

## ORIGINAL RESEARCHES

<https://doi.org/10.52418/moldovan-med-j.64-2.21.01>  
UDC: 616.831-005.4-053.2



## Ischemic stroke in children depending on risk factors

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Manuscript received June 18, 2020; revised manuscript April 12, 2021; published online April 28, 2021

### Abstract

**Background:** Ischemic stroke (IS) in children is a major neuropediatric emergency. The incidence of stroke in children is from 2 to 13 for 100000 children. IS in perinatal period occurs in 1 for 2300 – 5000 live births.

**Material and methods:** In 2010 – 2019 in the Republic of Moldova was carried out a retrospective as well as prospective study on a cohort of 458 children diagnosed with stroke. Were studied possible risk factors related to IS. Out of 458 children, 284 children with IS were selected and diagnosed during the reference period.

**Results:** IS was determined in 284 cases with the diagnosis of stroke (62%, 95CI 59.73-64.27). Among the most common risk factors for the development of neonatal IS are pathologies of amniotic membranes in 113 cases (39.8%, 95CI 36.9-42.7), pathologies of amniotic fluid with meconium in 135 cases (47.5%, 95CI 44.54-50.46), and history of urgent caesarean section in 132 cases (46.5%, 95CI 43.54-49.46). Among the etiological causes of IS in the studied children were: congenital heart anomalies in 52 cases (18.3%, 95CI 16.01-20.59), neonatal encephalopathy in 27 cases (9.5%, 95CI 7.76-11.24), genetic syndromes in 18 cases (6.3%, 95CI 4.85-7.75), sickle cell disease – 5 (1.8%, 95CI 1.06–2.54), MELAS syndrome – 4 (1.4%, 95CI 0.7-2.1).

**Conclusions:** IS risk factors are an important problem in clinical research. Most often, there is not a single risk factor responsible for the development of IS in children.

**Key words:** stroke, ischemic, children, risk factors.

### Cite this article

Sprincean M, Hadjiu S, Calcii C, Lupusor N, Revenco N, Groppa S. Ischemic stroke in children depending on risk factors. *Mold Med J.* 2021;64(2):5-11. <https://doi.org/10.52418/moldovan-med-j.64-2.21.01>.

### Introduction

Stroke is a rare pathology in children and adolescents, often underestimated. The incidence of ischemic stroke in pediatric patients according to several studies is from 2 to 13 of 100000 children, from 1 to 5 of 100000 children for hemorrhagic stroke and 0.67 of 100000 children for sinus venous thrombosis [1]. Ischemic stroke (IS) most often occurs in the prenatal period and in the first 28 days with a frequency of 1:4000 live newborns. IS can also occur during the fetal period, from the 14th week of pregnancy to birth. Perinatal IS is caused by an ischemic lesion that occurs from the 20th week of pregnancy to 28 days after the birth. Data from the literature show that perinatal IS occurs in 1 of 2300 to 5000 live newborns, with an estimated mortality rate of 3.49 for 100000 annually [2].

Studying the risk of IS occurring in children in aspects

of risk factors is a currently important issue for contemporary neurology both nationally as well as internationally and is an object of extremely valuable scientific studies. There is currently a large number of children in the Republic of Moldova who have had IS, and actual incidence of this pathology is not known.

The risk factors of IS in children and adolescents are different from those of adults. Scientific research revealed that IS in children is often the result of a simultaneously acting several risk factors. Thus, IS etiology in childhood is multifactorial. Were determined five main groups of stroke in children, such as: (1) diseases of the blood, i. e., Shonlein-Henoch disease, aplastic anemia, hemophilia, hemoglobinopathies, leukemia, von Hippel-Lindau syndrome; (2) various types of thrombocytopenies, coagulopathies and vasculopathies; (3) congenital heart anomalies; (4) congeni-

tal disorders of metabolism; (5) vasculitis, e. g., rheumatic vasculitis, primary cerebral vasculitis, Moyamoya disease, Takayasu's disease, Behçet's disease, etc. [3]. Genetic diseases are considered to be significant risk factors in more than half of stroke cases. Among genetic diseases at risk of developing of IS in children we should note tuberous sclerosis, fibromuscular dysplasia, Moyamoya disease, MELAS syndrome, hereditary connective tissue dysplasia, sickle-cell disease, hereditary hemorrhagic teleangiectasia, i.e. Osler-Weber-Rendu syndrome, hyperhomocysteinemia, homocysteinuria, Fabry disease, cerebrotendineous xanthomatosis etc. [4].

**The aim:** Studying the risk of stroke in children in aspects of risk factors based on analysis of statistical data and pathologies in newborns and children of pediatric age, with the aim of improving early diagnosis.

**Material and methods**

For the investigation we studied the possible risk factors for the development of IS in 458 children with stroke from the Republic of Moldova during the years 2010 – 2019. 284 children with IS diagnosed during the given period were included in the target group. The etiological diagnosis of IS included obtaining the historical data, i.e., prenatal history, diseases of mother, course of pregnancy, perinatal and post-natal history, neurological status and general somatic status, the results of neurological investigations, i.e., ultrasound visualization of nervous system and electroencephalography, and neurological imaging methods, i.e., magnetic resonance imaging and cerebral computed tomography.

**Results**

A retro- and prospective study of a cohort of 458 children from the Republic of Moldova who suffered stroke in the period from 2010 to 2019 was carried out. Clinical diagnostic and imaging methods have allowed the detection of stroke in children from the earliest stages of intrauterine development. The age of the children included in the study ranged from that of newborns to 18 years. 284 children with IS were selected, and was performed the analysis of etiology and predictive risk factors for the development of the disease.

The results of the study and statistical analysis of a cohort of 458 children with pediatric stroke revealed the following results of gender distribution, namely, in the review predominate the male patients, i.e., 272 cases (59.4%, 95CI 57.11-61.69), compared to the female patients, i.e., 186 cases (40.6%, 95CI 38.31-42.89) (fig. 1).

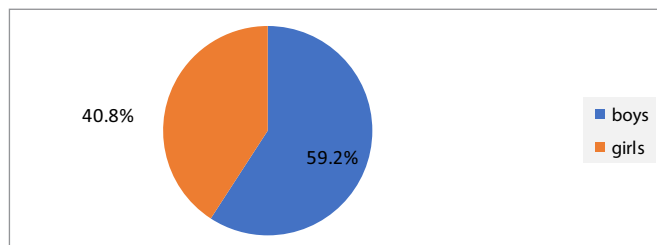


Fig. 1. Gender distribution of children investigated with stroke (%)

According to the obtained results, the structure of stroke in investigated children is as follows: SI in 284 cases (62%, 95CI 59.73-64.27), hemorrhagic stroke (HS) in 144 cases (31.4%, 95CI 29.23-33.35) and mixed stroke in 30 cases (6.6%, 95CI 5.44-7.76) (fig. 2).

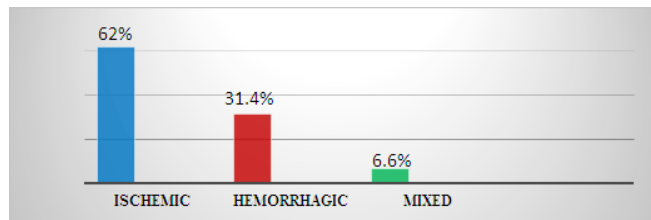


Fig. 2. Types of stroke in investigated children (%)

According to the results of the study, out of the total number of 284 children with IS, in 206 cases IS developed during the neonatal period (72.5%, 95CI 69.85-75.15), in 12 cases they suffered IS during the fetal period (4.2%, 95CI 3.01-5.39) and in 66 cases children suffered IS in early childhood and adolescence (23.20%, 95CI 20.69-25.71) (fig. 3).

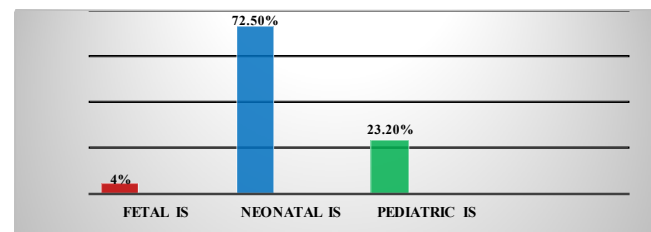


Fig. 3. Distribution of the patients according to the age of onset of IS

Data on the variables of neonatal IS showed the following results: pathologies of fetal membranes were in 113 cases (39.8%, 95CI 36.9-42.7), meconial amniotic fluid in 135 cases (47.5%, 95CI 44.54-50.46), early urgent caesarean section in 132 cases (46.5%, 95CI 43.54-49.46), placental pathologies in 104 cases (36.6%, 95CI 33.74-39.46), umbilical cord pathologies in 122 cases (43.0%, 95CI 40.06-45.94), and some other factors are shown in figure 4.

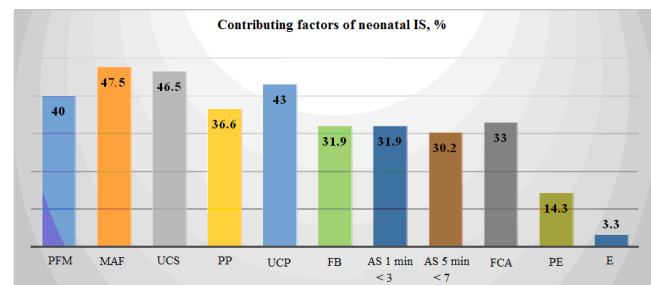


Fig. 4. Risk factors of neonatal IS (%)

*Note.* Pathology of fetal membranes, PFM; meconium in amniotic fluid, MAF; urgent caesarean section, UCS; placental pathology, PP; umbilical cord pathology, UCP; first birth, FB; Apgar score (1 min) < 3, AS 1 min < 3; Apgar score (5 min) < 7, AS 5 min < 7; fetal cardiac arrhythmia, FCA; pre-eclampsia, PE; eclampsia, E.

Analysis of obstetric history shows the presence of an unsatisfactory pregnancy development in about half of

cases. One of the risk factors in the development of perinatal pathologies is the maternal age, especially up to 18 years and that which exceeds 30 years. The age of mothers at birth of premature babies included in the study was from 17 years to 45 years (average  $25.4 \pm 5.2$ ). The total number of underage mothers was 11 (3.9%, 95CI 2.76-5.04), that of mothers over 30 years of age was 135 (47.5%, 95CI 44.54-50.46), 18 of whom were over 40 years of age (6.3%, 95CI 4.85-7.75). The vast majority of children in the study group came from rural areas, i.e., 187 children (65.8%, 95CI 62.99-68.61), while 97 children were urban (34.2%, 95CI 31.39-37.01). Analyzing the data of the obstetric history in the basic group we found that 103 of pregnant women (36.3%, 95CI 33.45-39.15) had miscarriages or stopping evolution of pregnancies. Pathological evolution of pregnancy is characterized by various complications arising from the first and second trimesters of pregnancy.

Among the significant risk factors for perinatal IS should be noted pathologies of the placenta, amniotic membranes, umbilical cord, meconium in amniotic fluid, eclampsia, urgent cesarean section, pre-eclampsia, first birth, low Apgar score, and oligoamnios. Thus, the most common complication of the antenatal period was the imminence of premature birth in 138 cases (48.6%, 95CI 45.63-51.57), pre-eclampsia in 42 cases (14.8%, 95CI 12.69-16.91) and eclampsia in 10 cases (3.5%, 95CI 2.41-4.59) (fig. 5).

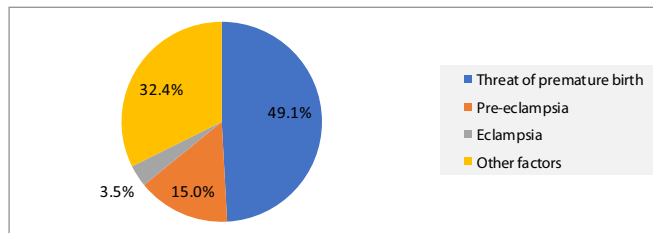


Fig. 5. Factors for perinatal IS

Among the etiological causes of IS in the studied children we should note congenital heart anomalies in 52 cases

Table 1. Etiology of IS in children

Etiology of IS	Abs. No.	%, 95CI
Congenital heart anomalies	52	18.3%, 95CI 13.21-17.99
Systemic diseases	45	15.8%, 95CI 13.63-17.97
Neonatal encephalopathies	27	9.5%, 95CI 7.76-11.24
Genetic syndromes	18	6.3%, 95CI 4.85-7.75
Sickle cell disease	5	1.8%, 95CI 1.06-2.54
MELAS syndrome	4	1.4%, 95CI 0.7-2.1
Metabolic diseases	8	2.8%, 95CI 1.82-3.78
Cerebral vasculitis	5	1.8%, 95CI 1.06-2.54
Infections	15	11%, 95CI 3.97-6.63
Moyamoya syndrome	4	1.4%, 95CI 0.7-2.1
Cerebral vascular anomalies	9	3.2%, 95CI 2.16-4.24
Coagulopathies	8	2.8%, 95CI 1.82-3.78
Posr varicella angiopathy	3	1.1%, 95CI 0.49-1.71
Oncological factors	5	1.8%, 95CI 1.06-2.54
Trauma	6	2.1%, 95CI 1.25-2.95
Non determined etiology	34	12.0%, 95CI 10.07-13.93

(18.3%, 95CI 16.01-20.59), systemic diseases in 45 cases (15.8%, 95CI 13.63-17.97), neonatal encephalopathy in 27 cases (9.5%, 95CI 7.76-11.24), genetic syndromes in 18 cases (6.3%, 95CI 4.85-7.75), sickle cell disease in 5 cases (1.8%, 95CI 1.06-2.54), MELAS syndrome in 4 cases (1.4%, 95CI 0.7-2.1), metabolic diseases in 8 cases (2.8%, 95CI 1.82-3.78) and also other pathologies which are presented in tab. 1.

## Discussion

The characteristics of variables of IS in children are very different from those of adults. Stroke risk factors are an important problem in clinical research. The diversity of risk factors creates a heterogeneous patient population. In addition, studies focused on pediatric stroke etiology are relevant for ischemic stroke, not for hemorrhagic one. Some studies have improperly combined ischemic and hemorrhagic strokes for risk analysis. More than half of children with stroke develop disabilities at an early and pre-school age. Repeated strokes are observed in 20% of patients [5]. Some authors note common risk factors for ischemic stroke in children, such as congenital heart defects, homocysteine metabolism disorders and thrombophilic disorders, as well as upper respiratory tract infections, mild head trauma etc. [6].

*Genetic diseases which are risk factors for IS in children.* Homocystinuria may cause IS and should be suspected in the presence of Marfanoid phenotype and mental retardation associated with the dislocation of the lens and occasionally *pectus excavatum*. Homocystinuria is a rare hereditary condition affecting amino acids metabolism, namely methionine. This autosomal recessive disorder is characterized by abnormal storage of homocysteine and its metabolites methionine, and S-adenosyl derivatives in blood and urine. Although homocystinuria is usually associated with ischemic stroke, the sudden occurrence of stroke as a result of homocystinuria is very rare in infancy. Increasing of thickness of carotid plaques was associated with high levels of homocysteine and with lowering the level of vitamin B12 and with following increasing risk of stroke. This association between homocystinuria and vascular complications was reported for the first time in 1976 [2] and since then, several studies have confirmed this association [7]. Nutritional deficiencies of folic acid or vitamin B12 can also cause hyperhomocystinemia, which leads to stroke.

*MELAS syndrome* or mitochondrial myopathy, encephalopathy, lactic acidosis and stroke is a multisystem and progressive neurodegenerative disorder. Cases of MELAS syndrome may occur sporadically or as hereditary transmission on a maternal line with a variable expressiveness of clinical manifestations. Patients with MELAS syndrome may have the following symptoms such as: mitochondrial encephalopathy, lactic acidosis and stroke events, but also with other manifestations such as headache, seizures, cognitive and verbal disorders, sensory neural deafness, muscle weakness and mental retardation.

*Hereditary dysplasias of connective tissue* are considered to be significant risk factors in about 10% of cases [8].

Genetic background of ischemic and hemorrhagic accident is often polygenic or multifactorial. It can be determined in some cases by a particular single gene disease, especially in children and young adults. Apart from the mentioned risk factors, many types of dysplasia of connective tissue can cause stroke. Hereditary dysplasias of connective tissue (HDCT) represent a group of hereditary single gene pathology determined by mutations in genes responsible for collagen synthesis and metabolism. HDCT may be characterized by severe manifestations, are relatively common and sufficiently understood at the molecular level to provide useful paradigms for a number of associated diseases [8].

Of the most prevalent HDCT should be noted Ehlers-Danlos syndrome, Marfan syndrome, osteogenesis imperfecta, spondyloepiphyseal dysplasia congenita, achondrogenesis, Stickler syndrome, hereditary angiopathy, Alport syndrome, benign family hematuria, etc. These are caused by mutations in collagen and the extracellular matrix genes. For example, mutations in the COL4A1 gene are considered to be the cause of small vessels anomalies in adults presenting ischemic stroke or intracerebral hemorrhage [9].

*Cerebrotendineous xanthomatosis* is a hereditary disorder, caused by mutations of the CYP27A1 gene, characterized by abnormal storage of lipids in many parts of the organism [9]. In this disorder in the organism of the patients certain lipids such as cholesterol cannot effectively decompose so these fats form fatty yellow nodules called xanthomas, which accumulate in the body, especially in the brain and in tendons. Symptoms may include diarrhea, cataracts and progressive neurological problems, such as seizures, movement disorders, stroke, dysarthria, sensitivity disorders, peripheral neuropathy, hallucinations and depression. Other symptoms may include fragile bones that are prone to fractures and an increased risk of developing cardiac or pulmonary impairment due to the accumulation of lipids [9].

*Fibromuscular dysplasia* (FMD) is a hereditary condition that causes cell growth of the arterial walls. Extracellular growth leads to narrowing the arteries and causing reduction of blood flow. It can also cause aneurysms and dissections in the carotid arteries with the development of a hemorrhagic stroke.

Genetically determined pathologies are increasingly

**Table 2. Genetic diseases which are risk factors for IS in children [9]**

Diagnosis/Pathology	Description	Genetic testing	Treatment
Homocystinuria.	Deficiency of cystathionine beta synthase, autosomal recessive inheritance.	Increasing the serum level of homocysteine.	Supplement of B6, B12 vitamins, folic acid, betaine. Diet with methionine exclusion and supplement of cysteine, C vitamin.
MELAS syndrome, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes.	Maternal inherited mitochondrial dysfunction manifested with lactic acidosis, seizures and IS episodes.	Increasing the serum level of pyruvic acid and lactate, biopsy of skeletal muscles.	Coenzyme Q10, idebenone, L-arginine, supplement of carnitine.
Ehlers-Danlos syndrome.	COL3A1 mutation in gene encoding procollagen type III. Clinical features are: thin lips, hyperelasticity of skin, increased softness of ligaments, articular hypermobility, vascular fragility which can lead to intrauterine rupture, IS, aortal dissection, tendon ruptures.	Clinical examination, biochemical analyses, molecular genetic analysis of COL3A1.	Beta blockers, surgery of dilated aorta.
Fibromuscular dysplasia.	Autosomal dominant inheritance, non-inflammatory non-atherosclerotic vessels pathology. Symptoms: focal arteriopathies, stenotic in children with IS. Can lead to vascular occlusion, dissections or aneurisms.	Clinical history, CT/MRI/angiography, diagnosis of pathological tissues of renal or temporal arteries.	Little studied. Screening of multi-systemic vascular complications.
Marfan syndrome.	Autosomal dominant inheritance, FBN1 mutation in gene encoding fibrillin 1. Skeletal symptoms are: high waist, long limbs, arachnodactyly, deformities of the chest and spine, etc. Cardiovascular manifestations are: aorta dissection, aorta aneurism, prolapse of mitral valve. Eye manifestations are: flattened cornea, myopia, crystalline subluxation. Neurovascular symptoms are from spontaneous intracerebral artery dissections to cardioembolization or aorta dissections.	Clinical examination, criteria of diagnosis. Molecular genetic analysis of FBN1.	Beta blockers, ACE inhibitors, surgery or conservative treatment of aortic aneurism.
Pseudoxanthoma elasticum.	Autosomal recessive inheritance, ABCC6 mutations, disorder to the assembly of elastic fibres. Cerebral vascular symptoms are: IS, intracerebral aneurisms.	Skin biopsy, sequencing of ABCC6.	Treatment in process of researches. Management of risk factors.

recognized as a cause of IS in children. Among the most common genetic diseases at risk of IS in children are: homocystinuria, MELAS syndrome, Ehlers-Danlos syndrome, Marfan syndrome, fibromuscular dysplasia, pseudoxanthoma elasticum etc. The list continues to expand, including mutations *COL4A1*, *ACTA2* and pericentrin (*MOPD2*) and syndromes, such as Alagille and PHACE. The most studied syndrome is Moyamoya disease (MMD), which is characterized by a progressive, usually bilateral stenosis or occlusion of intracranial internal carotid arteries, which involves the anterior and medial cerebral arteries. The cause of MMD disease is mutations in the *RNF213* and other mutations of *BRCC3 / MTCPI* and *GUCY1A3* [10]. Based on the study data presented, in 6.3% of studied children (95CI 4.85-7.75) had various genetic diseases, including homocystinuria; metabolic disorders occurred in 2.8% (95CI 1.82-3.78) of studied children. In 3.2% (95CI 2.16-4.24) of the children surveyed in the current study were cerebral vascular anomalies, and 1.4% (95CI 0.7-2.1) of children had Moyamoya syndrome.

Genetic arteriopathy caused by a deficiency of adenosine deaminase 2 (*ADA2*) has been reported with clinical characteristics that included intermittent fever, lacunar stroke from early childhood and acute onset eruptions; histopathological changes included compromised endothelial integrity, endothelial cellular activation and inflammation [11, 12].

*Hereditary coagulopathies and thrombophilia.* One or more prothrombotic conditions were identified in 20 to 50% of children who had stroke [13]. The main mutations associated with prothrombotic states are described in factor V Leiden, prothrombin G20210A, methylentetrahydrofolate reductase (*MTHFR*; C677T and A1298C), protein C, protein S, antithrombin and lipoprotein (a) [9]. Most stroke experts consider coagulopathy to be a potential risk factor for a stroke that usually works in combination with other factors, rather than being an independent causal mechanism. Thus, it is reasonable to look for more common prothrombotic conditions in patients with another identified stroke risk factor and in patients with a history of ischemic or thrombotic stroke; in this case, oral contraceptives may be discontinued in adolescents. If homocysteine is found to be high, specific diet or supplementation with folate, vitamin B6 or vitamin B12 can be administered and, in general, patients with a prothrombotic tendency should be consulted by a hematologist [9]. In 2.8% (95CI 1.82-3.78) of the children who had IS were diagnosed hereditary coagulopathies and thrombophilia.

*Acquired prothrombotic disorders* secondary to protein C and S deficiencies may occur in children with renal pathology and liver disease, including nephrotic syndrome with the loss of coagulation factors. Protein C deficiency was also reported in children taking valproate. The iron deficiency was reported in children with IS and venous thrombosis, with no other apparent etiology.

*Heart diseases* are the most common cause of stroke in infancy, representing up to one third of all strokes. In chil-

dren after heart surgery or with catheter, almost 50% of all cases of stroke occur within 72 hours. Prolonged cyanotic episodes provoke polycythemia and anemia, both increasing the risk of thromboembolic stroke. Embolic clots may occur in children with cardiomyopathies, rheumatic and cardiac diseases, artificial heart valves or valvular vegetations in endocarditis. Foramen ovale may occur in more than 35% of patients aged from one to 29 years, and this opening can serve as a prerequisite for venous embolic events in which it is necessary to move embolus from the right to the left side of the heart [2].

*Moyamoya disease* is a rare, progressive, occlusive disease of cerebral arteries, with a special involvement of circle of Willis and the arteries that vascularized it [10]. The affection can cause a transient ischemic attack or stroke with deterioration of brain functions and cause cognitive and developmental delay. Moyamoya disease most commonly affects children, being associated with the following clinical signs: headache, weakness, numbness or paralysis in the face, arm or leg, usually on one side of the body, visual disturbances, aphasia, developmental delay, involuntary movements, and cognitive decline. These symptoms can be triggered by physical exercise, crying, coughing, tension or fever.

*Sickle cell anemia (SCA)* is a very frequent cause of pediatric stroke, which occurs in 285 cases to 100000 children affected [7]. The stroke may occur earlier than the age of 18 months, but in most children the disease manifests after the age of five years. IS is more prevalent at the younger age. The stroke may occur in the absence of pain or aplastic crisis. Two-thirds of the children with SCA have had previous strokes, but without the treatment they will have a recurrence. Children with *sickle cell disease* make up another important group of patients at high risk of arteriopathies and stroke. Prior to using the modern primary prevention strategies, up to 11% of children with heart disease had a clinical stroke by the age of 20. In 1992 it was found out that transcranial Doppler ultrasonography (TCD) proved to be effective in identifying patients with sickle cell disease at high risk of stroke, and at present primary prevention is possible using chronic red cell transfusions in patients with sickle cell disease and increased cerebral blood flow on TCD. This approach decreased the prevalence of stroke by about 1% [14]. Based on the data obtained in this study, 1.8% (95CI 1.06-2.54) of the children who had IS have had sickle cell disease.

IS in *metabolic disorders* are rare, but important for children. Energy depletion leads to ischemic lesions in mitochondrial disorders. In TCA cycle disorders, toxic deposits lead to the destruction of brain tissue. For this reason, IS in metabolic disorders do not occur in a certain vascular territory; so, e. g., in MELAS syndrome stroke occurs mainly in the occipital area. Other metabolic problems, such as Fabry disease, lead to focal arteriopathy [9]. MELAS syndrome was found in 1.4% (95CI 0.7-2.1) of children included in the present study.

*Infection of the upper respiratory airways* causes local inflammation of the vascular wall with the development

of cerebral arteriopathy and increased prothrombotic potential. Arteriopathy resulting from a traumatic factor and increased physical activity causes a stroke in 17% to 33% of cases [9]. In present study, 11% (95CI 3.97-6.63) of the children had infections.

*Primary thrombophilia* caused by mutations in the genes of the haemostatic system is a risk factor for ischemic stroke in 10 – 50% of cases in patients under 18 years of age in the European population [15]. Studies of polymorphisms in the genes methylenetetrahydrofolate reductase (MTHFR), Leiden factor, prothrombin and fibrinogen showed their significant role in the development of stroke in children and adults [16]. However, there are no studies that consider a complex of 11 prothrombotic genes, taking into account all parts of the hemostatic system, i. e., vascular system, platelets and plasma.

Mutations in the MTHFR and MTRR regulate homocysteine metabolism, the excess of which is achieved by endothelial impairment and stimulating prothrombotic reactions [17]. An excess of homocysteine in adults has a systemic harmful effect on vascular endothelium, with the accumulation of low and very low density lipoproteins in the vascular wall, causing atherogenesis, and acts as vascular and clotting risk factors of ischemic stroke [17]. The role of homocysteine metabolism disorders in the development of ischemic stroke has not been adequately studied in children, which requires further researches.

About half of children with a stroke have a known predisposing condition, but in some of them the stroke is unexpected, such as in primary cerebrovascular disease, associated with congenital heart abnormalities, or in the presence of modifiable risk factors, such as hypertension associated with sickle cell disease. Genetic predisposition, trauma, infections and nutritional deficiencies appear to be important, although case control studies will be necessary to demonstrate causality. Appropriate screening for modifiable risk factors may prevent recurrence in some patients. In the long term, an understanding of multiple etiologies of childhood cerebral vascular disease and ischemic stroke can allow development of primary prevention for respective age group and, possibly, for adults [16].

With advances in neuroimaging, arteriopathy appears to be the predominant basic mechanism causing 53% cases of stroke. Furthermore, it is the most important predictor of recurrence, highlighting its role as a target for treatment to prevent the secondary stroke [16].

The most common arteriopathy established in IS is a unilateral intracranial acquired arteriopathy associated with basal IS, characteristically involving the junction of the distal internal carotid artery, proximal middle cerebral artery (MCA) and proximal anterior cerebral artery (ACA). This condition was originally conceived as a transient cerebral arteriopathy (TCA) and characterized by its duration, unilateral localization and the absence of long-term progress [18]. By traditional methods of initial imaging, TCA cannot be differentiated from progressive arteriopathy, such as Moyamoya disease (MMD) or vasculitis that presents

unilaterally, with a different duration and prognosis. Few clinical and radiological parameters can predict the evolution of unilateral intracranial arteriopathy in childhood. Patients with progressive arteriopathy have been found to have more often arterial occlusion, ACA involvement and abnormal collateral vessels, and that a predominantly cortical localization is associated with poor functional outcome. The differentiation between TCA and progressive arteriopathy may require further radiological assessment, such as magnetic resonance angiography (MRA) and conventional angiography, and generally the aggravation of the process after 6 months or bilateral involvement suggests a different arteriopathy than TCA [5].

Studies by Rivkin MJ, Bernard TJ, Dowling MM, Amlie-Lefond C. have shown that IS etiology in children is multifactorial and the risk factors are numerous and complement each other. IS are characterized by multiple signs and symptoms, most often subtle, make it difficult the early diagnosing. The patient investigation should be carried out by a multidisciplinary team, i. e., geneticist, neurologist, rheumatologist, nephrologist, etc. [19].

## Conclusions

Risk factors and causes of IS in children are heterogeneous and in many cases remain idiopathic. Investigations of variables and causes of cerebral ischemia in children can direct rational research and therapeutic strategies of IS in children. The comprehensive approach to the patient will ensure the certain diagnosis, which has a defining role for the decision of the treatment tactics and to determine the subsequent evolution of the disease. In high-risk families it is necessary to carry out genetic counseling and family planning in order to reduce the rate of morbidity, mortality and improve the quality of life of patients and their relatives.

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#### Authors' contribution

MS – designed the research, did statistics and interpreted the data, drafted the manuscript; SH – conducted/performed the laboratory work; CC – interpreted the data; NL – collected the data; NR – conceptualized the project and designed the research; SG – conducted the laboratory work, revised the manuscript critically. All the authors revised and approved the final version of the manuscript.

#### Funding

It was provided by *Nicolae Testemitanu* State University of Medicine and Pharmacy and Mother and Child Institute. The trial was the authors' initiative. The authors are independent and take responsibility for the integrity of the data and accuracy of the data analysis.

#### Ethics approval and consent to participate

The research was approved by the Research Ethics Committee of *Nicolae Testemitanu* State University of Medicine and Pharmacy (protocol No 69 of March 21, 2017).

#### Conflict of Interests

There is no known conflict of interests and financial or non-financial support associated with this publication.

