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Morphopathological particularities of cerebrovascular diseases for patients in the northeastern area of Romania

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Abstract

Cerebrovascular diseases (CVD) are pathologies caused by the primary or secondary damage of one or more arteries supplying the brain. Our study aims to create a link between the modifiable risk factors, the affected vascular territory and the clinical manifestation of CVD in patients from our geographical area. Our study proposes the retrospective analysis of a group of 70 patients diagnosed with ischemic stroke with spontaneous hemorrhagic transformation over a period of five years, between April 1, 2015 and April 1, 2018, admitted in the 1st Neurology Clinic, "Prof. Dr. Nicolae Oblu" Clinical Emergency Hospital, Iaşi, Romania. The pathology of strokes is determined by risk factors and comorbidities, which have a clear demographic pattern. The existence of a correlation between demographic risk factors of CVD and the clinical manifestation allows for the individualization of a clinical examination protocol leading to a rapid diagnosis.

Keywords: ischemic stroke, pathology of strokes, cerebrovascular diseases.

Introduction

Cerebrovascular diseases (CVD) are pathologies caused by the primary or secondary damage of one or more arteries supplying the brain (extra-/intracranial). This can occur through ischemic, hemorrhagic or mixed lesions of the cerebral tissue. In acute form, a stroke represents a severe neurological pathology with a reserved or lethal prognosis, determining a clinical syndrome through the ischemic or hemorrhagic lesions of the cerebral tissue [1].

CVD represent the first cause of acquired disability, the second cause of dementia and the third cause of mortality in industrialized countries. Prevalence in Romania is 13.9% in the case of over 70 year old persons, according to a paper written by a research group from Bucharest [2]. The Global prognosis is reserved: 20% mortality rate after one month and 40% mortality at the one-year mark. CVD also represent a cause for increased morbidity.

There are two kinds of stroke: ischemic (80%), divided into constituted infarctions and transient ischemic attacks; and hemorrhagic (20%), represented by spontaneous cerebral hemorrhages or hematomas.

Hemorrhagic transformation is a multifactorial phenomenon and involves the transformation of ischemic cerebral tissue into a hemorrhagic lesion through the rupture of blood vessels, the extravasation of liquids and consequent cerebral lesions. The rate of hemorrhagic transformation of ischemic strokes is estimated to be in the 30–40% range. This process can happen independently in embolic strokes or after thrombolytic therapy. In current times, with the increase in the use of anti-thrombotic therapy, the prevalence of hemorrhagic transformation is increasing and it occupies a central role in the discussion about the complications of cerebral infarctions [3].

The incidence of symptomatic spontaneous hemorrhagic transformation is between 0.6% and 20%. The incidence depends on factors such as age, serum glucose levels, and in some cases on the thrombolytic agent used, the way in which it was administered and the time lapsed between the debut of the stroke and the administration of the treatment [4].

The symptomatology is caused by the ischemia in a cerebral territory, phenomena which can be transitory, seconds to minutes, or can persist for longer periods of time. After such a lesion, permanent damage can occur because the cerebral matter is irreversibly damaged and an infarction takes place.

Neurological symptoms are not, sadly, pathognomonic for the certain diagnosis of cerebral infarction and their succession does not indicate the cause of the ischemia [5, 6]. All of these factors can delay a certain diagnosis and the correct and efficient implementation of an etiopathogenic treatment.

This pathology is multifactorial, among the causes being: age, smoker status, arterial hypertension, diabetes mellitus, obesity, chronic alcohol consumption and hypercholesterolemia. Of the modifiable risk factors, we count: hypertension and other cardiovascular diseases, diabetes, dyslipidemia. These are conditioned by geographical location and socio-economic status. Among the unmodifiable risk factors, we can count general status correlated with age, gender and ethnic background. Approximately 80% of strokes can be prevented only by lifestyle changes [7].

Our study aims to create a link between the modifiable risk factors, the affected vascular territory and the clinical manifestation of CVD in patients from our geographical area.

Patients, Materials and Methods

Our study proposes the retrospective analysis of a group of 70 patients diagnosed with ischemic stroke with spontaneous hemorrhagic transformation over a period of five years, between April 1, 2015 and April 1, 2018, admitted in the 1st Neurology Clinic, "Prof. Dr. Nicolae Oblu" Clinical Emergency Hospital, Iaşi, Romania.

Average age of the patients in the study group was 70.57 years old, with a mean deviation of 13.7 years, a minimum age of 20 years old and a maximum age of 91 years old. For the female patients, the average age was 72.61 years old, with mean deviation of 14.67 years and for the male patients of 68.78 years old, with a mean deviation of 12.87 years. In the analyzed group, the number of male patients was 37 and the number of female patients was 33. 58.28% of patients were from rural areas and 45.72% were from urban areas.

The clinical study was done by collecting the data from patient files: demographic data (age, gender, area of provenance), personal pathological history, comorbidities and risk factors (arterial hypertension, atrial fibrillation, diabetes, dyslipidemia, renal pathology history, neoplasms, and thrombotic risk quantified by chronic venous disease and mutations of Factor V Leiden). The behavior regarding smoking and chronic alcohol consumption was also noted.

Usual laboratory investigations from which glycemia at admission and the presence or absence of thrombocytopenia were noted.

From the clinical exam at admission, we noted the systolic and diastolic blood pressure.

The patients were examined using computed tomography (CT) in emergency, and during the evolution, we followed the topography and dimensions of the infracted area, the presence of sequellary infarctions, the mass effect of the lesion and the particular signs for hemorrhagic transformation.

Also, we noted the evolution of the neurological state of the patient: stationary, favorable, worsening, the appearance of complications or death. For the patients where hemorrhagic transformation occurred while being hospitalized the neurological symptoms that accompanied the event were noted.

The criteria of admission in the study were the presence in the patient file of a main diagnosis of CVD confirmed by CT. In the case of ischemic strokes with hemorrhagic transformation, this was documented either at admission or during the period of hospitalization.

In patients who have suffered major strokes, after which died in Hospital was practiced necropsy. From the cerebral lesions, biopsies were taken and usual Hematoxylin–Eosin (HE) staining was performed. The obtained results were compared with those in CT exploration of patients with the same type of stroke.

Results

The identification of the risk factors for hemorrhagic stroke, ischemic stroke or ischemic stroke with hemorrhagic transformation at admission or during hospitalization represents a basic requirement in the diagnosis and secondary prevention of this disease (Figure 1).

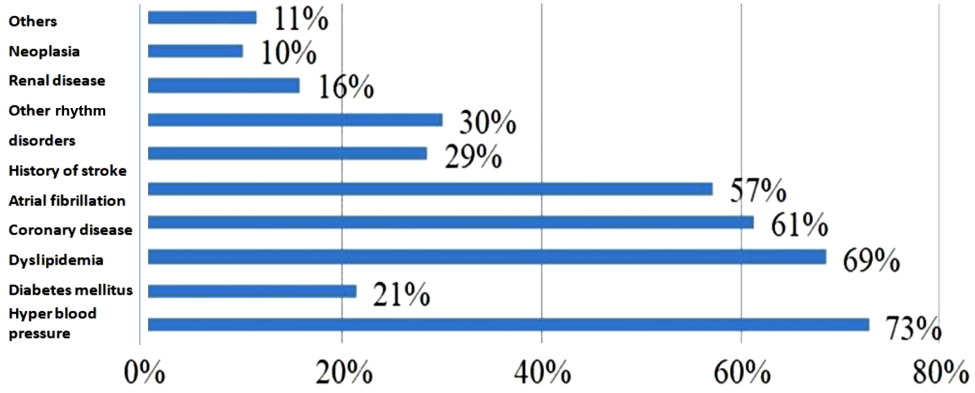

Figure 1 – ***Risk factor distribution in sample group.***

Myocardial infarctions, pectoral angina and ischemic cardiomyopathy of different causes were classified as coronary disease.

Dyslipidemia was documented by serum cholesterol values higher than 200 mg/dL and low-density lipoprotein–cholesterol (LDL-chol) higher than 100 mg/dL during admittance or in the patient's history.

For the diagnosis of arterial hypertension, a history of hypertension, chronic hypertension treatment or persistent systolic blood pressure over 140 mmHg during hospitalization were taken into account.

Other risk factors considered were an interatrial septal aneurysm, a left subclavicular theft syndrome and venous thrombosis of the lower members.

The majority of the patients included in the study had associated cardiovascular risk factors, which can frequently be found in the case of ischemic strokes. Of these well represented in this group were: arterial hypertension (72.85%), dyslipidemia (68.57%), atrial fibrillation (57.14%), history of stroke (28.57%), diabetes mellitus (21.42%).

Of all these predisposing conditions for stroke, the risk factors with the highest predictive value for the hemorrhagic transformation of an ischemic stroke were: atrial fibrillation, hyperglycemia associated or not to a poorly compensated diabetes, dyslipidemia.

Many of these risk factors were associated at the same patient (Table 1). In a large part (48.57%) of the cases, there are three or four associated risk factors and more than five simultaneous risk factors are present in 32.8% of patients.

Table 1 – ***Distribution of simultaneous risk factors***

Risk factors	No. of patients
1–2	10
3–4	34
>5	23

In the studied group, the time period lapsed between the first symptoms and presentation at the emergency room was noted.

Of the total of 70 patients studied, 51 presented with ischemic stroke and the rest with hemorrhagic stroke. Hemorrhagic transformation took place in 10 patients, of which in four patients, it was present at admission, and in six cases, it happened during hospitalization (Figure 2).

In the analyzed group, motor symptoms were most common (94.28%). These can be represented by hemiparesis or hemiplegia. the diagnosis of motor deficits was done through the evaluation of active segmentary movements using the *Medical Research Council* (MRC) Scale for motor deficits (0 – no contraction, 1 – minimal voluntary contraction, 2 – movement possible when canceling the effect of gravity, 3 – movement possible against gravity, 4 – movement possible against resistance, 5 – normal movement). Any result between 0 and 3 was considered a motor deficit.

The precocious identification of the complications of strokes and their treatment is defining, as this influences the mortality and the short and long-term functional prognosis. We note a high rate of correlation between hemorrhagic transformation and other possible precocious complications of an ischemic stroke. All of these manifestations were present at admission or appeared during the first week (Tables 2 and 3).

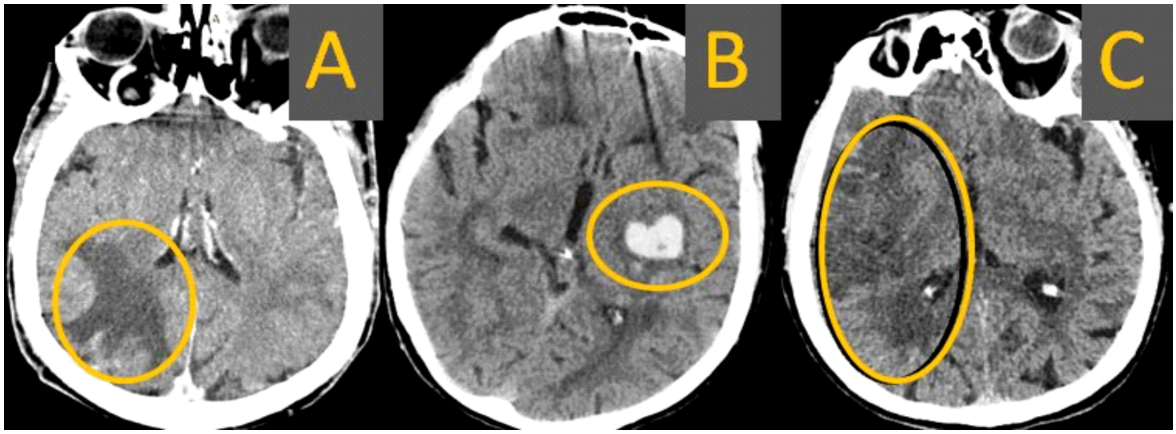

Figure 2 – ***CT examination in the case of ischemic stroke, hemorrhagic stroke and ischemic stroke with hemorrhagic transformation: (A) Ischemic right parieto-occipital edema without contrast uptake and without medial line mass effect – ischemic stroke right PCA, right lateral homonymous hemianopsia (occipital lobe) with light right hemiparesis (subthalamic area) and right hemihypoesthesia (parietal lobe); (B) Native CT, hyperdense hemorrhagic lesion in left interior capsule; (C) Native CT, hypodense area in the territory of the right MCA with minimal hemorrhagic transformation. CT: Computed tomography; PCA: Posterior cerebral artery; MCA: Middle cerebral artery.***

Table 2 – ***Frequency of complications***

Stroke complications			Simultaneous complications	No. of patients
Variable	***No. of patients***	***Percent***		
Respiratory tract infection	17	24.28%	*0*	21
Urinary infection	12	17.14%	*1–2*	39
Swallowing disorders	13	18.57%	*3–4*	10
Electrolyte disturbance	22	31.42%		
Epilepsy	2	2.85%		
Urinary incontinence	7	10%		
Depression	7	10%		
Cerebral edema	12	17.14%		

Table 3 – ***Main and associated neurological signs at admission***

Clinical neurological picture at admission			Associated neurological signs		
Variable	***No. of patients***	***Percent***	***Variable***	***No. of patients***	***Percent***
Glasgow Coma Scale (GCS)	14–52	74.28%	*Dysarthria*	6	8.57%
	15	21.42%	*Hemianopsia*	24	34.28%
	8–13	4.28%	*Hemihypoesthesia*	15	21.42%
	0–7	3%	*Vertigo*	7	10%
Aphasia	35	50%	*Cephalia*	16	22.85%
Motor deficiency	66	94.28%	*VIth nerve paresis*	51	72.85%
Visual field disorders	2	2.85%	*Conjugate deflection of the eyeball*	3	4.28%
			Signs of atherosclerosis	36	51.42%
			Others	20	28.57%

In the studied group, only in two cases, the ischemic stroke resulted in deep vein thrombosis and only one case presented hematemesis as a complication, in the absence of known digestive disease.

At admission, in the studied group, we noted the mean systolic blood pressure of 144.17±27.9 mmHg, with a maximum of 230 mmHg and a minimum of 80 mmHg. The mean diastolic blood pressure was 82.8±14.8 mmHg, with a maximum value of 130 mmHg and a minimum of 50 mmHg. Of the 40 (57.14%) patients with hyperglycemia, only 27.5% were previously diagnosed with diabetes, the rest of 72.5% presenting with hyperglycemia at admission without other determining factors. The glucose levels of these patients normalized in 1–2 days after admission.

According to the classification of blood pressure values in the *European Society of Hypertension/European Society of Cardiology* (ESH/ESC) 2013 Guide, the mean value of the study group's blood pressures is qualified as hypertension (systolic blood pressure over 140 mmHg and diastolic blood pressure over 90 mmHg).

The laboratory tests run at admission included serum glucose levels. Thus, the mean value for 70 cases was 132.97±52.68 mg/dL, with a maximum of 368 mg/dL and a minimum of 72 mg/dL. Normal glycemia values are between 65 and 110 mg/dL. To sum up, the mean serum glucose levels show a tendency towards hyperglycemia.

Imagistic studies using CT without contrast allows for the differential diagnosis between ischemic and hemorrhagic strokes, but the role of CT as a predictive parameter for hemorrhagic transformation is still debated.

In this paper, we examined the CT images obtained early after admission, in the first few hours (Table 4).

Table 4 – ***Distribution of patients by closed arterial branch***

Area of stroke	No. of patients	Percent
Carotid territory	2	2.85%
Anterior cerebral artery	2	2.85%
Right medial cerebral artery	32	45.71%
Left medial cerebral artery	24	34.28%
Posterior cerebral artery	16	22.85%
Vertebro-basilar system	1	1.42%
Cerebellar	3	4.28%
Anterior carotid artery	3	4.28%

In the case of patients, presenting with uncomplicated ischemic stroke, possible candidates for thrombolytic could not be evaluated because the time lapsed from the debut of the symptoms was impossible to quantify (Figure 3).

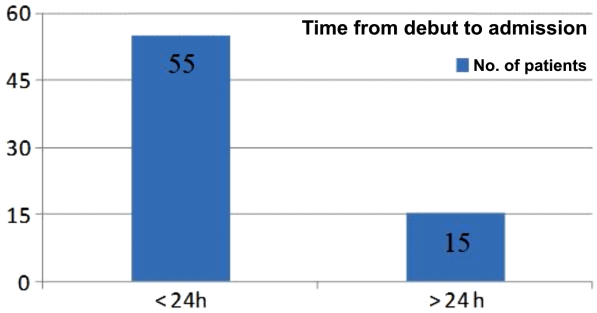

Figure 3 – ***From this graphic, we observe that 78.57% of patients with the debut of symptoms less than 24 hours before admission, allowing for acceptable clinical and imagistic diagnosis and appropriate therapy for ischemic strokes.***

The first imagistic feature studied was whether the patient had older cerebral infarctions.

From the 70 cases included, 30% had sequellary lesions visible on CT. These results reflect the recurrence of embolic events. The results of the statistic analysis show a large percent of medium-sized infarction areas: 70% (the volume of the infarction area was bigger than 1.5 cm^2 and involved the area supplied by one main artery). Massive ischemic infarctions (the volume of the infarction area was bigger than 1.5 cm^2 and involved the area supplied by two or more main arteries) happened in only 28.57% of cases.

Out of 70 cases, only in five particular aspects were described at CT. Noted were the bilateral disappearance of the ambiens nucleus and of the right interpeduncular nucleus, a spontaneous hyperdensity in the right middle cerebral artery (MCA) (suggestive for a thrombus), the disappearance of the intergyral sulcus, the loss of differentiation between the white and grey matter and spontaneous hyperdensity in the M1 Sylvian segment (suggestive for a thrombus). All of these are signs of hyper-acute ischemic stroke. All strokes that resulted in death were embolic and had an aspect of liquefactive necrosis on HE staining (Figures 4–6).

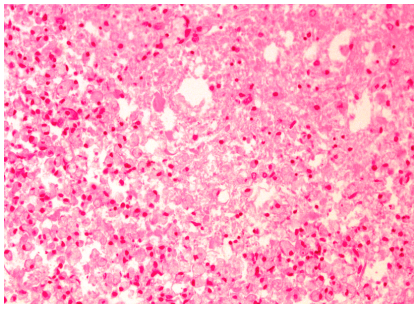

Figure 4 – ***Liquefactive necrosis surrounded by lipid-laden macrophages that ingested the products of degradation of dead neurons and myelin (HE staining, ×200).***

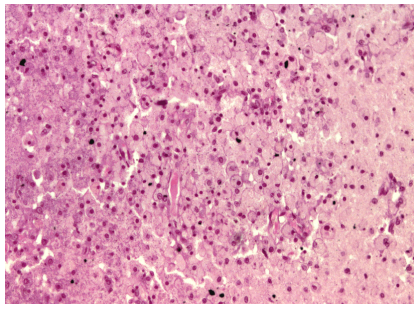

Figure 5 – ***Foamy macrophages that cleaned up the lipid debris from the liquefactive necrosis and newly formed capillary vessels (HE staining, ×200).***

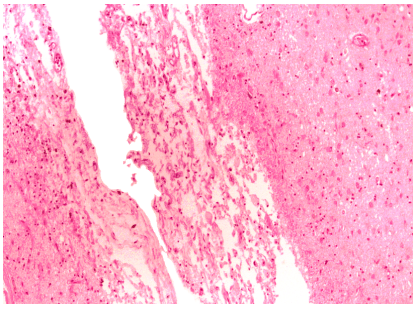

Figure 6 – ***Resolution of the liquefactive necrosis led to a cystic area surrounded by foamy macrophages, rare fibroblasts, rare lymphocytes, and few new capillary vessels. The nervous tissue around the cavity expressed reactive astrogliosis (HE staining, ×100).***

The mass effect of the infarction was present in 35.71% of cases. Of this group, where mass effect complicated the stroke, 28% had massive infarction and 68% had a medium area of infarction. Fifty-six percent of the patients in this group presented hematomas.

Discussions

Of the risk factors for stroke, some cannot contribute individually to the formation of the stroke, but can determine it if they are associated with other attributes [8]. Some cases of stroke do not have risk factors as currently recognized in medical literature but some of these parameters can indicate a higher chance of stroke [9].

The paper aims to discover unusual, rare associations of risk factors in the population of our geographic area, which lead to a high stroke potential.

In the case of our test group, we observe that the predominant localization of strokes with bleeding potential is the right or left MCA. In this case, the deeper territories represented by the basal nuclei and the thalamus were very rarely affected.

We note the fact that there were no bilateral ischemic strokes in the area of the MCA. In the case of multiple infarctions, these were common in the border area between the MCA and the posterior cerebral artery (PCA). The evaluation of the infarction area is of utmost importance because a wide infarction area is recognized as a risk factor for hemorrhagic transformation and as negative prognosis factor for subsequent evolution of the patient.

The physiological reason why a larger volume of the ischemic infarction predisposes the patient to hemorrhagic transformation is that more of the hematoencephalic barrier, where ruptures occur, is involved.

Hyperglycemia is considered damaging for cerebral metabolism in the infarcted area and can constitute a predictive factor for the hemorrhagic transformation of an ischemic stroke. Chronic hyperglycemia in the case of uncontrolled diabetes has the same risks as acute hyperglycemia, rising the risk of hemorrhagic transformation and unfavorable evolution. Acute hyperglycemia can occur because of the stress through the activation of the hypothalamic–hypophyseal–suprarenal axis or can be the expression of an undiagnosed case of diabetes or low tolerance to glucose.

The ratio of complications of ischemic strokes through hemorrhagic transformation is 1.18 times grater in patients from rural areas than in those from urban areas.

With ageing, changes occur in the small vessels of cerebral circulation and more cardiovascular risk factors appear [10–13]. In particular, it is demonstrated that amyloid angiopathy predisposes to hemorrhagic intracerebral bleeding [14]. At the same time, patients that have leukoaraiosis (the asymptomatic rarefaction of the white cerebral matter) as a mark of ageing increase the risk of hemorrhagic remaniation of ischemic strokes [15–18].

At the tissue level, the strokes produced by the stroke are necrotic. Uncrossed tissue will be removed by the macrophages and the reflexes coordinated by the destroyed nervous centers can be taken over by other cortical areas over time.

The clinical evaluation of patients with neurological symptoms has to account for the understanding of CVD classification and has to realize a rapid initial evaluation in order to stabilize vital signs and to determine whether intracranial bleeding is present, justifying reperfusion therapy in the case of patients with ischemic stroke. Forming an etiological hypothesis based on history, physical exam, and initial imaging study (usually a CT scan without contrast) is an integral part of the exploration protocol for these patients.

In specialty literature, other rare or very rare risk factors are described. Tyrosine kinase inhibitor therapy for chronic myeloid leukemia was associated with progressive peripheral arterial disease, and more recently, there were reported cases showing rare intracranial vascular stenosis.

Another rare cause is fibromuscular dysplasia, which represents a non-atheromatous vasculopathy, non-inflammatory of unknown origin, which mostly affects small and medium sized arteries. It affects mostly female patients and the renal, carotid and extracranial portion of the vertebral vessels [19–21].

Thus, the patient having a high risk for stroke has at least two elevated risk factors together with a small or medium risk factor. Patients having an association of 3–4 major risk factors already had sequellary lesions in over 30% of cases.

The association characterizing the study group is between arterial hypertension, dyslipidemia and atrial fibrillation, causing ischemic stroke in the right or left MCA territory. The clinical signs common to these cases are motor deficits and facial paralysis.

Adding smoking and/or chronic alcohol consumption to diabetes increases the risk for ischemic stroke by 47% and of hemorrhagic stroke by 155 in the test group.

Stroke risk higher than 30% is present in paraneoplastic syndrome and/or in patients who take anticoagulant therapy for a long time or who have chronic kidney disease.

The data in our study clearly shows a pathological mechanism mostly based on right MCA ischemia caused by atherosclerosis and dyslipidemia.

Conclusions

The results of this study must be interpreted carefully as the study was undertaken in one single hospital and thus does not reflect the situation in the general population. Patients with hemorrhagic or ischemic with hemorrhagic transformation stroke were evaluated only using CT scans, without benefiting from magnetic resonance imaging (MRI) scans. MRI has a much higher sensibility for the detection of hemorrhagic transformation risk in a patient, thus there was a chance that eligible patients were not included. Furthermore, some important information for determining the risk of hemorrhagic transformation in a patient with ischemic stroke were not included in patient files, such as: ferritin levels, urinary albumin, a complete lipid profile, including LDL levels, *National Institutes of Health Stroke Scale* (NIHSS) score at admission and dismissal and angiographic data. The pathology of strokes is determined by risk factors and comorbidities, which have a clear demographic pattern. The existence of a

correlation between demographic risk factors of CVD and the clinical manifestation allows for the individualization of a clinical examination protocol leading to a rapid diagnosis.

Conflict of interests

The authors declare that they have no conflict of interests.

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