed a significant association with CKD stages III – V (Chi-square = 8.45, $p = 0.016777$).

The patterns of micturition dysfunction described in children with VUP are diverse and changes over time: in infants it is characterized by low compliance, after 1 year, bladder instability, and after puberty the muscular insufficiency of the detrusor is noticed. Along with the ultrasound examination (detrusor thickness, post-micturition residue), the assessment of micturition behavior through urodynamic studies is necessary in order to assess the effectiveness of treatment (Alsaywid, 2021, Kim, 2018). In children with severe urinary dysfunction, with recurrent UTI and risk of early deterioration of renal function, the solution of Mitrofanoff vesicostomy and intermittent catheterization is viable. Multiple studies have supported this (Ezel, 2019, Sharma, 2019).

Hydronephrosis: There is controversy in defining, monitoring and therapeutic conduct in antenatal hydronephrosis diagnosed (Braga, 2013). It is difficult to determine which patients require surgical correction, in which time, and which the patients can be followed conservatively. The major goal that must govern is the preservation of kidney function. This sentence is supported by the works of many authors (Braga, 2013, Dias, 2009). No hydronephrosis degree, or impaired renal function and or response to the administration of furosemide at scintigraphy cannot tell which of renal units will degrade (Dias, 2009).

Dynamic scintigraphy with ^{99} Tc DTPA is a very important investigation for children with ureteropelvic junction obstruction, ureterovesical junction obstruction, vesico-ureteral reflux. In our study proved this advantage. Investigations has also the limits who consist in requirement very good hydration of child (because of the anesthesia during examination), renal curves are difficult to obtain in children under 3 years (motion artifacts), immature renal function under 6 months can give false results. This is in consensus with Zanetta and Nguyen In their studies (Nguyen, 2014, Zanetta, 2012). Antibiotic prophylaxis deserves to be considered, especially in cases where the diagnosis was made after the first episode of urinary infection. A review of 4 databases

made by Braga and co showed that antibioprophylaxis is important especially in cases with a hight degree of hydronephrosis, especially if was an UTI in antecedentss (Braga, 2013). The risk of urinary tract infection seems to be heigher in VUR and megaureter, and no so frequent in uropelvic junction obstruction, like in paper of Russu and co. (Russu, 2013).

II.2.4 Conclusions

Prenatal diagnosis of PBS plays a deciding role in renal disease progression. Induced preterm labor could prove beneficial for early upper urinary tract decompression, especially when vesicoureteral shunt placement is not available. Urinary tract infection was the main way of diagnosing VUP, but in recent years the detection by antenatal echography of gravida as well as postnatal evaluation of ANH has increased significantly the early diagnosis. Severe bilateral VUR, the high number of recurrent UTIs and the presence of micturition dysfunction were significantly associated with the advanced stages of CKD. The main unfavorable prognostic factor for CKD was creatinine level in the first postoperative year > 0.8mg%. Children with PUV, including those operated in neonatal age, require long- term follow-up to identify and treat early complications of CKD.

For postnatal diagnosis of antenatal hydronephrosis should follow a clear protocol in order to early detection of clinically significant malformations and adoption of therapeutic attitudes before the onset of complications, but also to avoid unnecessary investigations and treatments. It is necessary correct information to family, pre and post-natal and parental participation in decisions and investigations. A multidisciplinary team (nephrologist, pediatric urologist, radiologist, specialist in nuclear medicine, GP, psychologist) is very necessary to manage these patients.

II.3 UTI in children

Clinical aspects and evolution of urinary tract infection in preterm infants

Urinary tract infection is an important cause of morbidity and mortality in small children. It lies at the basis of about a quarter of reasons for addressing a pediatric practitioner. It is often the clinical expression of obstructive uropathy. UTI (urinary tract infection) is also one of the major causes of HTN and chronic renal failure in adolescents and young adults. A preterm newborn is a child with a gestational age less than 37 weeks and weighing less than 2500 g at birth.

Urinary tract infection in a preterm differs from that in a term baby by prevalence, etiology, clinical presentation and subjacent malformations. The nephrogenesis in this category of children is not complete, therefore any infectious, ischemic or toxic injury could cause kidney agenesis or abnormal development.

In addition to this, in preterm babies, antimicrobial defense barriers are over- come, decreasing cell-mediated immunity, opsonin’s activity, phagocytosis and vitamin A level.

For all these reasons, the incidence of UTI is 4-25% in preterm children, compared with 5.3 - 7,5% for term newborns (Khassawneh, 2022).

II.3.1 Aim

The aim of this study is a comparative analysis of cases of UTI in children 0-3 years old (preterm and term infants) admitted to the IVth Pediatric Clinic – Pediatric Nephrology Department, "Sf. Maria" Hospital for Children Iasi, between January 2007 – December 2011.

II.3.2. Material and method

We performed a retrospective study on a sample of 298 children 0-3 years, hospitalized with urinary tract infection (UTI). The study protocol included:

A. Demographic data: age, sex.
B. Diagnosis of UTI - supported by the presence of positive urine cultures (1-4) in terms of a clinical and biological suggestive aspect (fever, urinary and systemic signs, presence of inflammatory syn- drome, pathological urinalysis, leucocyturia).
C. UTI specific features in preterm infants by: degree of prematurity (birth weight classification: LBW (low birth weight), VLBW (very low birth weight) and ELBW (extremely low birth weight), UTI etiology, comorbidities, evolutional features, responsiveness to treatment and impact of urinary infections on kidney.

Statistical analysis applied in this study was one-dimensional and multivariate model. We applied χ^2 test, sensitivity, specificity, predictive values (PPV and NPV) and efficiency test. Data were processed using statistical functions (SPSS 15). We identified the clinical manifestations associated with UTI, the presence of urinary symptoms, morbidity states in preterm compared with term newborns. Biologically, we assessed the urinalysis urine cultures, leucocyturia, inflammatory syn- drome and CBC (cell blood count). The urine sampling was done by peripheral col- lection methods. We practiced direct microscopic examinations, leukocyte count, urine cultures and counting CFUs (colony forming units).

We defined a positive urine culture the presence of more then 10^5 CFU/mm ^{3} correlated with more than 10 leucocytes /field. We evaluated the response and evolution under first-line antibiotherapy, and after correction, according to the antibiogram. We drew conclusions regarding the sensitivity of different etiologic agents to antibiotics. We analyzed the correlation between reno-urinary tract anomalies and the incidence of UTI in preterm infants by imagistic evaluation (kidney and bladder ultrasound, voiding cystourethrography, and static radionuclide studies with Tc99DMSA).

II.3.3 Results

The study group consisted of 298 children aged 0 to 3 years, with ITU divided into 2 subgroups:

• subgroup 1 – children born at term and
• subgroup 2 – children with gestational age less than 37 weeks, weighing less than 2500 g.

Distribution of cases by gestational age (preterm or full term baby) weight, sex and age group are illustrated in Fig. 2.7, 2.8 and 2.9.

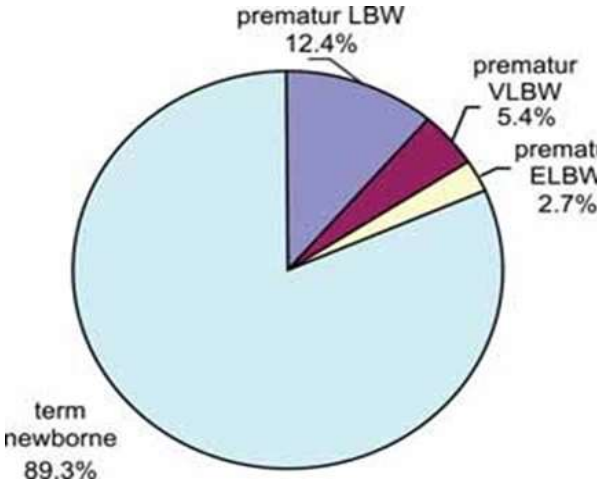


Fig. 2.7 *Patients distribution according to gestational age and birth weight*

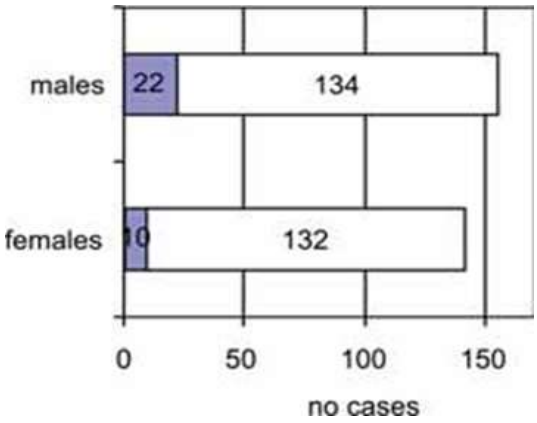
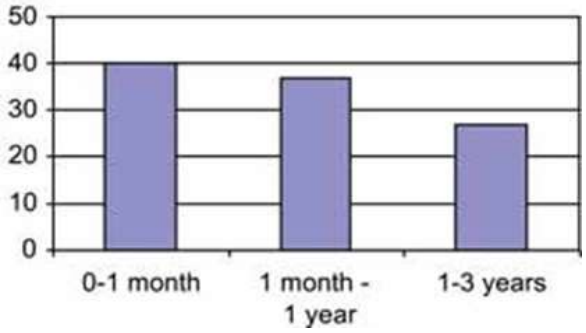


Fig. 2.8 *Patients distribution according to gestational age and sex*

UTI risk in subgroup 2 is influenced by age, being 3 times higher in preterm newborn babies, com- pared with children aged 1-3 (p = 0.0004, HR = 3.23, CI 95%: 1.85 ÷ 5.64). PPV cases with UTI in children born prematurely was 72.5%. The average age was 8,8 months on preterms, compared with 14.09 months of term babies. Depending on the degree of prematurity, we observed that most children were classified in LBW rate (73.3%) and 20% of them in VLBW rate.

Fig. 2.9 *Preterm patients' distribution according to age group*



The etiology of urinary tract infection is dominated in both subgroups by E. coli (60% in term children, 50% in preterm infants), Proteus mirabilis (12.5% preterm children 13% term children) and Klebsiella pneumoniae (9.37 % in preterm infants, 7.37% in term children). Opportunistic bacteria (Pseudomonas, Enterococcus, Acinetobacter) determines 16% of UTIs in preterms, compared to only 2% in term children. Urine cultures were negative in 12% of pre- terms, although clinical symptoms were suggestive of UTI. Clinical manifestations were different in the 2 subgroups, but fever was the clinical dominant sign in all patients (72% in subgroup 1 compare to 78% in subgroup 2). Loss of appetite was the first symptom in 55 % of preterms, compared to only 20% of those born at term. 25% of premature infants had prolonged jaundice (requiring phototherapy and induction).

Also 25% of them were associated with diarrhea, 22% interstitial pneumonia, and 19% had respiratory distress. In the subgroup of term infants, there was no case of respiratory distress or jaundice, and diarrhea and interstitial pneumonia were present in 10% of cases. In 22% of preterm babies, UTI start- ed with febrile seizures (compared to 4% of term children). 15% of cases associated dyspepsia (compared with 10% terms), and 6% had lethargy as a sign of UTI (compared to 2% on term infants). The onset of UTI by acute renal failure/ injury occurred in 12.5% of preterms and only 1% of term children. Acute renal failure was secondary to sepsis in all cases. Urinary symptoms were similar in the two groups, summarized in Table 2.5.

Table 2.5 *Urinary manifestations in study group*

	Modified urines	Disuria	Pollakiuria	Agitation on micturition	Hematuria	Modified urinary stream	No signs	AKI
Sublot 1	55%	25%	20%	26%	6%	8 %	19%	1%
Sublot 2	66%	6%	3%	32%	9%	6 %	26%	12,5 %

Urinary manifestations in the study group UTI relapses were present on 10% of preterms (50% with fever) and 15% on term infants (10% with fever). In the etiology of UTI, relapses prevailed with E. coli in term infants and bacterial associations (Candida sp + E.coli + Klebsiella pn) in preterms. Relapse in most cases was due to noncompliance in prophylactic therapy. Kidney scars assessed by radionuclide studies with Tc99DMSA were present in 4% of children subgroup 1 and 5% of those of subgroup 2. Radionuclide studies could not be carried out to all children with UTI relapse. Renal and urinary malformations in each subset of the study are given in Table 2.6.

Table 2.6 *CAKUT in study group*

	Vesico-ureteral reflux	Hydro-nephrosis	Renal hypoplasia / Renal agenesis	Duplex kidney	Kidney stones
Sublot 1(19%)	32 patients (12%)	15 patients	1 patient	1 patient	2 patients
Sublot 2(37%)	7 patients (22%)	4 patients	4 patient	1 patient	

CAKUT in study group 68% of preterm and 56% of term infants developed anemia. In the first subgroup the inflammation worsened the anemia. High neutrophilic count and leukocytosis was found in 75% and inflammatory syndrome in 68% of patients. 53% of preterms had different degrees of mal- nutrition (compared to 16% of term infants). Approximately two thirds of all patients presented significant leucocyturia. The first line anti- biotherapy was effective in most cases. Escherichia coli has developed resistance in al- most a quarter of patients. Antibiotics involved in microbial resistance were aminopenicillins (about 30% of cases), Sulfamethoxazole-trimethoprim (25% cases) and cephalosporins (25% cases), Nitrofurantoin and aminoglycosides (6% of cases). Proteus mirabilis has developed resistance in 8% and 2% of preterm and term children, respectively. Klebsiella pn. has developed resistance in nearly 5% of children both subgroups, especially to aminopenicillins. Enterococcus has developed resistance to Sulfamethoxasole-trimethoprim and aminoglycosides, and Pseudomonas to cephalosporins and aminoglycosides. 40% of

preterms had a positive history of multiple UTIs, 28% of whom did so as soon as birth. In 6.5% of them, the UTI was detected during a sepsis. In the neonatal period, the etiology was domi- nated by Enterococcus, Enterobacter, Klebsiella, and Acinetobacter, in 25% cases. In term children, relapse UTIs were found in 44% of patients, and only 9% of patients had recurrent UTI episodes after the newborn period.

II.3.4 Discussion

Prematurity in infants and small children causes a greater susceptibility to infections (besides pre- mature retinopathy, anemia and malnutrition), secondary to immunological deficits and organic im- maturity that these children are born with. UTI falls among the most common infections in newborns and small children, with an incidence ranging from 4-25% in preterms (according to various studies), and 5.3-7,5% in term newborns (Khassawneh, 2008, Garcia, 2002, Barton, 2008). Our study shows that UTI occurs three times more frequently in preterm than in term baby. The incidence of UTI in preterms was 10.75%, consistent with the literature (Khassawneh, 2008, Garcia, 2002). PPV of UTI cases in children born prematurely was 72.5%. In subgroup 2, gender distribution showed a predominance of UTI in boys (2,2:1) as in the study of Eliakim et al. (Eliakim,). Other studies show a ratio of up to 6:1 in favor of little boys (Barton, 2008). In term infants, the rate of UTI is higher for neo- natal boys and in 1-3 years old girls. The average age of children with UTI differs, being 8.8 months in former preterms, and 14 months in term children, data supported by field studies (Barton, 2008).

The clinical manifestations were different in the two groups. However, fever was a constant symptom present in both subgroups in 70% of the UTI episodes. This observation is similar to that of Khassawneh Mohammad et al (1). Loss of appetite, followed by failure to thrive was present in over half of preterm babies and the only symptom in 10% cases. A quarter of the preterm patients had prolonged jaundice and respiratory distress as signs of UTI onset (2). This signs were not found in term children, even though UTI occurred in the neonatal period. Francisco J. Garcia obtained similar data on jaundice as early sign in preterm newborns and in- fants with UTI (2,5). Comorbidities were recorded in both study sub- groups with a net predominance in preterms. Interstitial pneumonia was present in 22% of cases, di- arrhea in 25% of cases. Gastroenteritis can increase the possibility of periurethral colonization, and the risk of UTI in malnourished and preterm infants. On these infants, the antimicrobial barriers are sur- passed and cell-mediated immunity defense, opso- nines activity, phagocytosis and the vitamin A levels are decreased (6).

The incidence of comorbidities increases with the severity of prematurity and prone to malnutrition which affects preterms' nutritional recovery and antimicrobial defense. UTI evolution is com- plicated by malnutrition in 53% of preterm infants, compared with 16% of term infants, observation consistent with the literature (1,5). UTI onset by acute renal failure, secondary to a sepsis, occurred in both preterm and term infants, but the incidence was much higher in the first group (12.5% vs. 1%). Possible explanations for the high incidence of urosepsis in these children are the need of neonatal intensive care, subjected to invasive procedures, and prolonged parenteral nutrition. This clinical observation is supported by the study of M. Barton et al (Barton, 2008). In our study, the rate of neurological symptoms in preterm with UTI was 22% febrile convulsions and 6.25% lethargy, correlating with data from studies in the field (Bauer, 2003, Tamim, 2003). Anemia was found in 50% of children of both subgroups, caused by nutritional deficiencies and infectious disease. Significant white blood cell in urine improves diagnostic sensitivity and specificity of urine

culture by increasing the sample predictive values. The presence of white blood cells in urine and a clinical and biological syndrome suggestive of UTI (fever, inflammatory syndrome) associated with significant bacteriuria diagnoses a UTI in 91% of cases (with a variability of ± 0.04), decreasing the chance of a false positive diagnoses to 5 % (in terms of a NPV of 95%). A higher number of urine cultures (1-4, on average 2) on the same patient in- creases the sensitivity of the method at 97% (± 0,02). Urinary symptoms were similar in preterm and term infants, most often expressed by agitation on micturition and modify urines. Preterms presented twice as many CAKUT, 22% being diagnosed with various degrees of VUR (compared with 12% of term children). Bauer and Goldman recommends routine retrograde voiding cystography and ultra- sonography for CAKUT diagnosis in preterms with UTI (Eliakim, 1997, Bauer, 2003). The UTI etiology did not differ significantly in studied subgroups. The bacteria involved are Escherichia coli (60% in term infants and 50% in pre-terms), Proteus mirabilis (12.5% in preterms, 13% in term infants) and Klebsiella pneumoniae (9.37% in preterms, 7,37% in term newborn infants). The differences between the two subsets appear on the opportunistic bacteria (Pseudomonas, Enterococcus, Acinetobacter) that causes 16% of UTI in pre- terms, compared to only 2% in term infants.

Urine cultures were negative in 12% of pre- terms, although clinical symptoms were suggestive of UTI. UTI relapses are found in equal numbers of children in both groups, but the etiology is dominated by E. coli in term newborn infants, as it is in the case of preterms by bacterial association. Clinical studies in the field indicates a different etiological predominance, with Klebsiella pn., Candida, Enterococcus and E. coli being the most involved pre- terms UTI (Khassawneh, 2008, Bauer, 2005). Resistance to treatment of bacterial strains is a consequence of the excessive use of antibiotics in pediatrics. The antibiotic resistance to aminopenicillins ranked first then to Sulfamethoxazole-Trimethoprim and oral cephalosporins. The literature identified Trimethoprim resistance of Gram-negative bacilli in 9% of cases (Eliakim, 2003, Tamim, 2003). This difference is explained by the predominant use of aminopenicillins in treatment and prophylaxis.

II.3.5 Conclusions

UTI is a common cause of morbidity in preterm infants, the risk of urinary tract infection in- creasing with a smaller gestational age. Fever is a dominant sign of urinary infection in preterms (over 70% of cases), the rate declining along with the severity of prematurity. UTI associated comorbidities are more frequent as the degree of prematurity increases and the age decreases, respiratory distress and prolonged jaundice being the most important. Loss of appetite, followed by failure to thrive is present in more than half of preterm children with UTI. The presence of white blood cells in urine, and a clinical and biological syndrome suggestive for UTI has the same diagnostic meaning regardless of birth weight. CAKUT are found twice as often in preterm infants compared to term, imaging investigations becoming a necessity after the first episode of UTI. The etiology of urinary tract infection in both subgroups is dominated by Escherichia coli, Proteus mirabilis and Klebsiella pneumoniae. The implication of opportunistic bacteria in the etiology of UTI is 8 times higher in preterm infants. The etiology of UTI relapses in preterms is dominated by bacterial associations, while in the terms infants, by E. coli.Aminopenicillins Sulfamethoxazole -Trimethoprim and first and second generation oral cephalosporins induce bacterial resistance most frequently.

CHAPTER III. NEW INSIGHTS INTO THE HUMAN MICROBIOME AND ITS CLINICAL IMPLICATIONS IN PEDIATRIC PATHOLOGY

State of art into the human microbiome and its clinical implications in pediatric pathology

The human gut microbiota is a complex ecosystem that is essential for maintaining health and preventing disease. Hippocrates, in 400 BC, distinctly stated, "All diseases begin in the gut" (Sumida, 2019).

The gut microbiota comprises approximately 10–100 trillion microorganisms residing in the human intestine, forming a symbiotic relationship (Mocanu, 2023). These microorganisms include bacteria, viruses, fungi, archaea, and unicellular eukaryotes, collectively possessing 3.3 million genes (Yin, 2021).

The GI microbiota are represented by five primary bacterial phyla: the *Firmicutes* (synonym *Bacillota*) and *Bacteroides* (synonym *Bacteroidota*) phyla predominate the microbiome and represent more than 90% of total bacterial communities, while the *Proteobacteria* (synonym *Pseudomonadota*), *Actinobacteria* (synonym *Actinomycetota*), and *Verrucomicrobia phyla* are represented in smaller proportions (Bozomitu, 2022).

Although the *Bacillota phylum* consists of more than 200 different genera such as *Bacillus, Lactobacillus, Enterococcus, Ruminococcus* and *Clostridium*, and the *Clostridium genus* represents 95% of the phylum. The *Bacteroidota phylum* is predominated by the *Prevotella* and *Bacteroides genera*. The *Actinomycetota phylum* is significantly less abundant than *Bacteroidota phylum* and the *Bifidobacterium genus* is its main representative (Lupu, 2023).

The microbiome is not inherited, but acquired, and its composition is changing through different stages of each individual's life, with a unique composition and microbial diversity (Sharon, 2022). Its development starts early, in prenatal life, and continues during birth and through senescence (Piggott, 2020).

The following interfere with microbiome composition, leading the way to health or disease: sex; genetics; the mother's influence during pregnancy and birth; feeding practices in early childhood; dietary habits; antibiotics; tobacco and alcohol use; a sedentary lifestyle associated with the socioeconomic conditions; household pets; pollution; and geographical distribution (Dekaboruah, 2020, Piggott, 2020, Li, 2022).

The gut microbiota can also be characterized based on its functional diversity, which relates to its impact on systemic immunity and host defense against intestinal pathogens (Sumida, 2019, Yin, 2021).

The metabolism of microorganisms includes proteins, lipids, carbohydrate fermentation, bile acids, and vitamin synthesis (Evenepoel, 2017).

The microbial communities that colonize the human gut are extremely diverse and highly personal (Gibson, 2015). These microorganisms play a vital role in the digestion of food, the synthesis of vitamins and other nutrients, and the development and function of the immune system.

Gut microbiota structure and role are influenced by a variety of agents, including dietary habits, host genetics, and factors related to environment, with recent research exploring the ecological aspects that shape these microbial communities.

III.1 New Insights into the Human Microbiome and Its Clinical Implications in pediatric pathology

Although the mature adult gut microbiota is considered to be relatively stable, the developing infant gut microbiota (IGM) is constantly being reshaped, being prone to perturbation by external factors (Gibson, 2015). One of the most significant factors that can disrupt the development of IGM is the use of antibiotics, which are typically prescribed at a higher rate during the first years of life. Therefore, their impact on the infant's gut microbial architecture and host disease is becoming a key priority of current research (Cox, 2014). Antibiotics can disturb the microbial equilibrium, and create conditions that favor the growth of harmful bacteria. This can increase susceptibility to infections and other conditions such as allergies. Besides their direct effects on the gut microbiota, antibiotics also contribute to development of antibiotic-resistant bacteria (Mocanu, 2023). Gut microbes are recognized as a significant epidemiological source of resistance genes (resistome), previous research suggesting that the actual structure of gut-associated resistomes is still largely unknown and more diverse than previously thought (Moore, 2015). Antibiotic resistance is a public health problem today that threatens to undermine the effectiveness of antibiotics in treating infectious diseases. When antibiotics are used excessively, they can kill sensitive bacteria, leaving behind a population of resistant bacteria that can multiply and spread. This phenomenon has the potential to give rise to the emergence of antibiotic-resistant strains. Antibiotic prescription in infancy and childhood can lead to antibiotic resistance genes, posing a threat to effective disease treatment (Mocanu, 2023). Dysbiosis even extends its influence to encompass neuropsychiatric disorders such as depression, Alzheimer's disease, Parkinson's disease, autism, schizophrenia, and multiple sclerosis. Additionally, dysbiosis has a role in certain types of cancer, including oral, esophageal, pulmonary, pancreatic, and colorectal cancers. These complex interactions involve key relationships between the gut and lung, brain, heart, and skin (Xiao, 2020, Gebrayel, 2022, Christovich, 2022, Xu, 2022). By optimizing the early establishment of the microbiome, it may be possible to mitigate the risk of certain diseases and support overall health and well-being from an early age.

Overall, the study of intestinal microbes and their interactions with antibiotics and other environmental factors is a rapidly evolving field with significant implications for human health and disease. By better understanding these complex interactions, we can develop more effective strategies for preserving the health and well-being of individuals and populations (Gilbert, 2018). Preventive public health programs are crucial, and alternative strategies like probiotics, prebiotics, and dietary interventions are needed to preserve intestinal flora and reduce antibiotic use in agriculture (Dogra, 2020).

Understanding the role of the early disruption of the human microbiome and its impact on disease development is an active area of research. Scientists are investigating interventions such as probiotics, prebiotics, and microbial therapies to restore or promote a healthy microbiome in infants.

Disturbances in the balance of intestinal microbiota, known as dysbiosis, have been implicated in various health conditions. These range from localized issues such as inflammatory bowel diseases and celiac disease, to broader effects on osteoarthritis, skin conditions like psoriasis and acne vulgaris, vascular problems including atherosclerosis and thrombosis, CKD, chronic diseases of liver and lungs, such as obstructive diseases and asthma, as well as metabolic disorders like obesity, diabetes, and dyslipidemia.

My contributions in this field are summarized below.

Articles ISI – principal author

Mocanu, A.; Bogos, R.A.; Lazaruc, T.I.; Trandafir, L.M.; Lupu, V.V.; Ioniuc, I.; Alecsa, M.; Ivanov, A.; Lupu, A.; Starcea, I.M. Exploring a Complex Interplay: Kidney–Gut Axis in Pediatric Chronic Kidney Disease. Nutrients 2023, 15, 3609. IF= 5.9/2022, **Q1**, (First author), https://doi.org/10.3390/nu15163609

Lupu, V.V.; Butnariu, L.I.; Fotea, S.; Morariu, I.D.; Badescu, M.C.; Starcea, I.M.; Salaru, D.L.; Popp, A.; Dragan, F.; Lupu, A.; et al. The Disease with a Thousand Faces and the Human Microbiome—A Physiopathogenic Intercorrelation in Pediatric Practice. Nutrients 2023, 15, 3359. IF= 5.9/2022, **Q1**, (First author), https://doi.org/10.3390/nu15153359

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Lupu VV, Trandafir LM, Raileanu AA, Mihai CM, Morariu ID, **Starcea IM**, Mocanu A, Butnariu LI, Stoleriu G, Salaru DL, Chisnoiu T, Munteanu D, Mitrofan C, Lupu A. Advances in Understanding the Human Gut Microbiota and Its Implication in Pediatric Celiac Disease—A Narrative Review. Nutrients. 2023; 15(11):2499, IF= 5.9/2022, **Q1**, (Autor principal), https://doi.org/10.3390/nu15112499

Lupu VV, Adam Raileanu A, Mihai CM, Morariu ID, Lupu A, **Starcea IM**, Frasinariu

III.1.1 Aim of studies

These papers primary objective is to disseminate information regarding the effect of dysbiosis on the pathogenesis and evolutionary trajectory of pediatric patients. The microbiota of the intestines, as well as the microbiomes of specific organs (e.g., the heart, respiratory system, immune system, and renal system), have a significant influence on health and disease, which is being studied more and more recently.

In addition, given my area of expertise, I have endeavored to shed light on what is known about the connection between the intestinal-renal axis of a child, how dysbiosis, or an imbalance in the microbiome, affects CKD, and what pharmaceutical and non-pharmaceutical treatments exist for this condition.

III.1.2 Material and method

We conducted a narrative review of the literature using the databases PubMed, ScienceDirect, and Oxford Academic to identify relevant articles related to the intestinal microbiota and how dysbiosis can influence the onset and evolution of various pathologies. We insisted on less well-known topics, starting with the link between dysbiosis and autoimmune disease in children. We also evaluated the articles that discussed the role of dysbiosis not only in celiac disease but also in irritable bowel syndrome. Another direction was the intestine-heart axis and the impact of the microbiota on cardiac pathology in the child, with emphasis on congestive heart failure. Bronchial asthma, a common pathology in pediatric pathology, not only benefited from a special section, insisting on the articles that assessed the role of intestinal and respiratory dysbiosis in the pathogenesis of asthma but also in the response to therapy. The searches also focused on the intestinal kidney axis, with a selection of articles that assessed the role of the gut microbiota but also of the urobioma in pediatric patients with CKD of various etiologies.

We have highlighted the keywords and phrases commonly used to describe autoimmunity, SLE, heart failure, celiac disease, irritable bowel syndrome, bronchial asthma, and dysbiosis. The inclusion criteria concerned study groups of children (0–18 years old); although clinical research was limited, we chose to include the results obtained on adult groups or murine models in order to cover the information bias. Therefore, this paper is an intersection of current information on the pathogenesis, diagnosis, and management of the intestinal microbiota in light of the diseases described above and from the perspective of a causal relationship less exploited with dysbiosis, especially in pediatric practice. The criteria for excluding studies encompassed research involving study groups aged 18 and above, investigations centered on small patient cohorts lacking statistical significance, and studies afflicted by substantial subject attrition. A comprehensive approach was taken for inclusion criteria, encompassing data related to maternal dietary habits, peri- and postnatal factors, and the impact of probiotic, prebiotic, or symbiotic supplementation on both maternal and infant outcomes during pregnancy and lactation. Moreover, in instances where the existing literature concerning children was not sufficiently developed, the findings extrapolated from studies conducted on adult populations were utilized to chart potential avenues for future research. Extracted data encompassed the study's research design, patient group size, geographical location, conclusions drawn, as well as the theoretical and practical implications deduced from the research outcomes. For these purposes, we carried out a review of the literature from the last few decades.

III.1.3 Results

As previously mentioned, the human microbiota is categorized based on specific sites of interest. Disruptions in its equilibrium primarily arise in response to alterations in environmental factors, dietary habits, or antibiotic interventions. These disruptions have the potential to elevate the susceptibility to conditions such as atopy, autoimmune disorders, cardiovascular ailments, and malignancies (Requena, 2021, Lupu, 2023).

Beginning during the intrauterine phase, this dynamic microenvironment undergoes a series of developmental and adaptive changes that culminate in its gradual maturation. This maturation process involves the establishment of a delicate equilibrium between commensal and pathogenic microorganisms, which play a crucial role in the physiopathogenesis of various ailments (refer to Table 3.1).

Table 3.1 *The connection between the disturbance of the main microbial sites and organic diseases.*

Microbial Site	Affections Found in Dysbiosis
Skin	– atopic/seborrheic dermatitis; – acute urticaria; – acne; – psoriasis; – skin malignancies;
Respiratory system	– acute otitis media; – chronic rhinosinusitis; – bronchiolitis; – pneumonia; – asthma; – post damage scaffolds;
Genitourinary system	– bacterial vaginitis; – pelvic inflammatory diseases; – hysteromyoma; – endometriosis/adenomyosis; – sexually transmitted infections; – infection with papilloma virus/cervical dysplasia; – neonatal infections; – spontaneous abortion; – premature birth; – affecting fertility; – oncological pathology of the prostate; – kidney stones; – urinary tract infections;
Gastrointestinal system	– dental caries; – inflammatory bowel diseases; – celiac disease; – diabetes; – autism; – Henoch-Schonlein purpura; – Wiskott-Aldrich syndrome; – appendicitis; – sleep apnea syndrome; – chronic gastritis; – duodenal ulcer; – osteoarthritis; – psoriasis; – acne vulgaris; – atherosclerosis/thrombosis; – obesity; – hyperlipidemias; – depression; – Alzheimer's/Parkinson's disease; – schizophrenia; – multiple sclerosis; – neoplasms (oral cavity, esophagus, stomach, lung, pancreas, colorectal);

Microbiome and irritable bowel syndrome

Irritable bowel syndrome (IBS) is the most frequently encountered disorder of gut-brain interactions (Drossman, 2016), with a worldwide prevalence ranging between 7% and 15% of the general population (Ford, 2020, Oka, 2020). According to the Rome IV criteria (Fig. 3.1), it is characterized by mild to severe recurrent abdominal pain and bloating associated with alterations in bowel habits in the absence of organic disease or biochemical abnormalities (Mearin, 2016). Due to its symptoms, IBS is thought to be a disabling disease. It generates significant healthcare costs, reduces work productivity and school attendance, and decreases the health-related quality of life of the affected individuals (Canavan, 2014, Spiegel, 2009). Despite being a frequent entity in current gastroenterology practice, the physiopathology of IBS is not fully understood. It is considered to be a complex multifactorial disorder affected by several factors such as age, sex, genetics, diet, psychosocial status, altered microbiota, subclinical inflammation, and hypersensitivity of the neural network (Chen, 2021, Ansari, 2020). In recent years, accumulating evidence has suggested that the alteration of the gut microbiota plays an important role in the pathophysiology of IBS, as gut microbes exert effects on the host immune system, on gut barrier function, and on the brain-gut axis (Pimentel, 2020, Singh, 2021).

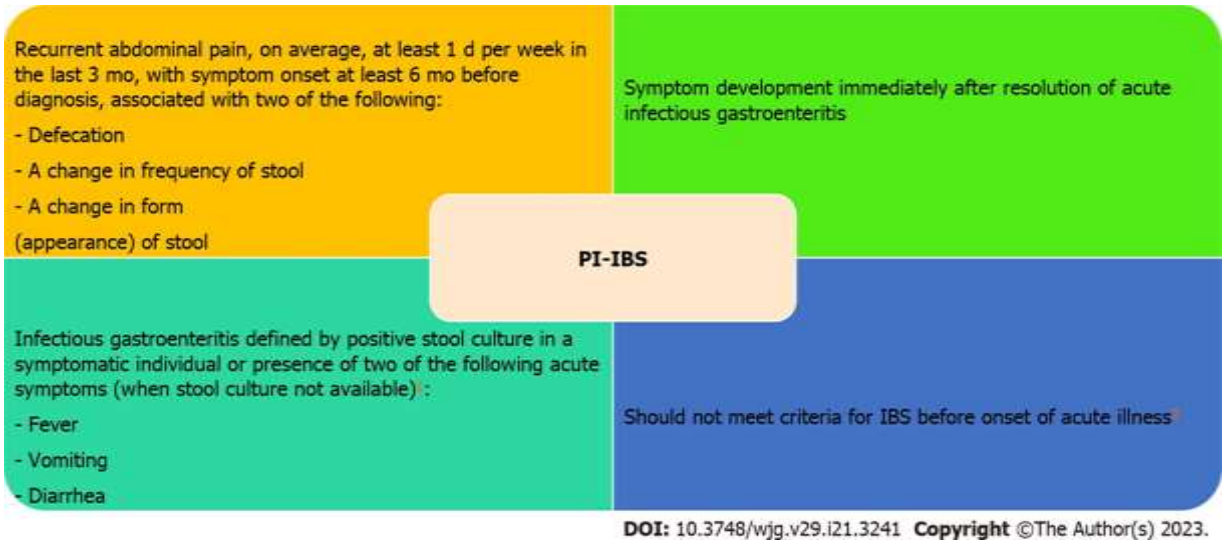

Fig. 3.1 Diagnostic criteria for post-infection irritable bowel syndrome (based on Rome IV criteria). 1Mentioning the exact date of onset of irritable bowel syndrome (IBS) symptomatology can also be suggestive for post-infectious IBS; 2Irregular bowel movements can be experienced even before the onset of the acute gastroenteritis episode (but not in association with frequent pain, as an IBS characteristic). IBS: Irritable bowel syndrome; PI-IBS: Post-infectious irritable bowel syndrome.

Microbiome and the SLE

In this study, the diagnostic lines follow two entities concurrently, namely SLE and systemic microbiota confined to various sites in the body. For an easier understanding, we will present in the following (Table 3.2) the main clinical aspects, investigations and diagnostic criteria that must be carried out/fulfilled in order to accurately define the notion of juvenile SLE and dysbiosis.

Table 3.2 Diagnostic lines in SLE and dysbiosis (adapted from Fava, 2019, Levy, 2012, Tucker, 2007)

	Systemic Lupus Erythematosus	**Dysbiosis**
Clinical exam	– Fever, fatigue, lymphadenopathy, downward weight curve; – Acute, subacute or chronic skin damage (photosensitive); – Oral/nasal ulceration; – Alopecia; – Vasculitis; – Livedo reticularis; – Subungual telangiectasia; – Raynaud's phenomenon; – Synovitis, serositis (Pericarditis, pleuritis), symmetrical polyarthritis at the metacarpophalangeal, proximal interphalangeal and knee joints (rarely erosive); – Neuropsychiatric manifestations (convulsions, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy and acute confusional state); – Renal damage objectified by proteinuria, cellular casts and alteration of renal function;	Sampling methods • pre-moisten swabs • skin surface scrapes • tape strips • skin biopsies • nasal tamponade; • nasal wash; • nasopharyngeal mucus examination; • saliva/sputum; • oral tamponade; • hypopharyngeal/ bronchoalveolar/ gastric aspirate; • pharyngeal exudate; • bronhoalveolar lavage; • brushing/bronchial biopsy; • stool sample; • rectal tamponade; • urine/semen/v aginal secretions examination; • vaginal scraping/biopsy;
Clinical investigations	– Blood count: pancytopenia (leukopenia/lymphopenia, thrombocytopenia, hemolytic anemia); – Renal tests (urea, creatinine); – Immunological investigations (ANA, anti-dsDNA, anti-Smith, anti-phospholipid, anti-ribonuclear, anti-Ro, anti-La, hypocomplementemia, and direct coombs test); – Skin/renal biopsy; – Ultrasonography; – Spinal puncture with cerebrospinal fluid analysis; – MRI;	
Diagnosis	<u>ACR (1997)</u> 1. Skin eruptions of the malar/discoid type; 2. Objectives of photosensitivity; 3. Oral or nasal ulcers; 4. Non-erosive arthritis at the level of the second/several joints; 5. Serositis; 6. Renal manifestations; 7. Neurological manifestations; 8. Hematological manifestations; 9. Immunological anomalies; <u>SLICC</u> – Lupus nephritis + one clinical and one immunological criterion;	
<u>Remarks -</u> Differential diagnosis in childhood: • Cytomegalovirus, Epstein Barr, Parvovirus 19, HIV; • Bacterial sepsis, Brucella, Leptospira; • Q fever, tuberculosis, Lyme disease; • Leukemia, lymphoma, neuroblastoma, histiocytosis; • Autoimmune diseases; medicines that induce lupus		

SLICC—Systemic Lupus Collaborating Clinics, EULAR—European League of Associations for Rheumatology, ACR—American College of Rheumatology, ANA—anti-nuclear antibodies, anti-ds-DNA—antibodies against double-stranded DNA.

Microbiome and Pediatric Asthma

The involvement of the microbiome in the emergence and development of bronchial asthma is therefore evident, with a peak of the impact especially found at the pediatric age (the first year of life) when the novice organism begins to adapt to the external environment, the need to implement collection protocols and study of biological samples, both for the purpose of research and to draw new lines in therapeutic practice. If, with regard to the research techniques, things are already well known, these being represented by 16S rRNA gene sequencing, shotgun metagenomic sequencing, RNA sequencing, proteomics and metabolomics study by mass spectrophotometry electrophoresis, chromatography, and others, Table 3.3 shows the main sites for collecting the biological samples necessary to study the human microbiome (especially intestinal and respiratory), harvesting techniques, but also the main advantages, disadvantages and mentions in relation to them (Wensel, 2022, Hu, 2023).

Table 3.3. Sites used in microbiomes research (adapted from Shah, 2021 and Abdel-Aziz, 2019)

Site	Sampling Technique	Notes
Upper respiratory tract	Nasal tamponade or washing	— Non-invasive, acceptable, easy to sample frequently; - predominance of *Moraxella*: increases the risk of exacerbations; - The predominance of *Staphylococcus* or *Corynebacterium* decreases the risk of exacerbations and respiratory diseases; - *Moraxella* in vitro was associated with epithelial lesions and increased expression of inflammatory cytokines;
	Saliva, oral tamponade, or mouthwash	- Non-invasive, acceptable, easy to sample frequently; - May show differences related to sex, pH, and dietary intake; - The results may be biased, depending on the amount of water ingested.
	Sputum (spontaneous or induced)	- May represent the microbiota from the lower respiratory tract; - It can be cross-contaminated with bacteria from saliva or the oral cavity; - Infants with *Moraxella* and *Haemophilus* were more likely to develop recurrent wheezing in childhood.
	Nasopharyngeal mucus	- Six months of life: the predominance of *Staphylococcus* increases the risk of wheezing in childhood; - Two years of life: the rhinovirus associated with the presence of *Moraxella* was associated with childhood asthma.
	Hypopharyngeal aspirates	- One month of life: colonization with *S. pneumonia, H. influenza, M. catarrhalis* increases the risk of developing recurrent wheezing and asthma in childhood; - One month: *Veillonella* and *Prevotella* were associated with the diagnosis of asthma at six years; — Hypopharyngeal microbiome modulates the effect of azithromycin.
Lower respiratory tract	Bronchoalveolar lavage and suction	- Invasive and presents a risk of cross-contamination during aspiration; - Reveals the growth of *Bacteroides, Pneumocystis,* and *Proteobacteria* in the case of asthmatic patients, unlike the control groups.
	Brushing and bronchial biopsies	- Represents the microbiota of the lower respiratory tract, including that associated with mucous membranes; — they are invasive and little used.
Intestine	Fecal matter	
	Rectal tampon	– May present cross-contamination with bacteria present on the skin.

The "gut" hypothesis" in HF suggests that there is a strong relationship between the gut microbiota, its metabolites and HF pathogenesis, as illustrated in Fig. 3.2 (Tang, 2019, Nagatomo, 2015).

Although this bidirectional communication is not fully understood, evidence indicates that this bacterial translocation appears in HF as a consequence of various mechanisms leading to structural and functional alterations of the GI tract, from splanchnic congestion to the host's immunological defense system (Mu, 2022).

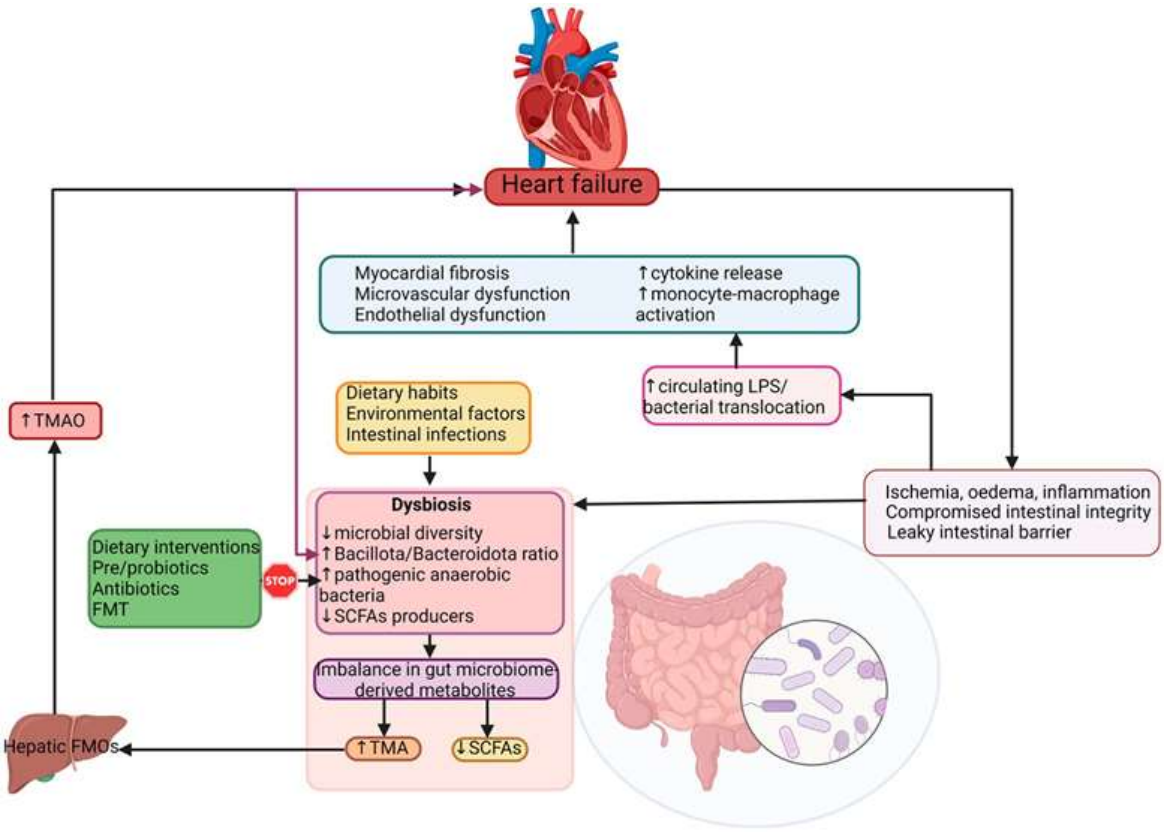

Fig. 3.2 *Concept of the gut-heart axis adapted to HF.*

Microbiome and Pediatric Celiac Disease

However, the current medical literature sustains the fact that a gluten-rich diet in a genetically predisposed individual does not offer full premises for CD autoimmunity (CDA) development, indicating the role of additional environmental factors, as well as gluten, in the disease pathological process (Bozomitu, 2022).

CD pathogenesis seems to involve several factors, including the type of birth, infant feeding techniques, and intestinal infections, as well as drug exposure, due to their ability to influence microbiota composition (Withoff, 2016), as shown in Fig. 3.3. It is well known that the human microbiome has a great influence on one's state of health, as well as their state of disease.

Gut bacterial community dysbiosis can alter the gastrointestinal microecological environment, turning into a pathogenic factor element for a broad spectrum of disorders, such as gastrointestinal, cardiac, respiratory, neurological, and metabolic diseases (Bozomitu, 2022, Lupu, 2023, Lin, 2016).

The recent advances in human microbiome study have offered evidence that diet is a major determinant of the intestinal microbiota's composition and function, and gluten can have an important influence on the gut microbiota's stability.

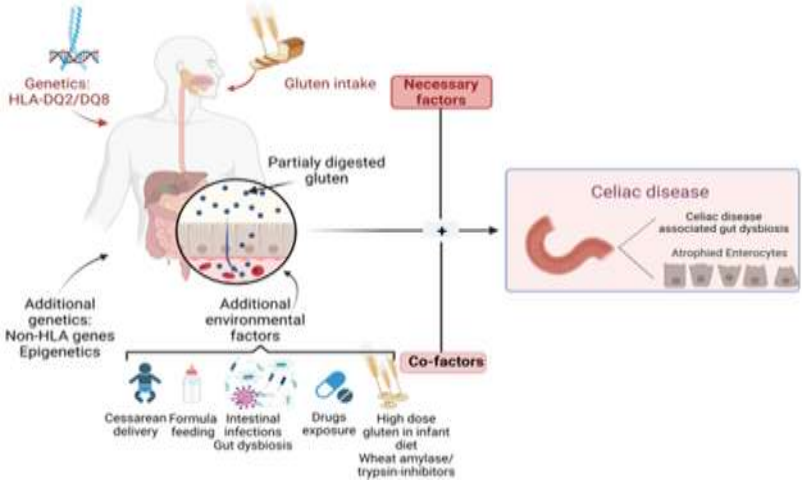

Fig. 3.3 *Genetic and environmental factors in CD*

Microbiome and Pediatric CKD

The relationship between gut microbiota and CKD is bidirectional and referred to as the kidney–gut axis (Evenepoel, 2017). This relationship is reciprocal: CKD can influence intestinal micro- biome composition and potentially lead to dysbiosis, while dysbiosis in CKD patients can increase levels of uremic toxins, further exacerbating CKD progression, as shown in Fig. 3.4.

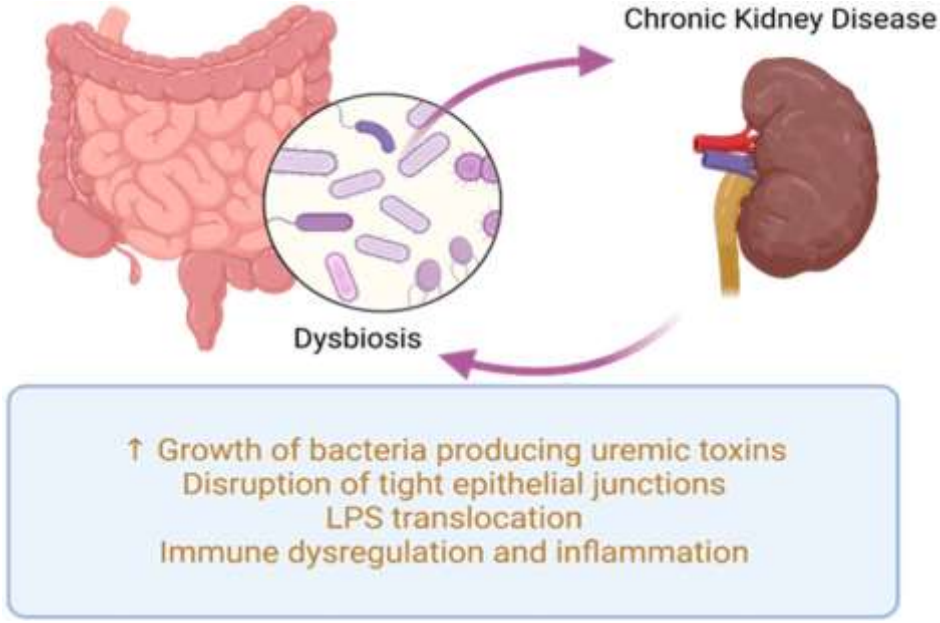

Fig. 3.4 *Common pathogenic processes in dysbiosis and CKD. LPS—lipopolysaccharides.*

Recognizing the intestine as a potential factor in CKD-related complications, therapeutic approaches targeting gut microbiota will have a significant impact on CKD management. Recent studies focused on adults with CKD have presented various mechanisms that establish a link between gut microbiota dysbiosis and kidney disease. These mechanisms include inflammation, impaired gut barrier function, changes in microbiota composition, immune response, accumulation of trimethylamine N-oxide (TMAO),

disruptions in short- chain fatty acids (SCFA) and their receptors, as well as uremic toxins (Hsu, 2022, Andersen, 2017). Dysbiosis fosters the proliferation of uremic toxin-generating bacteria (illustrated in Fig. 3.5), such as p-cresyl sulfate (p-CS), indole-3-acetic acid (IAA), IS, and TMAO, which accumulate in individuals with CKD (Zhao, 2021). Additionally, dysbiosis disrupts the integrity of tight junctions in the epithelium, resulting in bacterial LPS displacement, impaired immune function, and the onset of inflammation (Vaziri, 2015, Mafra, 2019).

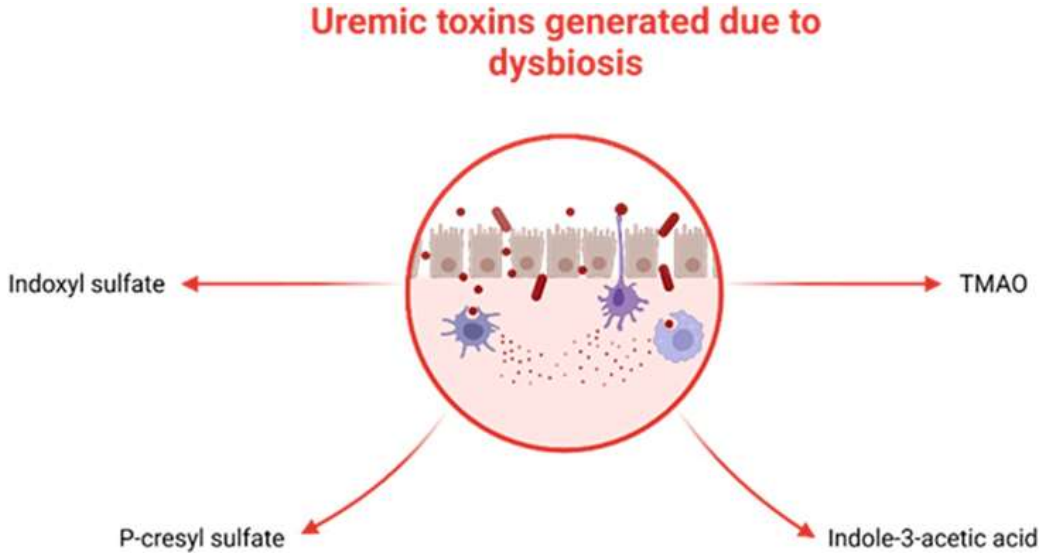

Fig. 3.5 *Uremic toxins generated by selected bacteria in the context of dysbiosis. TMAO.*

III.1.4 Discussion

The human digestive tract harbors the highest concentration and variety of microbiota in the body due to the availability of nutrients. Disrupting the healthy balance of these microorganisms leads to dysbiosis, which contributes to a range of issues such as gastrointestinal disorders, systemic metabolic diseases, and neurological impairments (Bozomitu, 2022). In cases of acute infectious gastroenteritis, the diversity of gut microbes diminishes (Downs, 2017). Several factors contribute to the disturbance of the native microbiota. Firstly, this disruption can arise from the interplay between pathogenic agents and the existing microbiota. Secondly, the host's mucosal immune response can also modify the microbiota, or both mechanisms may act in combination (Beatty, 2014, Ghoshal, 2022). Additionally, evidence suggests that the composition of the microbiota prior to an acute infection can influence the likelihood of developing post-infectious irritable bowel syndrome (PI-IBS) (Berumen, 2021). Although studies have assessed the gut microbiota profile of individuals with IBS, there is less consistency in the data regarding the alterations in the gut microbiome of PI-IBS patients. In a study that utilized real-time PCR to analyze rectal epithelium RNA expression, Jalanka-Tuovinen et al. (Jalanka-Tuovinen, 2014) determined that the intestinal microbiota of PI-IBS patients differed significantly from that of healthy individuals but resembled the microbiota of individuals with IBS-like symptoms (including irritable bowel syndrome, PI-IBS, and IBS-D). The researchers introduced the concept of an "index of microbial dysbiosis" (IMD) to characterize the intestinal microbiota of PI-IBS.

The IMD encompassed 27 genus-like microbial groups, with a notable twelvefold increase in the *Bacteroidota phylum*, which comprises species such as *Bacteroides* and *Prevotella*. The *Bacillota* phylum was comparatively less abundant, and fewer uncultured *Clostridiales* and *Clostridium* clusters were present. Moreover, dysbiosis correlated with the severity of gastrointestinal symptoms, but not psychological symptoms. The study also associated dysbiosis with biopsies that exhibited elevated levels of eotaxins, mast cells, goblet cells, and decreased enterochromaffin (EC) cells (Jalanka-Tuovinen, 2014). Similarly, Sundin et al. (Sundin, 2015) reported consistent findings when investigating the mucosal and fecal microbiota of PI-IBS patients. The fecal microbiota composition of PI-IBS patients significantly differed from that of both IBS patients and healthy individuals. Patients with PI-IBS showed reduced levels of *Bacillota,* encompassing *Clostridium* clusters IV and XIVa, and increased levels of *Bacteroidota*, including *Bacteroides species*. The reduction in fecal microbiota diversity correlated with heightened activation of lamina propria lymphocytes.

Notably, there was no substantial distinction between PI-IBS patients and healthy individuals in terms of the abundance of major bacteria responsible for producing butyrate. Within the spectrum of diseases stemming from disruptions in the intestinal microbiota triggered by diverse individual and environmental factors, autoimmune conditions like SLE, anti-phospholipid antibody syndrome, Sjogren's syndrome, systemic sclerosis, and rheumatoid arthritis have emerged, underscoring the intricate interplay between the microbiome and the immune system (De Luca, 2019, Rosser, 2017). This relationship between the microbiome and SLE was further elucidated through a randomized study conducted by Xiang K. et al., highlighting the potential presence of both factors that incite and shield against the onset and progression of the disorder (Xiang, 2021).

As exemplified by the microbiome-SLE association, ongoing research has brought to light significant changes, with the most noticeable being the shift in the *Firmicutes/Bacteroidetes* ratio. This shift is characterized by an increase in species like *Rhodococcus, Eggerthella, Klebsiella, Prevotella, Eubacterium,* and *Flavonifractor,* coupled with a decrease in *Lactobacillaceae.* This dysbiosis contributes to the amplification of chronic inflammatory responses and a decrease in immune tolerance, marked by an elevation in anti-double-stranded DNA antibodies and potential effects on renal function (De Luca, 2019, Xiang, 2022). Notably, Chen BD. et al. also underscore the presence of pathogenic species such as *Clostridium* ATCC BAA-442, *Atopobium rimae*, *Shuttleworthia satelles*, *Actinomyces massiliensis*, *Bacteroides fragilis*, and *Clostridium leptum* in samples obtained from SLE-positive patients, as compared to healthy individuals, with their levels diminishing following treatment (Chen, 2021). The primary mechanisms through which microbial metabolites, including short-chain fatty acids, free fatty acids, amino acids, and arachidonic acid, interfere with autoimmune processes orchestrated by T and B lymphocytes, dendritic cells, or macrophages include translocation, molecular mimicry, and the stimulation of antibody production due to the presence of diverse epitopes. The rationale supporting the concept of bacterial translocation involves the observation of heightened levels of procalcitonin—an inflammation and intestinal barrier damage marker—alongside elevated CD14 and α1-acid glycoprotein values, although this area remains under active investigation. Regarding the role of microbial metabolites in various pathologies, short-chain fatty acids (acetate, propionate, and butyrate) and polyamines seem particularly influential in SLE. These compounds impact autoimmune processes and bolster the integrity of the intestinal barrier, serving as crucial energy sources. These metabolites modulate immune function by curtailing the production of pro-inflammatory cytokines (IL-6, IL-12, IL-17,

IFN-γ, and tumor necrosis factor α) while promoting the synthesis of anti-inflammatory cytokines (TGF-β and IL-10) (Chen, 2022, Wen, 2021, Silverman, 2019).

The interplay between immune activity in the intestines and lungs finds its basis in the contemporary notion of the "common mucosal response." This concept sheds light on the integral role of the microbiome in the onset and progression of bronchial asthma, with its most pronounced impact occurring during childhood, particularly in the first year of life. This is a pivotal phase as the developing organism adapts to its external environment. Consequently, there is a pressing need to establish comprehensive collection protocols and delve into the analysis of biological samples, not only for research purposes but also to chart novel paths in therapeutic approaches. Examining the connection between microbial diversity and asthmatic phenotypes reveals intriguing findings. Heterogeneity within eosinophilic asthma has been identified, accompanied by a negative correlation between *Proteobacteria* and *Firmicutes*, and pulmonary eosinophilia. In cases of the neutrophilic form, reduced microbial diversity was observed, accompanied by an increased prevalence of potentially pathogenic organisms like *Haemophilus* and *M. catarrhalis*, alongside commensal species such as *Streptococcus* (Valverde-Molina,, 2023). Moreover, the significance of short-chain fatty acids, polyunsaturated fatty acids, and bile acids in the pathophysiology of bronchial asthma is noteworthy. Short-chain fatty acids, including acetate, propionate, and butyrate, originate from the fermentation of dietary fibers. Bile acids encompass cholic acid and chenodeoxycholic acid, while polyunsaturated fatty acids encompass omega-3 and omega-6 fatty acids such as α-linolenic acid, eicosapentanoic acid, docosahexaenoic acid, linoleic acid, and arachidonic acid. These metabolic components intricately modulate the body's allergic response (Lee-Sarwar, 2020, Bozomitu, 2022). Immune cells that are activated in the gut migrate through lymph and bloodstream to the lungs, where they exert their effector functions. This process subsequently shapes the generation of regulatory T cells, which, when produced early, contribute to safeguarding against long-term allergies (Ronan, 2021, Zhang, 2020, Annand, 2018, Chung, 2017).

The gut microbiota, as the central active constituents within the intestinal microecosystem, have demonstrated a robust influence on heart failure (HF). Beyond their connection to inflammation and heightened intestinal permeability, an investigation utilizing fluorescence in situ hybridization unveiled the presence of bacterial overgrowth forming mucosal biofilm and an increased bacterial adhesion in the mucus of the sigmoid colon among HF patients. The escalation of bacterial biofilm in close proximity to the intestinal mucosa has been associated with an augmented immunoglobulin A–anti-LPS (lipopolysaccharide) response (Sandek, 2012). In a study employing 16S rRNA gene sequencing, Sun and colleagues (Sun, 2022) scrutinized fecal samples from individuals afflicted with severe forms of chronic HF and compared these findings with those from healthy controls. Their results indicated reduced alpha diversity in chronic HF patients and substantial disparities in beta diversity between the two cohorts. The *Bacillota phylum* was prominent in the fecal microbiota of chronic HF patients, albeit in lesser proportions than in controls. Conversely, *Pseudomonadota* and *Actinomycetota* exhibited heightened levels in the HF samples compared to the controls. Particularly noteworthy was the finding that the *Pseudomonadota phylum*, rather than the *Bacteroidota phylum*, dominated the fecal microbiota of patients with severe chronic HF. Another recent study conducted by Zhang and colleagues (Zhang, 2023) concentrated on individuals with chronic HF, specifically in classes III and IV of the NYHA classification. This study identified substantial differences in both the alpha and beta diversity of gut bacterial communities between HF patients and

controls. Additionally, the researchers assessed phenylacetylglutamine (PAGln), a metabolite produced by the gut microbiota, which is recognized for its elevated plasma levels in patients with significant adverse cardiovascular events. Furthermore, insights from studies focusing on other inflammatory conditions may lead to the inference that the reduction of certain genera could contribute to the underlying mechanisms of HF. For instance, *Collinsella spp.* has been associated with type 2 diabetes mellitus (T2DM) and systemic atherosclerosis. Intriguingly, *Collinsella* was found in increased abundance among patients with atherosclerosis or T2DM; however, Luedde and colleagues (Luedde, 2017) observed a depletion of *Collinsella* in HF patients. This suggests that while *Collinsella* is abundant in atherosclerosis and T2DM, it appears to be present in diminished amounts in HF patients with conditions like ischemic heart disease or DM. This highlights the possibility that the reduction of *Collinsella* within the gastrointestinal microbiota could be a distinctive trait of HF (Luedde, 2017, Zhou, 2020).

The gut microbiome emerges as a central player in celiac disease (CD) pathogenesis by mediating interactions between the host's immune system, gluten, and environmental factors (Leonard, 2021). Various studies have delved into the connection between alterations in the gut microbiota and distinct environmental factors among individuals at risk of developing CD. Pozo-Rubio [24] examined the fecal microbial composition of at-risk children, revealing associations between specific pre-selected microbial taxa and factors like delivery mode, infant feeding practices, rotavirus vaccine administration, and antibiotic exposure (Pozo-Rubio, 2013). Likewise, Leonard et al. (Leonard, 2020) dedicated their research to investigating the impact of genetic and environmental risk factors on the intestinal microbiota's composition prior to the introduction of solid food and gluten in infants predisposed to CD. They found that genetically predisposed infants displayed reduced levels of several species including *Coprococcos, Streptococcus, Parabacteroides, Veillonella*, and *Clostridium perfringens* at four and six months of age (Leonard, 2020). This observation aligned with findings from Hov and colleagues (Hoy, 2015), who also identified lower *Coprococcoccus* levels in individuals genetically at risk for various autoimmune disorders (De Palma, 2010). Infants with genetic CD susceptibility demonstrated elevated levels of *Bacteroides* and *Enterococcus species,* corroborated by several studies (Leonard, 2020, Olivares, 2014, Yoshida, 2018). These increased levels of beneficial species tend to reduce microbial lipopolysaccharide production, ultimately enhancing the host's immune response [29]. Antibiotic exposure correlated with higher levels of *Bacteroides thetaiotaomicron* in the gut microbiota of at-risk four- to six-month-old infants, as this bacterium is pivotal in polysaccharide metabolism (Leonard 2020). Immunoglobulin A (IgA) stands as the primary representative of mucosal immunity. Emerging evidence highlights alterations in the humoral immune response of CD progressors at the age of five. These individuals exhibit elevated levels of IgA-positive-coated bacteria and distinct IgA targets within their gut microbiota compared to controls (Girdhar, 2023). Notably, CD progressors display heightened levels of taurodeoxycholic acid (TDCA) in their plasma (Girdhar, 2023), a microbiota-derived metabolite known to trigger inflammation and induce villous atrophy in mouse small intestines (Lauwers, 2015). Plasma TDCA levels could potentially serve as an early diagnostic marker for CD, and bacteria producing TDCA might offer a target for microbiota-modulation strategies in treatment (Leonard, 2020).

CKD undermines the integrity of the intestinal barrier by compromising the tight junctions between epithelial cells (Mafra, 2019). This impairment primarily arises from the presence of uremic toxins (Hsu, 2022), leading to an increase in intestinal permeability. This

heightened permeability facilitates the translocation of lipopolysaccharides (LPS) and pathogens across the digestive barrier. In CKD patients, the intestinal microbiota stimulates the immune system through T-helper cell activation, thereby amplifying cytokine production. Concurrently, LPS activates the innate immune response via the nuclear factor kappa B (NF-κB) and Toll-like receptor 4 (TLR4) pathways, fostering an inflammatory process and immune response (Hsu, 2022, Andersen, 2017). The presence of a leaky gut can result in inflammation, malnutrition, and an accelerated progression of CKD (Anders, 2013). Uremia significantly affects the biochemical environment, promoting disruptions in both gut microbiota and the intestinal barrier (Vaziri, 2013, Wong, 2014). Additionally, several factors contribute to the development of dysbiosis in this context, including elevated uric acid levels, inadequate dietary fiber intake (leading to reduced fruits and vegetables consumption, potentially causing hyperkalemia), and medication regimens, including the use of antibiotics (Vaziri, 2015). In patients with CKD, the production of uremic toxins negatively impacts the growth of intestinal microbes. Research indicates that individuals with end-stage kidney disease (ESKD) exhibit lower diversity in their gut microbiota compared to their healthy counterparts (Pisano, 2018). Earlier studies have also pointed to reduced levels of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus species* in CKD patients (Zhao, 2021). Moreover, multiple factors associated with CKD contribute to an imbalanced gut microbiota. These factors encompass inadequate dietary fiber intake, malnutrition, metabolic acidosis, medication usage (including antibiotics), increased elimination of urea in the intestines, accumulation of uremic toxins, and decreased intestinal motility. These alterations in the uremic milieu are associated with significant consequences, including the progression of CKD to end-stage renal disease, complications like protein-energy wasting, cardiovascular issues, and ultimately elevated mortality rates (Pisanu, 2018).

III.1.5 Conclusions

The human microbiota plays a crucial role due to nutrient bioavailability. Disturbances in this microbial equilibrium result in dysbiosis, contributing to various health issues. Disruption of the indigenous microbiota can occur through interactions between pathogens and microbiota or the host's mucosal immune response. Dysbiosis was linked to symptom severity and immune responses, while certain microbial groups showed altered abundance. Having an extraordinary variability, the human microbiome remains a subject of strong interest in medical studies, being proven to play a vital role in modulating the body’s homeostasis both by creating a predisposition to the development of various ailments when unbalanced and by forming a true line of defense against external elements, i.e., allergens and environmental factors. Dysbiosis is a key factor in IBS, HF, asthma, CKD, CD, and immune pathology. There are many methods available in order to modulate the dysbiotic intestinal microbiota, such as dietary interventions (which include prebiotics, probiotics, and postbiotics) and fecal transplantation. Treatment results vary, however, as they highly depend on the baseline characteristics of each individual, including genetic background, gut barrier function and microbiome diversity.

CHAPTER IV. ETHICAL AND SOCIAL PRACTICES IN PEDIATRIC NEPHROLOGY

State of art in ethical and psychological problems in pediatric chronic diseases

Health is complete physical, mental, and social well-being in the absence of disease or infirmity" (Callahan, 1973). A temporary or permanent loss of health transforms the person into a patient who goes to the doctor.

The patient should not be perceived as a "clinical case", but as a person who has a health problem that generates, in addition to physical suffering, psychological problems and disruption of social roles (working activity, mobility, family, and social relations). The ideal of health care is to maintain or restore the health and bio-psycho-social integrity of the person.

The concept of health holds significance beyond its theoretical aspects, as it carries far-reaching implications for practical applications, policy-making, healthcare provisions, and endeavors to enhance well-being (Leonardi, 2018). Chronic diseases are characterized by a duration exceeding three months, persisting for varying spans such as months, years, or a lifetime, necessitating ongoing treatment and care.

A notable percentage, ranging from 5% to 27%, of children contend with chronic ailments. Childhood chronic physical illness is linked to an increased susceptibility to emotional challenges, specifically depression and anxiety, during childhood. Nevertheless, there is limited understanding regarding the enduring impact of childhood chronic physical illness on mental well-being throughout one's life (Secinti, 2017).

Healthy children face a two to threefold increased susceptibility to psychopathological disorders. The presence of chronic illnesses and the stress stemming from caregiver circumstances lead to a continuous deterioration in the quality of life for families with chronically ill children, with depression affecting 57% of mothers and 30% of fathers (Ferro, 2015).

The impact of chronic illness extends well beyond the individual diagnosed with the condition, affecting not only parents and siblings, but potentially even future generations. A growing body of evidence emphasizes the substantial distress and psychological burden borne by family members and caregivers of those with chronic illnesses (Fletcher, 2021). In fact, the levels of anxiety and depression experienced by informal caregivers often mirror those of the afflicted individual, surpassing those seen in healthy individuals (Patterson, 2017).

When a person faces a health threat as a result of recognizing a physical symptom or receiving a clinical diagnosis, they form beliefs about the illness based on their perceptions, interpretations, and comprehension of the illness and its treatment (Petrie, 2006, Fletcher, 2021). These beliefs assume a pivotal role as intermediaries between the actual experience of the illness and subsequent coping mechanisms and overall well-being. Disparities in both physical and psychological outcomes among individuals diagnosed with the same ailment can be attributed, at least in part, to variations in how they perceive and conceptualize their illness (Fletcher, 2021).

Quality of life (QOL) corresponds to the World Health Organization's definition of health, encompassing physical, mental, and social well-being, yet it acknowledges the presence of disease.

The origins of the term "quality of life" within the realm of healthcare can be traced back to the World Health Organization's definition of health, established in 1948 (Post,

2014). The first evaluation of QOL is the Spitzer QL index, which was formulated for use by medical practitioners (Spitzer, 1981).

The contemporary understanding of QOL is framed around an individual's personal perception of their health status, which encompasses symptom management, biological functioning of the body, role functioning, involving integration into work, family, and society. For those dealing with chronic illnesses, their behavior plays a pivotal role in self-care, demanding motivation and preparation.

It entails acknowledging and accepting the illness, navigating the crisis stemming from physical and mental distress, adjusting to changes in self-perception, and actively participating as a member of the care team.

Compliance refers to a patient's adherence to medical appointments, treatments, and prescribed regimens, serving as an essential prerequisite for successful therapeutic outcomes. Improving the QOL is the goal of the care of the chronically ill and the measure of its quality (Flanagan, 2017).

The first contact with the patient has a double purpose: a technical one and a psychosocial one. In general, doctors are pressured by time and there is virtually no therapeutic relationship between doctor and patient.

Although biotechnology has developed a lot in recent years, more and more patients require psychotherapy, partly because the doctor spends on average 7 minutes with each patient, while the therapist spends at least 30 minutes. Competence and patience are the means by which the doctor can gain the confidence of the patient. Informing the patient, in a language as accessible as possible, is the result of a dialogue that continues at successive meetings. The patient's questions reveal his level of understanding and his need for information, which must be adequately met.

The importance of communicating with the patient is recognized, the patient must sign an informed consent. In the case of chronic diseases, a large part of the care takes place in the outpatient area, or at home, which does not absolve the doctor/sister of responsibility, but compels him to share it with the patient.

Communication of the diagnosis of a chronic, potentially lethal disease is mandatory in order to ensure the participation of the patient in therapy and care (Andersen, 2023). The environment is hospital, but an intimate environment is chosen in which the patient and very close people can express their reactions and psychological shock unreservedly.

The doctor must give the patient a clear picture of the disease and its prognosis, be prepared with competent answers to the inherent questions that arise. The tone of the conversation must be moderately optimistic, so that the patient understands that the treatment to be undertaken has a curative intention, or to improve QOL. The emotional reaction of the medical staff to the chronic/terminal patient is strong, resulting from disappointment with the limits of medicine and the feeling of wastefulness of the work performed. The expression of these emotional reactions must be suppressed to a sober attitude of compassion, without, however, reaching to an indifferent attitude, which is quite condemnable.

The control of your own reactions must be prepared in time and is based first of all on avoiding identification with the patient and, secondly, on involvement in the care of the chronic/terminal patient must be dominated by professionalism and not sentimentalism. This idea is best understood in the true sense by those who care daily for patients with terminal organ failure (renal, hepatic, cardiac, etc.).

Medical staff (physicians, nurses, therapists, ambulance staff) are directly involved in the trauma of patients, and this, over time, exposes them to secondary traumatic stress (Orrù,

2021). This secondary traumatic stress is specific to the medical sector, coexists, but is different from professional exhaustion (burnout).

Over time, and in small doses, the ability to feel and take care of others is eroded by the excessive use of empathy. You can also experience an emotional blockade that is manifested by the reaction to different situations other than is normally expected. Once the stress of compassion is triggered, the doctor or nurse develops a distant attitude that can be interpreted by the patient as lack of interest. If you do not intervene in time to restore the psychological and emotional balance of the medical staff, it can lead to professional abandonment.

To prevent the stress of compassion, it is necessary to intervene in 3 directions: awareness, balance and relationship (Rauvola, 2019). Unfortunately, there is a tendency to forget that doctors and nurses are not robots, but people who, in turn, need satisfaction and understanding from patients and society in general.

ESRD, defined as the terminal evolution stage of several renal diseases, currently has a few evolutionary alternatives: death, renal replacement therapy (artificial kidney - haemodialysis, peritoneal dialysis) and kidney transplant. If the first alternative is unacceptable in the 21st century, the patient is left with the other alternatives (renal replacement therapy, kidney transplant).

The cutting-edge haemodialysis or peritoneal dialysis findings are remarkable from a technical and medical point of view; however, the consequences of organ insufficiency are unfortunately just partially corrected, with major repercussions on general health and quality of life (Roventa, 2011).

Most patients find it impossible to continue their education, profession and have a perturbed family life, their loved ones being put through significant efforts. Integrating the chronic kidney disease patient into a haemodialysis schedule leads to long-term adaptive changes, both physiological and pathological, as a response to chronic stress, and also to dialysis-specific changes.

The unfortunate consequences of terminal chronic renal failure negatively reflect upon somatic, mental and intellectual growth and development. Disabling osteodystrophy and protein-caloric malnutrition associated to end stage chronic renal disease are severe in children and bear strong debilitating potential.

A peculiar perception of pain and of the workmanship of the dialysis session, coupled with somatic changes, shape the particular character of the chronic kidney disease child. In this sense, medical therapy of the chronic kidney disease must be backed by adequate psychological support.

Treating the dialysis children need a multidisciplinary care including medical, psychological, family, educational and religious support. The assistance of terminal patients is reserved for people with a balanced mental structure, ready to control their reactions, showing a behavior adapted to the special conditions of this kind of activity.

The treatment of chronic, life-threatening diseases such as cancer, or terminal renal failure is a great challenge, requires special preparation, perseverance and patience, and satisfaction lies in the trusting relationship that the physician and his entire team share with the patient.

This is because, when a chronic disease cannot be cured, maximizing quality of life becomes an essential goal of health care.

The ultimate goal of contemporary medicine is to overcome life-threatening barriers and to give higher chances of survival to categories of sick people for whom fate is cruel.

IV.1 Introduction in ethical and social practices in Pediatric Nephrology

This very important subject, which reflects the preoccupation of our team, is covered in a few articles, book chapters, and presentations at national and international conferences. A resume of this activity is listed below.

Articles ISI – principal author

Gavrilovici C., **Starcea M.,** Hiriscau I., Miron I., Oprea L. The Social Meaning of Death and Its Implications for Organ Procurement. Revista de Cercetare si Interventie Sociala (2017), 58, 221-232, IF= 0.838/2017, Q3, (Autor principal), http://www.rcis.ro/ro/section1/146-volumul-582017septembrie/2392-the-social-meaning-of-death-and-its-implications-for-organ-procurement.html

Articles BDI - principal author

Starcea M., Iorga M., Sztankovszky L.S., Munteanu M., Doctor-Patient Relationship In Children's Chronic Kidney Disease And Its Importance For The Quality Of Life For The Dialysis Patient, European Journal of Science and Theology, June 2014, Vol.10, No.3, 27-36, (Autor principal), https://www.researchgate.net/publication/289485226_Doctor-patient_relationship_in_children's_chronic_kidney_disease_and_its_importance_for_the_quality_of_life_for_the_dialysis_patient

Iorga M., **Starcea M**., Munteanu M., Sztankovszky L.S., Psychological and social problems of children with chronic kidney disease. European Journal of Science and Theology, February 2014, Vol.10, No.1, 179-188, (Autor principal), https://www.researchgate.net/publication/281752734_Psychological_and_social_problems_of_children_with_chronic_kidney_disease

Book chapter

Gavrilovici C., **Stârcea M**., Cadrul de analiză etică în practica medicală pediatrică, în Constatntin Iordache, Alina-Costina Luca, Tratat de intoxicații acute la copil, editura Junimea, 2019, (ISBN 978-973-37-2287-8), cap. XVII, pag. 541 – 554.

IV.1.1 Aim

Chronic kidney disease is defined as an irreversible loss of renal functions, which results in a decreasing glomerular filtration rate. The incidence of CDK varies for different age groups, between 19-33%. 70% of children suffering from CDK develop terminal stage by the age of 20 (Ardissino, 2003). Except renal transplantation, which is desideratum of life of these patients, the dialysis represents the only way to stay alive. A transplant patient will not fully meet the WHO definition of health, but will get the chance to enjoy life, so increase the quality of life (Varni, 2007). In this reason the medical staff who treats chronic patients must to be fully involved into solving his patients‟ medical and psychosocial problems.

The aim of this review is to highlight the main desire of health care, in the case of patients with CKD, that of increasing the quality of life. We also evaluated the involvement of the medical team in assisting the terminal patient, both in terms of organ sampling and in relation to his death.

IV.1.2 Material and method

The time of diagnosis of chronic renal failure and the predialysis care may be important factors related to the quality of life of patients on dialysis treatment. Late diagnosis of chronic renal failure and the consequent lack of predialysis care adversely affect the quality of life of hemophilia patients.

Early diagnosis and regular dialysis care should be encouraged to improve the quality of life during dialysis treatment (Sesso, 1997).

Evaluation of severeral problems that are present in patients with CKD is the way to establish guidelines for therapy in these cases.

IV.1.3 Result

Depression and other psychological problems - the personality profile is very important for the survival rate of the chronic renal failure patient. Psychological support is necessary in order to avoid or diminish the severity of the following depressive syndrome. Depression is generally accepted as the most common psychological problem in chronic renal patients.

Although depressive symptomatology is commonly encountered in dialysis patients, the syndrome of clinical depression includes sadness, guilt, hopelessness, helplessness and changes in sleep, appetite and libido (Finkenstein, 2000).

Depression in chronic renal patients is seen as a predictable and frequent complication. Somatic factors such as uremic toxicity, atherosclerosis, neurological disorders, anaemia, cardiovascular disorders and metabolic disorders are also involved in the aetiology of the depression (Roventa, 2011).

As the impact of depression on survival was maximal in the first few years of dialysis, monitoring for depression should be incorporated into routine care from the start of dialysis together with evaluative interventions that might enhance survival (Shulman, 1989).

The cognitive deficit: the prevalence of cognitive deficits is particularly high in subjects with end-stage renal disease. While it is sufficiently well documented that ESRD is linked with a change in cognitive function, little is known about the influence of different dialysis modalities on cognitive function. Some data suggest that patients with ESRD treated with chronic ambulatory peritoneal dialysis (CAPD) had consistently better cognitive function than patients treated with hemodialysis (Radić, 2010).

Addiction to the machine - those who undergo hemodialysis, continuous cyclic peritoneal dialysis or nocturnal intermittent peritoneal dialysis manifest an addiction to the machine without precedent in the history of medical technology. Those treated by continuous ambulatory peritoneal dialysis are tied to a repetitive circadian ritual of dialysis exchanges.

All these patients are severely dependent on a medical procedure and on certain medical staff. On the whole, a patient's psychological response to the illness depends on his premorbid personality, on the level of family and social support and on the progression of the underlying disease.

The Model Health Behavior and QOL - data on the morbidity and mortality of this patient category offers an incomplete image of the efficiency of the medical act, given that

the concept of chronic kidney disease management is in full development, one of its key components being the patients' perception of their own health (Noordzij, 2005).

Stress - the cause of so much distress is the sum of stressors associated with end- stage renal disease and its treatments: illness, family changes, dietary constraints, time restrictions, functional limitations, financial constraints, changes in employment, change in sexual function, medication effects and awareness of impending death etc.

Even minor stress was significantly predictive of changes in dietary compliance. The results suggest that minor stress may affect health status in the chronically ill by reducing compliance behaviours (Hitchcock, 1992).

Noncompliance - the compliance has a major role in the treatment of hemodialysis patient. It requires committing considerable time (several hours/session, many sessions/week), adjusting their food and drink behaviour (fluid restrictions and diet) and taking pills regularly.

The noncompliance among patients (especially teenagers) is a major problem. Studies are describing that noncompliance is inversely related to survival and that patient characteristics may be predictive of compliance under certain circumstances (Wiedebusch, 2010).

Family support - the child's illness is causing a lot of problems into family life. Psychological problems were revealed also in parents' profiles (anxiety and depression) and relationships with other families are also affected. Mothers seemed to be more touched. Internal family relations and couple/marriage is influenced by the child disease.

Family support has an important impact of child's QOL.

IV.1.4 Discussions

Guidelines intervention for helping children with chronic kidney disease - having kidney failure influences a child's self-image and relationships with peers and family. It can lead to behaviour problems and make achieving goals more difficult. Being aware of these problems can help you recognize that your child may need some additional guidance or understanding at times. The most important areas of intervention are presented below.

Family support - positive correlations were found between age on diagnosis of renal failure and fathers' depression and anxiety scores. Mothers' anxiety and depression scores were also positively correlated with those of father (Fielding, 1985). The child's illness was reported to have caused disruption in family life by most parents in the dialysis group (77%) significantly more often than by parents in the non-dialysis group (31%) (p = 0-002).

Disturbance was commonly explained in terms of the restrictions imposed by the child's condition or treatment, including dialysis, which made family outings or holidays difficult to organize.

Higher family conflict predicts also more externalizing symptoms and higher number of prescribed medications; higher family cohesion predicted fewer hospitalizations. Non-traditional family structure predicted higher number of prescribed medications (Soliday, 2001).

School - assuring a normal life is very important for dialysis child. Negative consequences include the impossibility of continuing to attend school. With a schedule including 3 dialysis sessions per week, such children find it impossible to continue their formal studies, being doomed to illiteracy and the impossibility of socio-professional insertion. Learning problems could be the consequence of missing classes or the impossibility to focus during tasks. Data on school performance have shown that children with CKD are at risk for impairment.

Dealing with low self-esteem - learning problems and physical consequences of the illness contribute to a lower self-esteem. They could feel depressed and powerless. Interventions are needed to equip children with the capacity to manage their health, participate in community, engage in 'permissible' recreational activities, progress in their studies, and remain vigilant in dialysis and treatment responsibilities, for improved health and treatment outcomes (Tjaden, 2012).

Following medical instructions - children can refuse the medical treatment or dialysis program. In case of noncompliance or non-adherence, the psychological therapy is a must. The teenagers are usually difficult patients, due to their age's psychological, physical and social needs (Tjaden, 2012).

Engaging sports or physical activity - usual limited, the physical activity is important for two aspects: integrate the child in social activity (play, games, competition, fun etc) and having benefits on the physical and psychological life (feeling powerful and independent).

Making friends - children with kidney disease may have trouble in making friends. The physical activity restrictions (and sometime the smaller stature) the drug treatment or the dialysis program, the food and drinks restriction could limit them for socializing. Most children in this situation are choosing friends among those who are hospitalized with or among those in the same medical situation (peritoneal or hemodialysis). Special camps or extracurricular activity could be a solution for integrated them in a group of children of their own age (Mehls, 2007).

Working - to enter in the workforce is difficult for persons with kidney problems. Few of them are succeeding in finishing college or university. Most of them are graduating schools, elementary schools or high-schools, if the dialysis programs are permitting them to reach classes or support teachers are provided to their homes. Missing classes or school abandon is frequent. Family support and school policies are important for the child.

Religious/spiritual coping - among other variables that influence the health behaviour, religious/spiritual coping mechanisms are an important strategy to cope with the disease. Important studies showed that religious practice (attending church every week) is influencing the quality of life of patients with kidney chronic disease in dialysis program (Valcanti, 2012). Positive religious coping was associated with better overall, mental and social relations

The social meaning of death and its perception relative to children's CKD

As currently practiced, donation after cardiac death inevitably raises more concerns than donation after brain death. The process is more complex, and the potential donor is not dead when life-sustaining measures cease.

The tightly scheduled management of the donor patient and the transplantable organs particularly for non-heart-beating donors (NHBD), but also for brain dead patients must satisfy a number of important ethical principles, including the dead donor rule, respect for family wishes, prohibition against euthanasia, and informed consent. In a practical discourse there are no big differences between "almost dead", "maybe dead" or "probably dead" because all could mean "as good as dead".

In a moral stance all these connotations cannot equate "dead for sure". Instead, the ethical acceptability of harvesting viable vital organs would depend on two conditions: the valid consent of the donor and an acceptable risk-benefit ratio for both the individual patient and society (Monteverde, 2012; Miller, 2012). That means that organs could only be removed if the patient or his or her surrogate has consented to the removal and the patient's clinical prognosis show no potential recovery.

This approach separates questions surrounding the determination of death from questions about the ethical permissibility of retrieving viable vital organs for transplantation. Death would no longer be a requirement for organ removal (Monteverde, 2012).

Thus, death is both a biologically based and socially constructed notion about which there is little prospect for social consensus in the near future. While attorneys will always claim that defining death is classically a legal problem and doctors would consider themselves experts in testing the death, none of them have authoritative insights into moral, spiritual and social factors to set a conclusive criteria.

It is the individual who place his own background, values, traditions and beliefs on the seat of the moral judgement.

In face of all these disparities, health professionals should respect the cultural, religious and social diversity.

IV.1.5 Conclusions

Treating children with chronic kidney needs a multidisciplinary care: medical, psychological and social intervention. The medical problems are doubled by the psychological effects and factors reflecting the personal profile, the age difficulties, the family type and educational level. Involving into the specific age activities with the limits imposed by the disease could create a suitable style according to their needs.

Restrictions in food and liquid diet, physical activity, sexual activity and emotional stability are feeling like an unsupportable board. Risks are joining the dialysis program (like school abandon or difficulty to socialize due to the dialysis schedule) but psychological and family support is an important factor for quality of life and survival.

"Donation after cardiac death" protocols allow clinicians to harvest viable vital organs as soon as the cardiopulmonary arrest is considered irreversible, usually minutes after the diagnosis of a loss of circulatory and respiratory function. Although these patients are not cerebral death, the irreversibility of circulatory death makes them suitable donors for organ donation, provided that organ sampling takes place as soon as possible.

SECTION B - PERSPECTIVES IN THE PROFESSIONAL, ACADEMIC AND SCIENTIFIC FIELD

This proposal for the development of an academic career is based on the experience gained during nearly 24 years of activity at the Faculty of Medicine, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi.

I will develop educational activities for training students, residents, and PhD candidates by promoting the acquisition of "hands on" skills in basic patient care and fostering their teamwork training. I will promote the adoption of problem-based strategies for differential diagnosis of the main symptoms in pediatrics, a crucial aspect of pediatric clinical practice.

I would like to continue the student and resident clinical case presentation sessions in pediatrics and nephrology specialties. Being one of the four senior specialists in pediatric nephrology in our country and serving as the coordinator of the residency program at our university, I bear a significant responsibility in preparing my residents for the demands of a dynamic and growing specialty. This involves the seamless integration of various disciplines, including intensive care, neurology, cardiology, gastroenterology, genetics, and oncology. Ensuring our residents are well-equipped to face these challenges is at the core of my mission, as it contributes to the advancement and excellence of our field.

I am already a team member on multicentric projects, which confirms once again my qualities in establishing partnerships and involving my team in multicentric team work in the pediatric nephrology specialty:

- The experimental demonstration project PN-III-P2-2.1-PED2019-2832 "Development of a multigenic model for the establishment of the genetic profile in corticosteroid-resistant nephrotic syndrome in a pediatric sample in Romania", in collaboration with the Department of Pediatric Nephrology and the Medical Genetics Laboratory of the University of Medicine Târgu Mureș, the Pediatric Nephrology Cluj-Napoca, and the Division of Pediatric Nephrology, Fundeni Institute
- Project 35150/17.12.2021 Immunological and biological predictors of renal graft survival: a pilot study in collaboration with the Section of Pediatric Nephrology, University of Medicine and Pharmacy Iuliu Hațieganu Cluj-Napoca, and Nephrology, University of Medicine and Pharmacy Victor Babeș, Timișoara.
- International research project "Immunology of Complement-related Kidney Diseases" (C3 Nephropathy, Hemolytic, and Atypical Uremic Syndrome), in collaboration with the Laboratory of Immunology and Medical Genetics of Semmelweis University, Professor Zoltán Prohászka, and the Centers of Pediatric Nephrology in Timisoara, Cluj, Bucharest, and Targu Mures.

I will aspire to continue and expand my commitment to becoming an expert both in the field of university education and in the medical domain. Improving the quality of the didactic act must be guided under the slogan "excellence through prosperity, progress through innovation", in accordance with the Strategic Plan of the University of Medicine and Pharmacy Grigore T. Popa for the years 2021-2024.

The fundamental goal is to harness the most appropriate means by which prosperity can generate performance and excellence. Modern academic management must be open to freedom of thought and expression on a background of professional, moral, and social responsibility, and the preparation of students must be done in an academically rigorous and performing program to become doctors with high professional competence, able to practice this profession at international standards.

I believe that all my current and future professional achievements will contribute to the improvement of the performance and reputation of the teams I am part of, as well as the "Grigore T. Popa" University of Medicine and Pharmacy, Iasi.

The professional perspective, in order to increase the quality of the medical record, the addressability in the specialty, but also the professional visibility of myself and the team I lead, in the country and abroad, I propose the establishment of:

- Advanced Care in Nephrology department, equipping it with equipment (a mobile water preparation station for dialysis, an acute dialysis machine).
- Urodynamics Department and the specialization of the department's doctors

I will also campaign for the development of collaboration with kidney transplant centers and access to electron microscopy (which will increase the value of the diagnosis of kidney diseases).

I will participate in clinical trials in priority areas of activity, and I will continue to register our patients in the European registers of renal diseases:

- The European Rare Kidney Disease Registry (ERKReg) includes 21 countries, 45 pediatric units, and 12 adult nephrology units.
- The PodoNet Registry: 32 countries, 104 nephrology centers

I will collaborate with the other pediatric nephrology centers for the creation of the Center of Excellence in Renal Diseases.

The future directions assume my acceptance:

- Improving the didactic activity through the permanent optimization of the didactic materials (classical and multimedia), according to the specific analytical programs, the promotion of active-participative methods centered on the student, the proposal of optional courses on pediatric nephrology topics for VMG students, but also a postgraduate course for pediatric nephrology residents
- Continuous training for improving the two foreign languages of teaching, obtaining the European C1/C2 level,
- Developing interpersonal and didactic communication skills,
- Developing the skills of writing scientific articles,
- Constant involvement in the actions carried out at the university level, and the elaboration of a treaty of pediatric nephrology

All these have as their main objective the construction of an educational system synchronized with everyday realities, which, under the conditions of the permanent support of the University of Medicine and Pharmacy Grigore T. Popa, will generate valuable specialists.

This habilitation thesis details my scientific, professional, and academic history in the field of Pediatrics from 2011 to 2023, after earning the degree of doctor of medical sciences.

The possibility of supervising PhD students would motivate me significantly to continue my development as a university professor and doctor.

Last but not least, I propose to promote the reputation of the School of Pediatrics and, in particular, to develop the School of Pediatric Nephrology in Iași, ensuring the future continuity of the specialty by training young physicians and instructional staff.

I also plan to increase the international visibility of pediatric nephrology and pediatrics by expanding scientific exchanges between Romania and other nations (such as the partnership for PhD candidates with Semmelweis University in Budapest).

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