Dopaminergic Centers Neurodegeneration

Biochemical and radiologic approach

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Parkinson's disease is the second pathological neurological condition that affects millions of people annually. Up to now there is no curative treatment for this condition. Our study was conducted on a group of 99 patients who were followed periodically, clinically and radiologically for a period of three years after diagnosis with Parkinson's disease. The results of our study show that MRI examination can be an important tool for differential diagnosis, etiopathogenicity and the prognosis of these patients. Patient follow up is required in personalizing and improving current treatment schedules of Levodopa.

Keywords:Parkinson's treatment, Parkinson's disease MRI, follow up protocol, behavioural disorders

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Parkinson's disease, also called *shaking palsy*, has been known since the 19th century. The first attempts to treat the disease date back to the late nineteenth century, when atropine or belladonna root extracts were started [1].

Modern treatment with L-dopa and dopamine agonists have superior efficacy but do not have curative action.

Patients diagnosed with Parkinson's suffer because of a neurological or idiopathic degenerative condition that primarily affects the motor system. Thus, nervous cells are not destroyed by a virus, but by a process of degeneration, whose origin seem to have a neurotoxic and genetic component. Other causes associated with the etiopathy of Parkinson's disease are stroke and drugs [2,3].

The social impact of this disease is extremely important for both the patient himself and the fact that it is the second pathological neurological condition as a frequency[4].

The number of centers dedicated to the treatment of Parkinson's disease has increased in recent years. An association of Parkinson's patients have also been created. These have greatly contributed to the development of a better knowledge of Parkinson's disease and the problems faced by patients among the general public.

The onset of the disease is unknown, studies estimate the place of the beginning of degeneration process in gut to parasympathetic neurons level , 10- 20 years before the most obvious clinical signs are motor movements, related to agitation, stiffness, slow motion, difficulty walking, thinking problems and behavioural disorders.

These are called *parkinsonism*, or a *parkinsonian syndrome* [5]. In the advanced stages of the disease dementia, depression and anxiety can occur. Other symptoms include sensory, sleep and emotional problems-*nonmotors symptoms* [6,7].

The positive diagnosis is based on the clinical examination and on the medical history of the patients. Patients who develop similar clinical manifestations of Parkinson's disease following a stroke or, especially, drug use, fall into the diagnosis of Parkinson's syndrome plus [8-10].

Among the radiological methods, MRI has become more accurate in diagnosing the disease over time, especially through the T2 and SWI sequences, and both can demonstrate the characteristic aspect of the substance nigra [11].This refers to the disappearance of swallow tail aspect at this level [12]but the technique is also used to exclude other diseases that may be secondary causes of parkinsonism, such as encephalitis, chronic ischemic lesions, tumors and hydrocephalus[13, 14].

PET-CT can measure the metabolic activity of dopamine carriers from basal ganglia, reducing their activity characterized by Parkinson's disease.

Currently, the drugs used to treat this disease are levodopa (always combined with a dopa decarboxylase inhibitor and sometimes with a COMT inhibitor), dopamine agonists and MAO-B inhibitors [11].

The purpose of this study is to evaluate the efficacy of modern current drug therapy for Parkinson's disease by correlating clinical and imaging data.

Experimental part

Material and methods

The study group included 99 de novo patients diagnosed with Parkinson's disease, out of a total of 283, in the Department of Neurology at the Emergency Hospital "Prof. Dr. N. Oblu" hospitalized during 01.01.2015 - 31.12.2018.

On this group of patients we conducted their demographic and clinical analysis, clinical examinationand psychiatric in order to highlight clinical, motor and non-motoric manifestations and of these, which are the most useful therapeutic measures. We have assessed the evolution of Parkinson's disease in these patients for a period of 3 years: 2015-2018.

This was possible by an follow up at a 6-month interval, occasionally being clinically reviewed. The MRI investigation was repeated over 12 months.

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Results and discussions

Our clinic's hospitalization registry shows 99 patients diagnosed with Parkinson's disease in 2015-2018, out of a total of 283 who were hospitalized within that time (fig. 1).

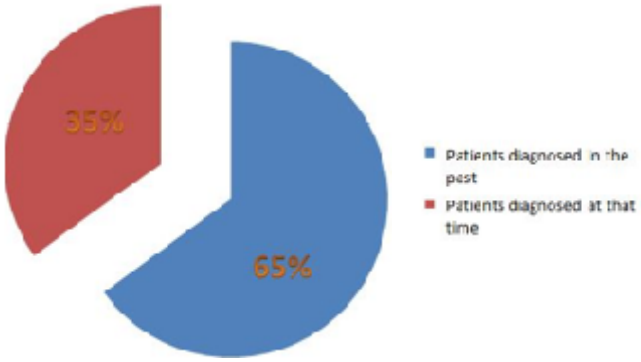

Fig. 1 Percentual distribution of newly diagnosed patents

Age related distribution results in the group of patients studied is: 3 persons with an age belonging to the category of under 40 years; 34 people belong to the 40-60 age category and 246 people belong to the over 60 category. The incidence is therefore wider in the over 60 age group followed by the 40-60 age group.

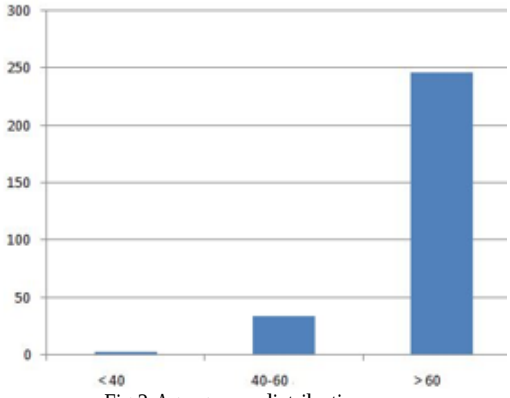

Fig.2 Age group distribution

The distribution by gender the group studied reveals 140 men (49%) and 142 women (51%). A slight predominance of females over males (fig. 3).

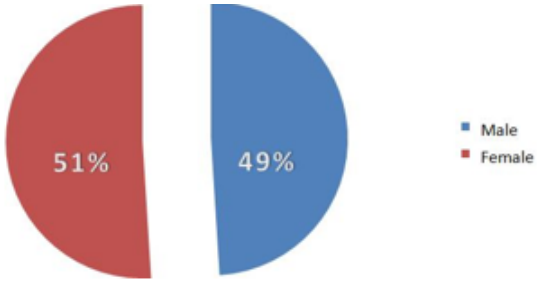

Fig. 3 Patients distribution by gender

The patients studied showed motor clinical manifestations marked by tremor and muscle stiffness but also disautonomic (tables 1, 2).

The neuropsychiatric manifestations are present by: psycho-emotional lability, tendency to impulsiveness, depressive phenomenon in different grades of psychopathological intensity, psychotic disorders such as hallucination, confusion (table 3).

The drug treatment was administered according to the age of the patients. The age of 60 years is correlated with a late stage of illness in most cases (table 4).

In the radiological study we investigated the patients using MRI, after clinical diagnosis and then after one year. The images point indirect signs of basal ganglia disorders (fig. 4, 5, 6).

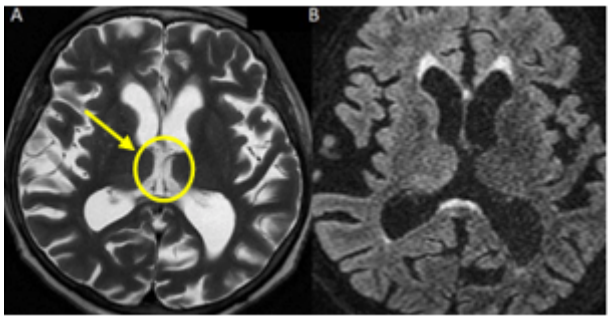

Fig.4 Patient with Parkinson's disease in Hydrocephalus *ex vacuum*; A=Expansion of bilaterally symmetrical intergranular spaces. The arrow indicates a bilateral swallow tail sign; B=Chronic lesions, one year after.

Tremor	Muscular rigidity	Bradykinesia	Postural instability
269	258	256	199
95%	91%	90%	52%

Table1
THE MAIN MOTOR MANIFESTATIONS

Digestive disorders	Olfactory disorders	Cardiac disorders	Urinary disorders	Sleepiness disorders	Sensory disorders	Thermoregulation
70	65	60	5	40	50	7
24%	23%	21%	1%	14%	17%	2%

Table 2
DISAUTONOMOUS DISORDERS IN NON-MOTOR SYMPTOMATOLOGY

Depression	Psychotic symptomatology (hallucination, delirium)	Cognitive dysfunction	Dementia
160	20	138	56
56%	7%	48%	19%

Table 3
NEUROPSYCHIC DYSFUNCTION IN NON-MOTOR SYMPTOMATOLOGY

	IMAOB (Rasagilina)	I-COMT (entacapone)	Dopaminergic agonist (Ropinirol, Pramipexol)	L-dopa and benserazida
40-60 ans	3%	25%	53%	59%
> 60 ans	7%	37%	81%	95%

Table 4
MEDICATION OF MOTOR SYMPTOMS IN PARKINSON'S DISEASE

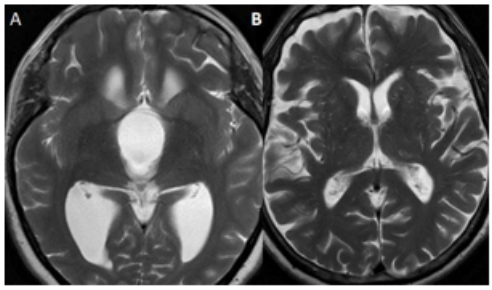

Fig. 5 A=Passive supratentorial hydrocephalus; B=Supra- and and subtentorial, symmetrical, central and peripheral cerebral atrophy that causes ventricular system expansion and exaggeration of intergiral sulci, aproximately one year after.

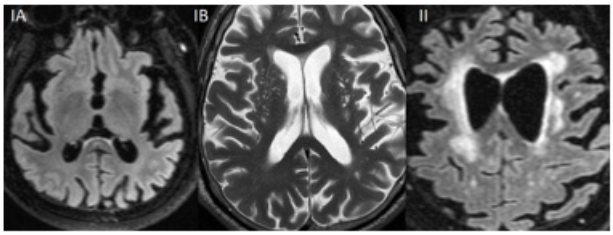

Fig.6. 71 year old patient with galloping neurodegenerative lesions; IA=Moderate cortico-subcortical cerebral atrophy associated with millimeter lesions in hypersensitive T2, FLAIR, discrete hyposemnal T1 located in the supratentorial white matter, with no tendency to confluence suggestive of non-specific degenerative vascular lesions (Fazekas 1 score); IB=Diffuse brain atrophy in combination with atrophy of the corpus callosum; II=Cortico-subcortical atrophy over and subtentortal associated with FLAIR, T2 confluent hyperstimulation lesions, located in diffuse white, periventricular and hemispheric bilayer, suggestive modifications of Fazekas III arteriosclerosis.

Since only 5-10% of levodopa crosses the blood-brain barrier, the rest is metabolised to dopamine elsewhere in the body, causing nausea, vomiting and orthostatic hypotension. Carbidopa and benserazide are dopa decarboxylase inhibitors, do not cross the blood-brain barrier and inhibit the conversion of levodopa to dopamine beyond the brain [15-17].

This type of medication has as its effects the appearance of dyskinesia as well as fluctuations in its efficacy. Shutting down levodopa medication can have dangerous side effects such as neuroleptic malignant syndrome [18].

Taking less doses of levodopa or using a controlled release version may reduce the risk and severity of these complications. Intestinal infusions of levodopa (Duodopa) can cause gastroparesisgastroparesisbut are the latest efficient treatment for advances Parkinson diseases.

MAO-B inhibitors (safinamide, selegiline and rasagiline) increase the amount of dopamine in the basal ganglia by inhibiting the activity of monoamine oxidase B (MAO-B), a dopamine-degrading enzyme. As dopamine agonists, their MAO-B inhibitors produce more effective PDOD symptoms. There are few studies on their efficacy at advanced stage, suggesting that they are useful in reducing fluctuations between on-line and off-line periods. An initial study indicated that selegiline in combination with levodopa increased the risk of death, but this was later disproportionate [19].

Tremor is the key motor symptom in Parkinson's disease, present in 95% of patients. The tremor is accentuated or initiates rest and emotional situation, intense stress, concentration or fatigue. This is the most noted symptom at the neurology consultation.

Muscle rigidity is evident in the majority of cases, with a frequency of 91%. This muscular tension disorder determines the attitude characterized parkinsonian patients (fuga attitude) with a slight flexion in all joints. Daily activities (performing body hygiene, lifting a chair) are performed with difficulty, demanding according to gravity, personal care. When rigidity is accentuated, lumbar, posterior cervical pain may appear.

Muscular hypertonia is objectified through: cogwheel sign, Noica sign, exaggerated posture reflex, palmo-mental reflex, sharp oral reflex, exaggerated nasopalpebral reflex, plantar skin reflex, decreased abdominal skin reflex or abolit.

Bradykinesia is present in the majority of cases, a proportion of 90%, it is shown as slow, in different grade, daily activities. The difficulty of walking appears in the initiation of walking or absence of automatic movements, by small hesitant steps, difficulty or blockage of return. Bradykinesia is visible by micrograph (small writing, illegible), hypomimic (decreased movements imitate), rarely blinked eyes and hypophony (voice decreased).

Postural instability is less common, but it appeared in an important stage in the evolution of the disease, because postural instability is difficult to treat and a source of disability in an advanced stage of the disease.

The most common non-motor manifestation encountered are digestive disorders with a percentage of 24%, followed by cardiac manifestations, represented by orthostatic hypotension 25%.

The digestive manifestations are present by:

-Deglutition disorders - dysphagia for solids and liquids, occurring as a result of inability to push the pharyngeal food balls and that the inability to contract the upper esophagus, appears late in the course of the disease, with intermittent, more rarely permanent appearance.

-Sialorrhea, appears due to the inability to swallow saliva, which accumulates in the oral cavity, it is correlated directly proportional to the severity of the dysphagia.

-Slowing intestinal transit (constipation).

-inability to push the pharyngeal food balls and that the inability to contract the upper esophagus, appears late in the course of the disease, with intermittent appearance more rarely permanent.

The most common non-motor manifestations are followed by a percentage of 24%, followed by cardiac manifestations, represented by orthostatic hypotension 25%[20, 21].

Urinary disorders are of 1% frequency, and are present by:

-Frequency of urination

-Urinary retention disorders;

-Difficulty of complete and incomplete urination;

Disturbances of thermoregulation are present by hyperhidrosis;

Sleep disorders are manifested by the difficulty of sleeping and the inability to mention sleep, with frequent nocturnal awakenings. Most often occurs reversal of the sleep-wake rhythm (nocturnal insomnia and exaggerated daytime sleepiness).

Cognitive conditions have a high share of 48%. Cognitive conditions can also occur in patients recently diagnosed with Parkinson's disease. In MP are frequent affections of executive functions, such as planning and decision-making ability, working memory, language, Visio-spatial ability (especially the perception and interpretation of visual information), reaction time, and 'Warning. Since Parkinson's disease is a progressive disease, cognitive conditions worsen in a short time.

Depression is the most common form of psychic manifestation in Parkinson's disease, with a frequency of 56% in the group studied, characterized by a state of sadness, loss of hope for a long period of time, losing the interest for activities made for pleasure [22].

The dementia is present by the disorders of recovery, confusion incas of recognition and computation, disorientation in an advanced stage with a frequency of 13%.Throughout the study, psychotic symptomatology is present by a frequency of 16%.

Novel compounds such as L 4 (IC50 = 0.11 .mu.M), L8 (IC50 = 0.18 .mu.M), L16 (IC50 = 0.27 um) and L17 (IC50 = 0.48 .mu.m) had selectivity and MAO inhibitory activity B similar to Selegilina. These or others could improve the treatment of Parkinson's disease [23].

Parkinson's disease still affects cerebral circulation and especially the ventricular system. A new model called Modified Gray Wolf Optimization (MGWO) was proposed based on the traditional Wolf Wolf Optimizer (GWO), which acts as a search strategy for selecting features. It uses different types of data sets related to voice, handwriting (spiral and meander) and speech. The presentation algorithm contributes to prediction of Parkinson's disease with an estimated accuracy of 94.83%, a detection rate of 98.28% [24].

Data from our study shows that MRI equipment used with even less than 3T power may indicate some brain damage with a direct or indirect diagnosis of Parkinson's disease. Once those aspects have been detected and recorded, remote tracking and assessment of a patient's prognosis is much easier and more accurate.

The current optimal treatment consists in the continuous administration of L-Dopa derivatives via the portable Duodopa (PDP) pump without feedback. Closed loop control for PDP thus provides a fully automated drug infusion without breaking down, by infusion proportional to the reduction in plasma dopamine levels. This results in the alleviation of side effects caused by incorrect doses in drug therapy[25, 26].

Conclusions

The results of our study show at least a temporary improvement in the quality of life of the patients in the study group following the initiation of progressive release levodopa treatment correlated with the administration of dopamine inhibitors. MRI technology is indispensable in achieving a differential diagnosis but, monitoring the response of dopaminergic centers to medicative treatment. We believe that the use of advanced radiological techniques such as 3T IRM or PET-SCAN can significantly enhance the results of Parkinson's disease.

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