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RESEARCH ARTICLE

STUDY OF SOME IMMUNOENZYMATIC PARAMETERS IN PEDIATRIC ISCHEMIC STROKE

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ABSTRACT

Background: Ischemic stroke (IS) in children is a major neurological emergency, being a primary cause of morbidity and mortality. It is detected in the neonatal period in one of 2500 – 4000 live births, and in children over one month of age it is found at 1,2 – 8 per 100000. **Aim:** Studying of immunoenzymatic parameters in IS in children for the assessment of pathogenesis, early diagnosis and predictive factors of the disease. **Materials and methods:** During 2017 – 2019 in the Republic of Moldova, was carried out a prospective study on a sample of 53 children with IS, which are formed study sample (SS), in which in the acute phase of the process using ELISA immunoassay were analyzed the serum levels of the following markers: endoglin CD105 (ENG), antiphospholipid antibodies (APA) and interleukin-6 (IL-6). These markers were also assessed in 53 practically healthy children which formed control sample (CS). **Results:** The average values of immune markers in the acute period of IS were as follows: (1) ENG – 2,06±0,012 ng/ml (F=84,812, p<0,001); (2) APA – 11,37±0,046 U/ml (F=60,701, p<0,001); (3) IL-6 – 22,02±2,143 pg/ml (F=43,810, p<0,001), which were significantly different from the values detected in practically healthy children. **Conclusions:** In children with IS in the acute period some immunological parameters changes which show the role of these parameters as biomarkers which are involved in ischemic processes of the brain. New longitudinal studies in children with IS may improve early diagnosis and treatment of these children.

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INTRODUCTION

The problem of ischemic stroke (IS) in children is a very complex and insufficiently studied at the current stage of the development of neurological science; the causes being multiple, complex, the disease evolving very rapidly, so the current situation not sufficiently correspond to the modern demands in the area (deVeber, 2012). However, some aspects remain relatively constant, which creates real premises for solving, at least in part, some of the problems raised by the scientific community. At the same time, more in-depth research into the etiological causes, evolution and manifestations of IS faces ethical and moral dilemmas in diagnosing at the earliest stages of the process. The etiological and patogenetic factors of IS are diverse in type and manifestations, in some cases the general picture may lack risk factors as a determining factor for their diagnosis (Nelson, 2007).

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Stroke is a rare disease in children and adolescents, often underestimated, with a major impact on morbidity and mortality. The incidence of pediatric stroke according to several studies is from 2 to 13:100000 children for ischemic stroke, from 1 to 5:100000 children for hemorrhagic stroke, and 0,67:100000 children for cerebral venous sinus thrombosis. Ischemic stroke (IS) most often occurs in the prenatal period and in the first 28 days with a frequency of 1:4000 live newborns (Rivkin, 2016). Fetal IS occurs between the 14th week of gestation until birth. Perinatal IS is caused by an ischemic lesion that occurs from the 20th week of gestation to 28 days after the birth. Data from the specialty sources suggests that perinatal IS occurs in 1 in 2300 – 5000 live newborns, with an estimated mortality rate of 3.49:100000 annually (Rosa, 2015). Neonatal IS is a subcategory within perinatal IS. These possible data are underestimated due to obscure clinical manifestations of neonatal IS. Neonatal AVCI causes significant morbidity, severe long-term neurological and cognitive deficits, including cerebral palsy, epilepsy, neurodevelopmental disabilities, behavioral disorders, impaired function of vision and language. In some children neonatal stroke is recognized only retrospectively after

manifesting hemiparesis or seizures on the first months of life (Freundlich, 2012). Establishing etiology of IS in children is a very important topic, since the process caused by multiple etiological factors, different from the adult. The various aspects of etiology and pathogenesis of IS in children have been analyzed mainly keeping in mind of risk factors. Neuroinflammation is the main pathogenetic mechanism underlying IS development in children. Serum level of inflammatory markers responsible for the onset and pathogenesis of IS is important for the assessment of inflammatory responses after a stroke in children. Investigations into the establishment of the cellular physiopathological etiology and mechanisms of cerebral ischemia in children can guide rational research and therapeutic strategies in pediatric IS. In the research of immunoenzymatic changes an important factor is neuroinflammation. In the IS, regardless of etiology, the death of neurons is associated with a decrease in blood flow and therefore lack of oxygen and glucose in the brain tissue. It is known that the increasing the vascularization in the ischemic penumbra is positively correlated with the survival rate of patients with stroke. In addition, increased angiogenesis has been associated with improved functional outcomes in both animal models as well as in IS (Coelho Junior, 2016). These issues were analyzed by Coelho Junior H. J. *et al*., Gambassi B. B. *et al.*, and Diniz T. A. *et al*. The above studies showed that neuroinflammatory mechanisms are associated with severe motor sequelae after IS. Recovery physical exercises can help restore motor skills and functions more quickly. However, in pediatric IS such an approach may encounter difficulties caused by undeveloped motor abilities, keeping in mind the necessity of assistance for children in rehabilitation and maturation. For example, pediatric IS leads to significant morbidity and mortality compared to IS in adults. Considering the onset during childhood and impact on the quality of life of the child and family, the economic costs and emotional burden for society increased. The study by Elkind M. S. *et al*. describes neuroinflammation as one of the main mechanisms underlying the occurrence and development of stroke. In this context, it is current and important to assess the serum level of inflammatory markers, responsible for the onset and pathogenesis of stroke and its recovery. Clinical studies and investigations by researchers in the field have shown that inflammatory responses after stroke in children are different from those of stroke in adults (Elkind, 2009). Data from sources on biomolecular topics highlights the major role of biomarkers in diagnosing and evaluating neurological outcome, as well as pathogenesis and recovery of IS in children. The range of biomarkers that have importance in the matter includes some inflammatory markers, i. e., pro-inflammatory cytokines such as IL-6 and IL-1β, but also other molecules and other biological factors, including vascular endothelial growth factor (VEGF), ciliary neurotrophic factor (CNTF), S100B protein, CD105 endoglin, antiphospholipid antibodies (APA), etc. (Elkind, 2009; Hadjiu, 2010; Sprincean, 2018).

Aim: Studying the immunoenzymatic parameters in IS in children to improve the knowledge of pathogenesis, early diagnosis and predictive factors of the disease.

MATERIALS AND METHODS

During 2017 − 2019 in the Republic of Moldova, a clinical study was carried out within the framework of the State Program "Systemogenesis of Risk Factors, Optimization of HealthCare Service, Sustainable Evaluation and Mathematical Modeling of Stroke", with the project for children: "Evaluation incidence, prevalence, risk factors, and research of clinical, neuroimaging, neurophysiological and neurotrophic management of strokes in children". On the basis of this project was conducted a prospective study on a sample of 53 children diagnosed with IS have been examined and consulted at the Institute of Mother and Child. In the 53 patients with IS (study sample, SS), during the acute period of the disease, serum levels of some enzyme immunoassay markers were assessed by ELISA, including CD105 endoglin, antiphospholipid antibodies (APA) and interleukin 6 (IL-6). As reference values were considered the serum levels of the above mentioned markers in a sample of 53 "practically healthy" children (control sample, CS). Initially, clinical symptoms of IS were registered, followed by imaging findings, as well as venous blood sampling with centrifugation, separation of serum for storage at (−20°C). In the samples were determined the serum concentration of above biomarkers. Enzyme immunoassay was carried out using ELISA method at the SYNERGY-H1 analyzer (USA, BioTek). The results were analyzed using statistical methods of determining frequencies, confidence interval, averages with standard deviation and standard error as well as Pearson correlation, compared to the chi-square, the T-Student test, i.e., the possibility of matching the results in the sample with the results of general population. The approval of ethical aspects and consent to participate in the study was carried out in accordance with the protocol No 69 dated March 21, 2017, which was approved by the Research Ethic Board of State University of Medicine and Pharmaceutics Nicolae Testemitsanu.

RESULTS

According to the research objectives, in patients with IS in the acute phase of the disease we determined the serum concentration of several biomarkers, including CD105 endoglin, as well as some pro-inflammatory markers, i. e., APA and pro-inflammatory cytokine, IL-6. The serum concentration of inflammatory markers was appreciated to determine their involvement in the mechanisms of angiogenesis and vasculogenesis, as well as the correlation of the values of inflammatory markers with the degree of CNS impairment, depending on the evolutionary stage of the disease and the age of the child. It is known that endoglin (ENG, also known as CD105) is a membrane homodimer glycoprotein that can bind the β1 and β3 isoforms of the transforming beta growth factor (TGFβ). Endoglin is a receptor associated with TGFβ and is required for both vasculogenesis and angiogenesis (10). Thus, the serum concentration of CD105 is lower in acute IS, and endoglin deficiency can slow recovery processes in IS. Has been showed what CD105 expression induced by hypoxia hypoxia-inducible factor-1 (HIF-1a), which binds directly to the hypoxia response element in the CD105 promoter (11). Hypoxia is a complicated biological process, and the CD105 expression regulated by hypoxia is possibly involved in several neurophysiological paths. CD105 is known to exert its effect on angiogenesis by TGFβ signaling. In our study, we assessed ENG serum levels in children in the acute IS phase revealing that in SS the mean value is significantly lower than in CS ($F=84.812$, $p<0.001$), the maximum values was 4.02 ng/ml, and the minimum was 1,88 ng/ml. In children from SS the average level of the endoglin was 2.06±0.012 ng/ml and does not exceed the level of 2.23 ng/ml, while in CS the

average level of ENG was 2.51±0.071 ng/ml, reaching the maximum value of 4.02 ng/ml (Fig. 1). As shown in the figure below, the serum level of ENG is significantly decreased in the group of children with IS. It was sowed that the worse the child's condition, the lower the ENG values. This fact suggests severe disorder of vasculogenesis and angiogenesis processes, and therefore ENG can be considered a strong biomarker of IS and early indicator of neurologic sequelae in these children. Antiphospholipid antibodies (APA), which are belongs to the group of pro-inflammatory cytokines, are other markers analyzed in the presented study. The increased level of APA was shown to be associated with increased blood clotting state leading to IS and other ischemic events (Avcin, 2008). APA comprises a heterogeneous group of autoantibodies. Several mechanisms are shown to be involved in the thrombotic process in patients with IS. However, APA is considered to be a marker of both autoimmune diseases as well as IS, as it can activate clotting cascades causing cerebral ischemia (Hunt, 2008).

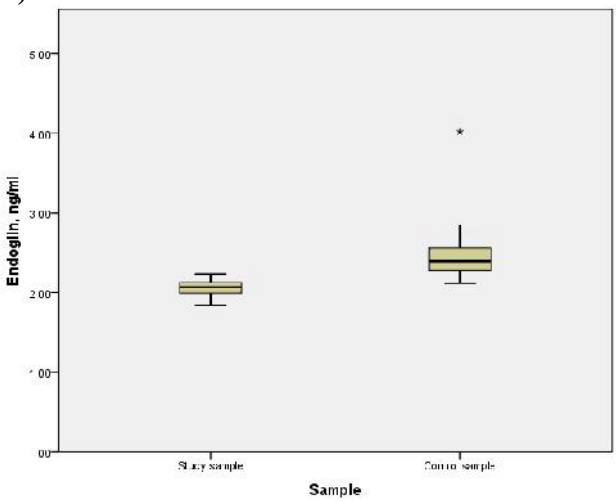

Figure 1. Serum levels of endoglin in children with IS compared to the sample of "practically healthy" children, ng/ml

In SS were recorded a mean APA values of 1.37±0.046 U/ml compared to the mean level of 0.92±0.021 U/ml recorded in CS. Although apparently the figures do not differ as obviously as in the case of other biomarkers, a statistically significant difference can be observed between the groups included in the study, which suggests the presence of inflammation in IS (F=60.701, p<0.001) (Fig. 5).

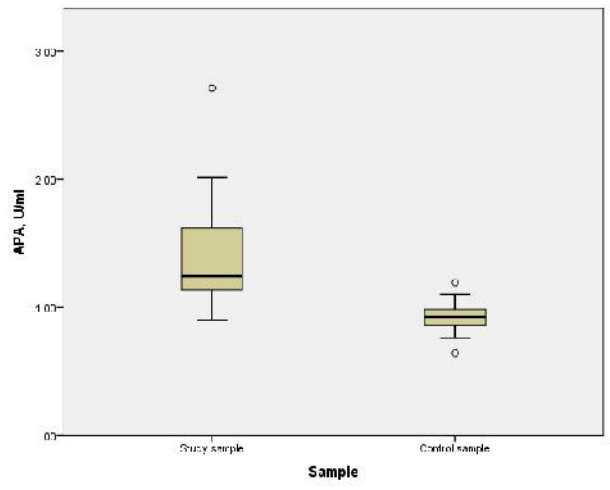

Figure 2. Serum levels of APA in children with IS compared to the sample of "practically healthy" children, U/ml

Molecular markers of inflammation have been shown to be useful in the management of stroke patients in the acute phase of the disease in assessing the outcome and preventing the risk of neurological sequelae (Muñoz-Cánoves Muñoz-Cánoves, 2013). One of the inflammatory mediators is IL-6, which is elevated in children with IS. Inflammatory cytokines such as IL-6 contribute to early neurological deterioration and increase the volume of ischemic focus. Evaluation of IL-6 in children in the acute phase of IS allow to predict not only the severity of the case but also can help to determine the neurological outcome of patients. Increased serum levels of IL-6 correlated with the severity of acute phase of IS in children and also showed a clinical value for predicting the outcome (Mallick, 2014). In the present study, in SS was determined the mean serum level of IL-6 of 22.02±2.143 pg/ml, ranging from 4.58 pg/ml to 65.71 pg/ml, showing the presence of inflammation in IS. However, in CS the mean value was 10-fold lower (2.38±0.302 pg/ml), with variations from 0.01 pg/ml to 5.38 pg/ml, which determine significant statistical difference (F=43.810, p<0.001) (Fig. 6). So, serum IL-6 levels can be used for determining the severity of IS. Increasing in the level of inflammation produced by inflammatory cells, glia and neurons caused the increasing the level of IL-6 which lead to worsening the patient's condition (r_{xy} = 0.706).

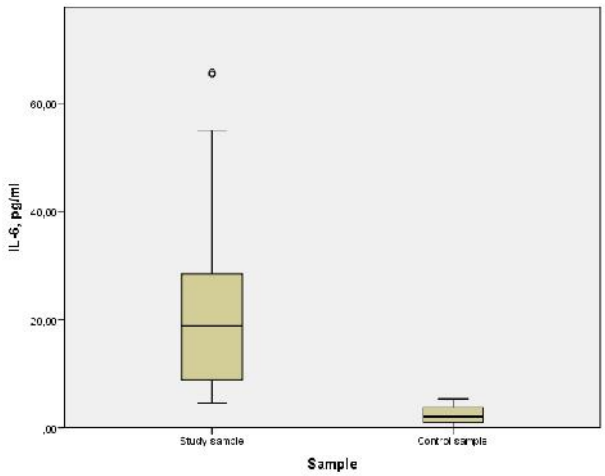

Figure 3. Serum levels of IL- in children with IS compared to the sample of "practically healthy" children, pg/ml

The present study showed that serum levels of APA and IL-6 are significantly increased in children with severe stroke (p<0.001), thus, so the more severe the degree of CNS impairment, the more prominent increasing the serum concentrations of respective biomarkers. Some imaging and additional investigations were carried out in children from the study sample. Thus neurosonography at birth was normal in 34 of cases (64,2%; CI 95% (51,2-77,1)). Of the patients with revealed pathology periventricular stasis was most commonl, i. e., in 10 of cases (18,9%; CI 95% (8,3-29,4)), followed by periventricular ischemic changes in 5 of cases (9,4%; CI 95% (1,6-17,3)). In 2 cases, periventricular and intraventricular ischemic changes or leukomalacia was detected. The involvement of the white substance was not identified in any of the patients. At admission, the share of children with no changes on neurosonography remains constant, i. e., 34 cases, but some structural changes occurred. Thus, single periventricular cysts were diagnosed at 11 of cases (20.8%; I 95% (9.8-31.7)), multiple periventricular cysts at 4 of cases (7,5%; CI 95% (0,4-14,7)) and in 4 other cases have been identified multiple small and large intracerebral cysts.

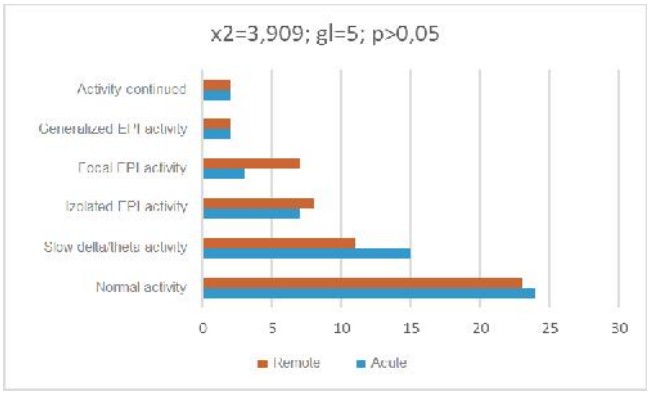

Figure 4. Changes detected using EEG in the acute and remote period, abs

Electroencephalography (EEG) was carried out both in the acute and remote period, but significant statistical differences were not observed. In both stages less than half of the children in the study sample had no pathological changes, i. e., in 24 of cases in the acute period (45,3%; CI 95% (31,9-58,7)) and in 23 of cases in the remote period (43,4%; CI 95% (30,1-56,7)). The changes detected are shown in Figure 4. Computed tomography (CT scan), angio-CT, magnetic resonance imaging (MRI) and angio-MRI are used to differentiate ischemic stroke from hemorrhage, to determine the cause and mechanism of stroke, to define the extent of the stroke and to identify arterial occlusion. The condition of arterial collateral circulation, the type and extension of the clot can be evaluated using imaging. Cerebral CT scan is a diagnostic technique that allows the reconstruction of the cerebral cross sections of the patient, providing detailed information about the structure and anatomy of the brain and, to some extent, its functionality. CT scan allows visualization of cystic and necrotic changes, calcifications, brain tumors, excludes acute intracerebral hemorrhages. CT scan is the method of choice in diagnosing stroke in the acute stage of the disease. Compared to MRI, CT scan has some disadvantages due to insufficient contrast resolution of the white brain and posterior fossa. This technology allowed the evaluation of soft tissues on by cross-sectional images, thus introducing a new era for neuroimaging. Even after the advent of magnetic resonance imaging (MRI), the availability, ease of acquisition and diagnostic capacity of CT are sufficient to attest this technique as the first-line imaging method for the evaluation of CNS and the assessment of outcome or the probability of the future development of neurological sequelae, i. e., the presence of intracerebral cystic formations, ventricular dilation, or periventricular leukomalacia.

On the CT scan in the acute and remote period it was found that in about 2/3 cases pathological changes are absent, and the manifestations detected in the remain cases consists mainly in predominantly of not-too-large foci. At the same time, it is important to note that remote changes as a large ischemic foci or ischemic foci spreading to the hemisphere were absent. The differences identified in the CT manifestations are statistically significant (Table 1). Brain MRI provides useful information for assessing the degree of brain pathology in IS, and is a valuable tool in the determining the outcome of neuropsychic disability. MRI provides useful information for the diagnosis of IS, for the determining of treatment strategies in the acute phase of the process and in the assessment of outcome. At the acute stage, it is important to diagnose the IS early and differentiate it from pathologies that can mimic a stroke.

Thus, brain MRI is important for differentiated diagnosis with some pathologies such as brain malformations and metabolic or neurodegenerative disorders. Imaging findings in MRI sequences help determine the mechanisms of stroke, which have an impact on outcome and therefore play an important role in treatment decisions. It is essential to evaluate the correlation the clinical manifestations with imaging findings, precise locate the topography and the extent of the lesion. Brain MRI visualizes the consequences of ischemia and abnormal development of brain tissue. Recent developments in MRI imaging show a great promise for detecting the development of focal ischemic brain lesions in the early stage of the process. Combining with angio-RMN, this method allows the precise location, extent, mechanism and viability of tissue lesions of acute stroke in an imaging study, and allows the differentiated visualization of the cortex and white substance, the degree of myelinization according to age. Brain MRI was performed in the acute and remote stage in all children included in the study sample. Unlike CT scan data, the results of MRI showed the remote imaging manifestations of the process to be much more favorable than in the acute stage. Considerable changes in the acute period converting into foci of gliosis or smaller cysts, the differences are statistically significant. It is important to note that in remote stage no foci of porencephaly has been viewed detected (Table 2). Analysis of the correlation of laboratory markers and imaging data showed a direct correlation of studied markers with one exception of endoglin which demonstrated a inverse correlation with ultrasound data al birth and changes on CT scan (Table 3). Correlational analysis of remote outcomes which included laboratory markers and imaging data showed a strong direct correlational between the indicators studied (see Table above). This allows us to state that the factors chosen to assess the health of children suffered from stroke are demonstrative.

DISCUSSION

Choi*et al*. and Walker *et al*. studied endoglin (ENG, also known as CD105), a receptor associated with the transforming growth factor β (TGFβ), required for both vasculogenesis and angiogenesis, and its importance in the development of cerebral vascularization and in the pathogenesis of vascular diseases, including IS in children (10). ENG is an essential component of the endothelial nitrous oxide synthesis activation complex. Animal studies have shown that the ENG deficiency affects the recovery of stroke. ENG deficiency also affects the regulation of vascular tone, which contributes to the pathogenesis of cerebral arteriovenous malformations and vasospasm (Choi, 2013). Choi E. J. *et al*. and Walker E. J. *et al*. in his studies on CD105 in IS showed that ENG was highly expressed in the penumbra region of human stroke focus, where an increase in angiogenesis was determined (Liu, 2014). The role of ENG in stroke is very complex. The expression ENG amplifies TGFβ signaling and promotes the remodeling of the new vascular wall. Over expression of ENG also protects against TGFβ-induced apoptosis of endothelial cells. Reducing vascular cell apoptosis after hypoxia improves blood intake to ischemic tissue. The increase in the expression of ENG in endothelial cells could also be dangerous, since the permeability of the blood-brain barrier has been increased in some of the capillaries expressing a high level of ENG, which has been accompanied by the infiltration of mononuclear cells into surrounding brain tissues (Choi *et al.*, 2013).

Table 1. Pathology revealed using acute and remote CT scan.

	Acute			Remote			p
	Abs.	P, %	CI 95%	Abs.	P, %	CI 95%	
No pathology	30	56,6	43,3-69,9	34	64,2	51,2-77,1	χ^2=14,250; gl=5; p<0,05
Ischemic focus – 0,5×0,5 cm	6	11,3	2,8-19,9	15	28,3	16,2-40,4	
Ischemic focus –1×1 cm	12	22,6	11,4-33,9	2	3,8	(-1,4)-8,9	
Lacunary ischemic focus	2	3,8	(-1,4)-8,9	2	3,8	(-1,4)-8,9	
Large ischemic focus	2	3,8	(-1,4)-8,9	-	-	-	
Ischemic focus spreading the hemisphere	1	1,9	(-1,8)-5,5	-	-	-	

Table 2. Revealed changes on MRI in acute and remote stages of the process

	Acute			Remote			p
	Abs.	P, %	CI 95%	Abs.	P, %	CI 95%	
Small foci of gliosis	19	35,8	22,9-48,8	38	71,7	59,6-83,8	χ^2=15,895; gl=4; p<0,01
Small cysts 0,5×1,0 cm	17	32,1	19,5-44,6	9	17,0	66,9-27,1	
Medium cysts	7	13,2	4,1-22,3	3	5,7	(-0,6)-11,9	
Large cysts	5	9,4	1,6-17,3	3	5,7	(-0,6)-11,9	
Porencephaly	5	9,4	1,6-17,3	-	-	-	

Table 3. Correlation of laboratory markers and imaging data during acute stage

		USG (at birth)	EEG	CT scan	MRI	PedNIHSS score
Endoglin, ng/ml	r_{xy}	-0,499	-0,293	-0,427	-0,444	-0,434
	p	0,000	0,033	0,001	0,001	0,001
APA IgG/ IgM, U/ml	r_{xy}	0,496	0,334	0,532	0,552	0,553
	p	0,000	0,015	0,000	0,000	0,000
IL-6, pg/ml	r_{xy}	0,761	0,686	0,733	0,881	0,901
	p	0,000	0,000	0,000	0,000	0,000
USG (at birth)	r_{xy}		0,613	0,825	0,849	0,833
	p		0,000	0,000	0,000	0,000
EEG	r_{xy}			0,740	0,767	0,807
	p			0,000	0,000	0,000
CT scan	r_{xy}				0,828	0,848
	p				0,000	0,000
MRI	r_{xy}					0,983
	p					0,000

These findings suggest that the ENG over expression could affect the integrity of the vessels wall. Alternatively, the lack of ENG expression can indicate severe vascular damage. ENG is involved in the pathogenesis of post-ischemic brain lesions in humans. ENG abnormality could lead to long-term neurological damage or cognitive impairment after acute ischemic stroke. Studies have revealed that decreased serum ENG in IS is characteristic in major ischemic events with severe neurological manifestations. Presented clinical trial in children with IS showed that the level of CD105 in the acute phase of the pathology is lower in the study sample compared to the control sample, which is consistent with the results of other experimental and clinical studies. Neuroregeneration is determined by the ability to regenerate of tissues, cells or cellular products (Elkind, 2009). Antiphospholipid antibodies (APA) are a marker of autoimmune diseases; APA can activate endothelial cells, platelets and clotting cascades and may be implicated in IS. APA induces a pro-inflammatory and procoagulant state in the microvascular endothelial cells of the human brain. Local ischemia caused by micro-vessel thrombus breaks the blood-brain barrier (Hunt, 2008). In patients with IS, APA-triggered leukocyte adhesion and complement activation appear to increase the permeability of the blood-brain barrier. A flow of autoantibodies and cytokines peripheral products could then lead to neurotoxicity. The release of IL-6 is followed by damage of neural and astrocyte cells in patients with IS, as is the case in patients with autoimmune diseases (14). The serum concentration of APA is higher in the acute period of IS. In the presented clinical trial in children with IS, the level of APA in the acute phase of the process was showed higher in the study sample than in the control sample, which is consistent with the results of other experimental and clinical studies and demonstrates the importance of this marker in ischemic brain processes. McCann S. K. *et al*., Cramond F. *et al*. and other authors have shown that following IS cytokine levels increases as a result of increased production of IL-1, IL-6, IL-10, tumor necrosis factor alpha (TNFα) and transforming growth factor beta (TGFβ) by inflammatory, glial and neuron cells, which mediators are best studied in stroke (McCann, 2016). IL-1β and TNFα have been associated with exacerbation of stroke lesions, while IL-6, IL-10 and TGFβ have been found to be neuroprotective. There is some scientific evidence that IL-6 can be used as an inflammatory marker for IS (McCann, 2016; Hicks, 2013). Thus, according to these studies, the serum level of IL-6 is higher in acute IS. The present study in children with IS found the level of IL-6 in the acute phase of the disease higher in the study sample than in the control sample. These data are consistent with the results of other experimental and clinical studies. The results of the assessment of biomarkers such as endogline, APA and IL-6 largely determine of the diagnosis, the severity of the disease and the prediction of remote neurological outcome. The likelihood of neurological sequelae increases with increasing of the values of some studied markers i. e., APA, IL-6 and decreasing in others, i. e., ENG, which allow correcting the therapeutic strategy using the medications adapted as early as possible in all patients suspected of IS. We suggest of direct correlations between immunological data and the volume of ischemic focus.

The more extensive the volume of the damaged brain focus detected using MRI, the higher the values of biomarkers, such as IL-6 and APA, and lower CD105. Experimental and clinical research of biomarkers promotes new discoveries in the field of pediatric neurology. Molecular markers of inflammation have been shown to be useful in the management of stroke patients in the acute phase of the disease and in assessing outcome and preventing the risk of neurological consequences. The serum concentration of inflammatory markers was appreciated to determine their involvement in the mechanisms of angiogenesis and vasculogenesis, as well as the correlation of the values of inflammatory markers with the degree of CNS impairment, depending on the evolutionary stage of the disease and the age of the child. It was found that the lower the endoglin values, the worse the status of the patients. This fact suggests the implication in pathogenesis the processes of vasculogenesis and angiogenesis, and CD105, being a valuable biomarker in IS, can be considered a suggestive indicator for the remote outcome of neurolgic sequelae in children with IS. APA is believed to be associated with hypercoagulation leading to IS and other ischemic events. APA comprises a heterogeneous group of autoantibodies. Several mechanisms are believed to be involved in the thrombotic process in patients with IS. However, APA is considered to be a marker of both autoimmune diseases and IS, as it can activate clotting cascades causing cerebral ischemia. Inflammatory cytokines, e. g. IL-6, contribute to early neurological deterioration and increase the volume of ischemic focus. Evaluation of IL-6 in children in the acute phase of IS can predict not only the severity of injuries, but also the neurological outcome of patients.

Conclusion

In the acute period of IS in children the serum levels of APA and IL-6 are increased, while the level of CD105 was diminished. According to modern data from the literature, the views on biomarkers changes in IS over time drastically recently. Thus inflammatory markers, as well as many other molecules and biological factors, including cytokines derived from tissues, growth factor-like molecules, hormones and micro-RNA can play an important role in the diagnosis and outcome of IS in children. The study of biomarkers could be a challenge in the diagnosis and prognostic evaluation of the onset, pathogenesis and recovery of IS. Many molecules are currently being studied that can become promising and encouraging biomarkers. Therefore, experimental and clinical research of biomarkers should be promoted for further discoveries in the field of pediatric neurology, in order to improve the diagnosis and treatment of IS in children.

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