

DOCTORAL SCHOOL IN MEDICAL SCIENCES

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**QUALITY OF LIFE IN CHILDREN AFTER
AN ISCHEMIC STROKE:
MEDICAL-SOCIAL CONSIDERATIONS**

321.05 - CLINICAL NEUROLOGY

Summary of the doctoral thesis in medical sciences

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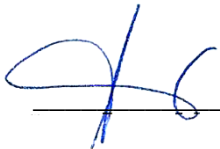
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INTRODUCTION

Actuality and importance of the researched problem

Stroke represents a major medico-social problem, an important cause of mortality and the main cause of disability in the population worldwide [1, 2]. Prospective research states that this condition is expanding annually, in terms of incidence and prevalence, and World Health Organization (WHO) experts report that strokes will become the main cause of mortality by 2030 [3].

Although pediatric stroke is included in the category of rare neurological diseases in children, it represents an important cause of long-term disability and significant neurological deficits [4, 5]. The authors of several studies report that up to 20% of affected children die after an ischemic stroke, and more than 50% of those who survive have neurological sequelae, among which, most frequently, hemiparesis [4, 6].

Quality of life has the greatest relevance among the most important outcomes assessed after stroke [7], as it provides a comprehensive assessment of health status that includes physical, mental and social well-being, a concept of the WHO health definition [8, 9, 10]. Depending on the type and severity of stroke in children, in the post-stroke period, multiple brain injuries can be encountered that cause consequences in all domains of quality of life (physical, psychological, cognitive and social disorders) [11, 12]. The assessment of the quality of life of children with stroke provides complementary information on health status, and beneficial or negative influences of treatment and medical care [13].

At the same time, sleep disturbances occurring after a stroke predispose to recurrence, decrease quality of life, increase the risk of mortality and are associated with poorer functional outcomes [11, 14, 15].

The purpose of the research: the evaluation of the peculiarities of the quality of life of a child with a history of pediatric ischemic stroke under the influence of rehabilitation programs for the assessment of the medical and social prognosis.

Research objectives: (1) Demographic, causal and clinical-paraclinical analysis of children who suffered a pediatric ischemic stroke; (2) Complex evaluation of children with ischemic stroke in the antecedents by assessing the quality of life, the specifics of neurological deficits, the particularities of sleep disorders and the rehabilitation program; (3) Estimation of the relationship between the quality of life of the child who suffered an ischemic stroke and the degree of neurological deficit, sleep disorders, the serum level of the S100B protein and the recovery program; (4) Assessment of potential negative prognostic factors of low quality of life in children who suffered ischemic stroke according to the studied parameters.

1. ISCHEMIC STROKE - PECULIARITIES IN CHILDREN

The incidence of pediatric stroke varies from 1,3 to 13 per 100,000 children (aged 29 days to 18 years) [16], and the most common involvement is the middle cerebral artery (MCA) [17].

Scientific research has demonstrated that pediatric ischemic stroke can be induced by a multitude of etiological factors, with more than 100 causes reported [18]. Also, the congenital heart malformations, some genetic diseases and sickle cell disease are considered the most common causes of stroke in infants, and vasculopathies and hypercoagulation states - among adolescents [19, 20].

Data in the biomolecular scientific literature highlight the major role of biomarkers in the assessment of neurological prognosis and stroke recovery in children. In the list of included biomarkers, the most studied is the S100B protein, which possesses intracellular and extracellular properties. Intracellularly, this protein is part of calcium homeostasis, having a role in transferring signals from its secondary messengers [21, 22].

Considering the onset of stroke in childhood and the impact on the quality of life of the child and his family, the economic costs and the emotional burden on society are great, as pediatric stroke

affects the physical, cognitive abilities and quality of life of children and their families [23]. *The quality of life* is defined by the physical, mental and social well-being, as well as the patient's ability to perform their usual tasks of their daily existence [9, 24]. Although stroke *survival* is a key indicator, studying the quality of life is an important feature of survivors and provides information on how stroke treatment and complications affect the child and their ability to function at home, school, and community environments [24, 25, 26].

At the same time, the prophylaxis, diagnosis and treatment of sleep disorders in children who have suffered a ischemic stroke represent an important section in the rehabilitation process of these children. Also, the caregivers of children without post-stroke sleep disorders must be educated and motivated to respect sleep hygiene, to create favourable conditions for the rehabilitation process [27].

Consensus guidelines for management of pediatric stroke suggest that early and continuous rehabilitation therapy is essential [28]. Medical rehabilitation is a continuous process, which starts from the wards/departments within the hospital and continues to outpatient clinics and community locations/centres. The quarterly rehabilitation therapy is only applied in the hospital by the rehabilitation doctor, physiotherapist, physiotherapist, etc.

2. RESEARCH METHODOLOGY

2.1 General characteristic of the research: research group and sample size

The study was a cross-sectional one carried out within the project "*Evaluation of incidence, prevalence, risk factors, research of clinical, neuroimaging, neurophysiological and neurotrophic remedial aspects of strokes in children*", being carried out under the auspices of the state program "*Systemogenesis of risk factors risk, optimization of the medical assistance service, sustainable evaluation and mathematical modelling of strokes*", No. 17.000418.80.07A, accomplished within the Neuropediatrics Clinic of the Department of Pediatrics of "Nicolae Testemitanu" SUMP during the years 2019-2021. Fifty eight subjects with a history of ischemic stroke (6 months and more after illness) were included.

The subjects included in the study met the following inclusion criteria: (1) Children of both sexes, aged 3-12 years; (2) The diagnosis of ischemic stroke in the anamnesis performed following the criteria of the ICD-10 Classification of the World Health Organization, confirmed by imaging method on CT and/or MRI brain images, or both; (3) Age of stroke more than 6 months; (4) The written consent of the child's parent or legal custodian.

Exclusion criteria were: (1) Neonatal stroke; (2) Hemorrhagic stroke; (3) Children with neurodegenerative, congenital genetic, Central Nervous System demyelinating diseases; (4) Refusal of the parent or the child to participate in research.

The sample size required for the study

To determine the required number of patients for the study, the following formula was used:

$$n = (Z)^2 \frac{P(1-P)}{e^2} \quad \text{where:}$$

n- The volume of the representative sample;

Z- 1.96 for the 95.0% confidence interval;

e- accepted error, e=0.001,

P- according to bibliographic data [Mallick AA, O'Callaghan FJ. *The epidemiology of childhood stroke. Eur J Pediatr Neurol, 2010 May;14(3):197-205*] the incidence of stroke is 1.3 per 100 thousand children (P=0.000013)

After entering the data in the respective formula above, it was obtained:

$$n = 0,000013 \times 0,999987 (1,96/0,001)^2 = 49,9,$$

and with a 10.0% non-response rate, the representative sample was obtained consisting of **55 patients** with ischemic stroke

The detailed research design is represented in figure 1

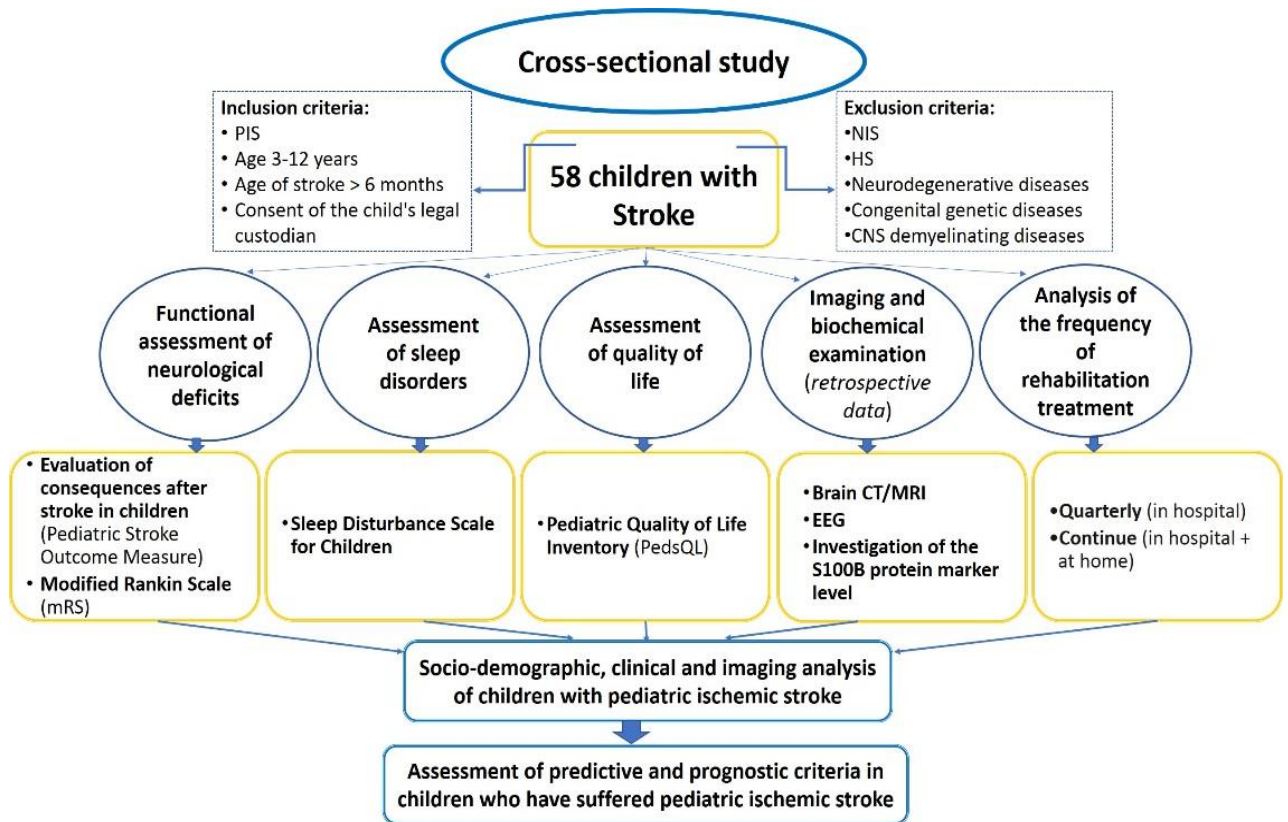


Figure 1. Overall study design

Note. IS - ischemic stroke, PIS - pediatric ischemic stroke, NS - neonatal stroke, HS - hemorrhagic stroke, CT - computed tomography, MRI - magnetic resonance imaging, EEG - electroencephalography

2.2 Research methodology

The **general research methods** used were: (1) Clinical method (clinical and neurological examination); (2) Instrumental methods (electroencephalography, imaging); (3) Immunoenzymatic tests (S100B protein); (4) Statistical-mathematical method.

The methods and sources of primary data collection: (1) The clinical-anamnestic questionnaire; (2) Standardized questionnaires; (3) The data of outpatient records.

3. CHARACTERISTICS OF ISCHEMIC STROKE IN CHILDREN

3.1 Description of the socio-demographic, clinical and imaging characteristics of the ischemic stroke of the subjects included in the research

According to the division by sex, a prevalence of the male sex was found, constituting 62% or 36 subjects, and the female sex 38% or 22 subjects. The subjects included in the study were aged between 3 and 12 years, with an average age of 5.3 ± 2.5 years, Median – 4.5, IQR- 4.2. Out of the total number of 58 children, 26 or 44.8% suffered an ischemic stroke during infancy, 20 or 34.5% - during early childhood, 8 or 13.8% - during preschool and 4 or 6.9% of children in school age.

Etiological factors potentially associated with ischemic stroke were determined by cardiac pathology (17%) and infectious (13%), Centrale Nervous System arteriovenous malformations (7%), hereditary genetic syndromes (5%) and coagulation disorders (7 %) (Table 1).

Table 1. Causes of ischemic stroke in children in the total study group, abs., %

Causes of ischemic stroke	abs.	%	95% CI
TOTAL	58	100	
Undetermined etiology	26	44,8	31,8-58,5
Congenital heart malformations	10	17,3	8,5-29,4
CNS infections	8	13,8	6,1-25,4
Arteriovenous malformations of the CNS	4	6,9	1,9-16,7
Coagulability disorders	4	6,9	1,9-16,7
Hereditary genetic syndromes	3	5,1	1-14,3
Hypovolemia	3	5,1	1-14,3

Analyzing the location of the ischemic stroke, the predominance of the left hemisphere was highlighted in 26 cases or 44.8% (figure 2).

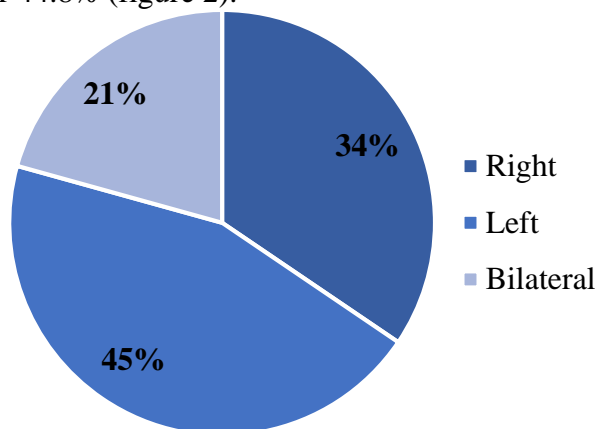


Figure 2. Stroke lateralization according to the results of imaging examinations, %

Brain CT and/or MRI imaging assessment data suggested that 41 or 70.6% of patients had predominant involvement of the middle cerebral artery (MCA), followed by the posterior cerebral artery (PCA) in 7 cases or 12%, then the anterior cerebral artery (ACA) in 5 cases or 8.7% (figure 3).

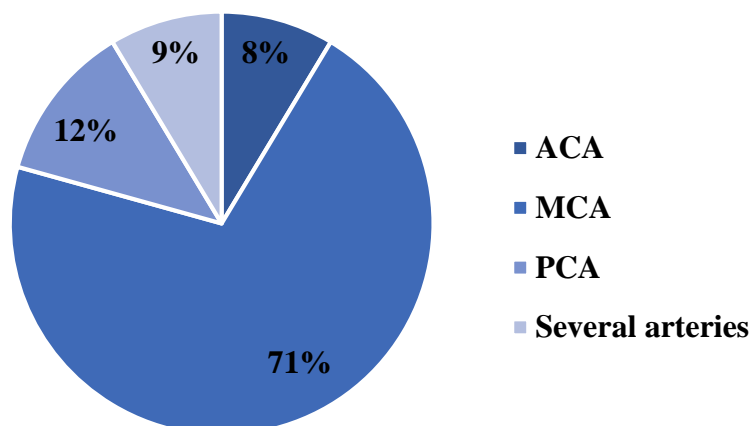


Figure 3. Structure of the study group according to cerebral artery involvement in stroke, %

Analyzing the results of electroencephalography and clinical examination, 36.2% (21) of the subjects presented post-stroke structural epilepsy, while 63.8% (37) did not present this diagnosis (figure 4).

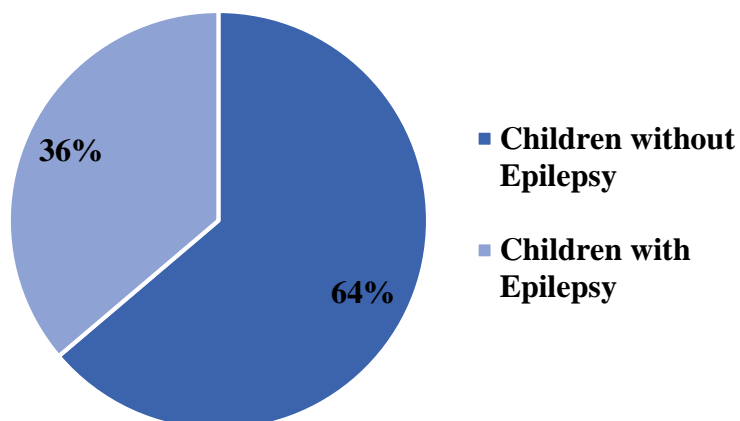


Figure 4. **Structure of the study group according to epilepsy diagnosis, %**

From the point of view of the program (frequency) of rehabilitation treatment applied to children, 47% (28) of the subjects benefited from continuous rehabilitation treatment, i.e. both during the child's hospitalization and at home, carried out by parents or specialists in the field of rehabilitation. Quarterly rehabilitation therapy was applied to 53% (30) of the children, carried out only in the hospital by the rehabilitation doctor/physiotherapist/physiotherapist (figure 5).

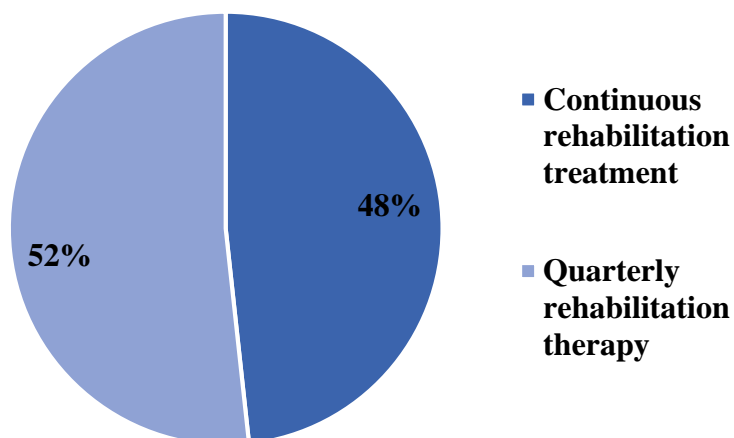


Figure 5. **Frequency of rehabilitation treatment performed in post-stroke children, %**

As can be seen in figure 5, more than half of the children with ischemic stroke did not benefit from continuous rehabilitation treatment, the consequences of this fact having repercussions on all aspects of the quality of life.

3.2 Functional evaluation of the neurological deficits of the subjects included in the research

Stroke can have significant neurodevelopmental consequences in children, particularly physical development and locomotor function. Most of the children included in the research after the onset of the ischemic stroke episode, according to the patient's outpatient record, presented a motor deficit of different degrees of severity, such as mild degree, which did not later influence daily activities, moderate or severe degree. Most children presented with hemiparesis/hemiplegia – 40 (69%), followed by those with tetraparesis/tetraplegia – 11 (19%) and monoparesis/monoplegia – 7 (12%) subjects (table 2).

Table 2. Type of motor deficit of the subjects, abs., %

Parameters	Total, (n = 58)
Type of motor deficit, abs., (%)	
• Monoparesis/ Monoplegia	7 (12%) (CI 95%: 4,9 – 23,3)
• Hemiparesis/ Hemiplegia	40 (69%) (CI 95%: 55,5 – 80,5)
• Tretraparesis/ Tetraplegia	11 (19%) (CI 95%: 9,8 – 31,4)

The score of neurological deficits after sustaining a stroke, according to the standardized PSOM neurological evaluation tool, allowed the assessment of the degree of severity of the motor deficit. Thus, the PSOM neurological deficits score varied from 0.5 to 10 points, with a median score of 2.5 ± 2.6 points (figure 6).

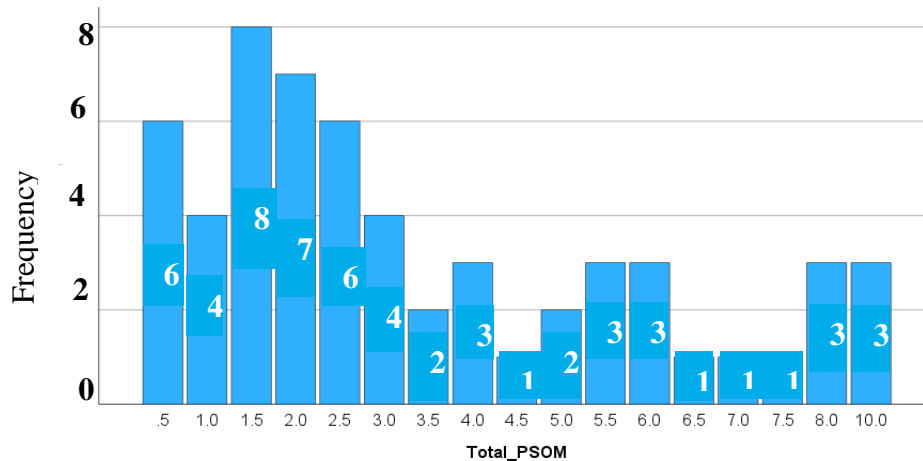


Figure 6. Frequency of total PSOM score, points

According to the results of the interpretation of the total score of the PSOM scales, only 9 (15.5%) of the children had no neurological deficit, 16 children (27.6%) had a mild neurological deficit, 17 children (29.3%) had moderate neurological deficit and 16 children (27.6%) severe neurological deficit.

3.3 Analysis of sleep disorders in the child who suffered an ischemic stroke

According to the standardized T score of the SDSC questionnaire, 74% (43) of the participants had poor sleep quality, presenting different sleep disorders, and 26% (15) - had good sleep quality (figure 7).

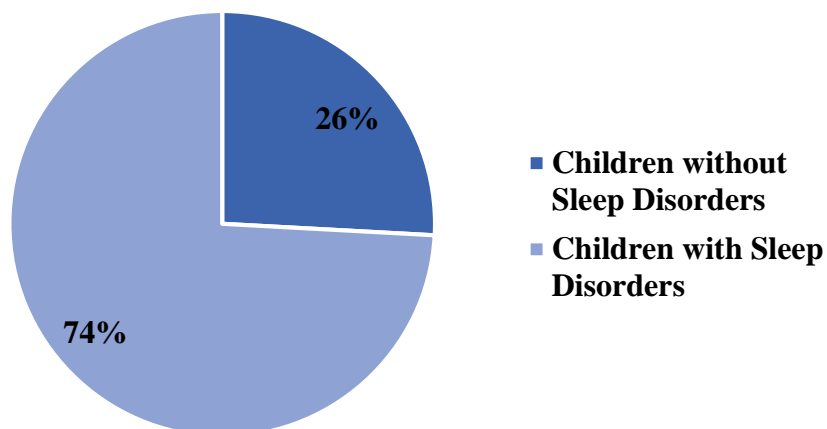


Figure 7. Structure of the study group according to the presence or absence of sleep disorders, %

According to the 6 subscales (categories) of SDSC sleep disorders, the most common sleep disorders were sleep initiation and maintenance disorders that occurred in 48.3% (28 subjects) of children, breathing disorders in sleep – at 38% (22 subjects), sleep-wake transition disorders – 38% (22 subjects) and pathological daytime hypersomnolence – 29.3% (17 subjects). Parasomnias and nocturnal hyperhidrosis occurred in 10.3% (6 subjects) and 12% (7 subjects), respectively.

Thus, it is observed that almost half of the children with ischemic stroke had sleep initiation and maintenance disorders, and a third of them had sleep breathing disorders, sleep-wake transition disorders, and excessive daytime sleepiness. Sleep disorders present in children after stroke may worsen disease progression, neural plasticity and recovery mechanisms of the brain after stroke, influencing quality of life by maintaining disability.

4. CHILDREN'S QUALITY OF LIFE AFTER ISCHEMIC STROKE, CORRELATION WITH DETERMINANTS OF NEUROLOGICAL DEFICIT, SLEEP DISORDERS, FREQUENCY OF REHABILITATION METHOD AND POTENTIAL NEGATIVE PROGNOSTIC FACTORS

4.1 Quality of life in children with ischemic stroke: general, medical and social aspects

The average total score calculated according to the PedsQL quality of life questionnaire, represented by the accumulated points on the scale of physical, emotional, and social well-being and preschool/school activity, was 56.2±25.2 points, varying between 9.5 and 95.6 points.

The lowest average score was registered on the scale indicating the limitation of the role of school and preschool activities, with a value of 47.1 points (±33.5), suggesting that children with ischemic stroke included in the study seem to feel the greatest burden of the disease through the prism of fitting into the preschool and school space. With the help of another scale of PedsQL, we assessed the degree of participation and social involvement of post-stroke children. This scale indicated children's absence from preschool and school activities due to poor physical health and/or the importance of regular check-ups. This fact was demonstrated with the help of the physical health score, the second scale with the lowest average score – 51.3 points (±31.5). The highest average score recorded was that of the emotional function - 72.0 points (±17.4), suggesting that parents of children with different degrees of disability offer appropriate psycho-emotional support to their children, the latter having a relatively good emotional state (table 3).

Table 3. Scores obtained by children with ischemic stroke in the PedsQL questionnaire, points

Quality of life scales	Mean, points	Std Deviation	Std Error	95% CI	Min	Max	Reference values
Physical functions	51,3	31,4	4,13	43,0-59,6	0	100	0-100
Emotional functions	72,0	17,4	2,29	67,4-76,6	20	100	0-100
Social activities	55,1	29,5	3,87	47,3-62,8	0	100	0-100
Pre/school activities	47,1	33,5	4,40	38,2-55,9	0	100	0-100

According to the total quality of life score, 38 (65.5%) of the children included in the study accumulated a score of less than 70 points, which is considered a very low quality of life, 5 (8.6%) of the participants presented a score between 71 – 80 points, which corresponds to a quality of life at a low level, 9 (15.5%) - a score between 81 – 90 points, which corresponds to a quality of life at moderate level and 6 (10.3%) of the subjects - a score higher than 90 points, corresponding to a high quality of life (figure 8).

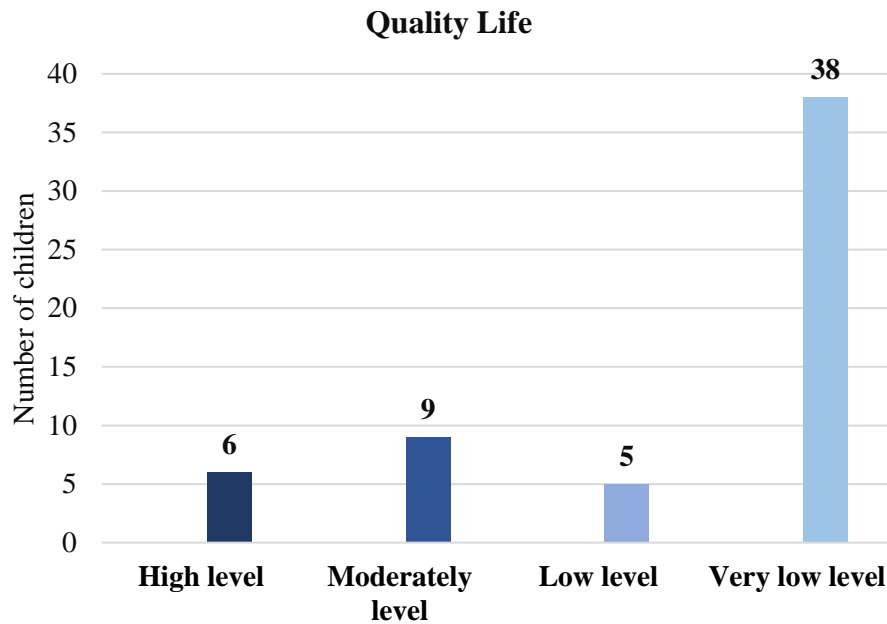


Figure 8. **The structure of the study group according to the accumulated total score of the quality of life, abs.**

We aimed to evaluate whether there were differences between the means of the quality of life score of children with ischemic stroke, depending on age, by ANOVA statistical analysis, adjusted with the help of the Bonferroni multiple correction test (table 4).

Table 4. **ANOVA statistical analysis, mean quality of life score in age groups 3-4 years, 5-7 years, 8-12 years, multiple Bonferroni correction**

Source of Variation	Sum of Squares	Degrees of Freedom	Mean of Squares	F	p
Among groups	42000.942	2	2100.471	3.592	.034
Within groups	32164.716	55	584.813		
Total	36365.658	57			

As can be seen in table 4, the analysis of the variance of the sum of squares of the score between groups with the variation within the groups revealed that the variation between the groups was greater, i.e. that there was reason to suggest that differences between the groups were significant. A statistically significant F parameter (3.59) was also obtained ($p < 0.05$), so we could suggest that the average score of the quality of life was statistically significantly different in the groups of children depending on their age.

The results of PedsQL scores on the physical scale ranged from 0 to 100 points, with a mean of 51.3 ± 31.5 , with a lower mean level in female subjects (46.4 vs 54.2 ; $p > 0.05$) and a statistically significant reduced score in children aged 3-4 years (39.5 vs 65.4 ; $p < 0.05$) (table 14).

The PedsQL scale on the emotional component varied from 0 to 100, with an average of 72.0 ± 17.4 , with a lower average level being recorded in female children (68.2 ± 18.5 vs 74.3 ± 16.6 ; $p > 0.05$) and children aged 3-4 (69.1 ± 17.5 vs 76.0 ± 15.3 ; $p > 0.05$).

The PedsQL quality of life score on the social scale ranged from 0 to 100, with a mean of 55.1 ± 29.5 , with a lower mean level being recorded in male patients (54.3 ± 29.6 vs 56.4 ± 29.9 $p > 0.05$) and those in children aged 3-4 years (48.1 ± 28.5 vs 67.8 ± 26.3 ; $p > 0.05$).

The PedsQL quality of life score on the preschool/school activities scale ranged from 0 to 100, with a mean of 47.1 ± 33.5 , with a lower mean level being recorded in females (46.7 ± 33.6 vs 47.3 ± 33.9 ; $p > 0.05$) and statistically significantly reduced in children aged 3-4 (36.2 ± 37.1 vs 65.0 ± 17.9 ; $p < 0.05$).

4.2 The relationship between the quality of life and the degree of neurological deficit, sleep disorders and the frequency of the applied rehabilitation method

Analyzing the relationship between the mean PedsQL quality of life score and the mean PSOM neurological deficits score, we observed that the PSOM score correlated negatively and highly with the PedsQL score, (Pearson's correlation coefficient being -0.7 ($p < 0.0001$)) (figure 9).

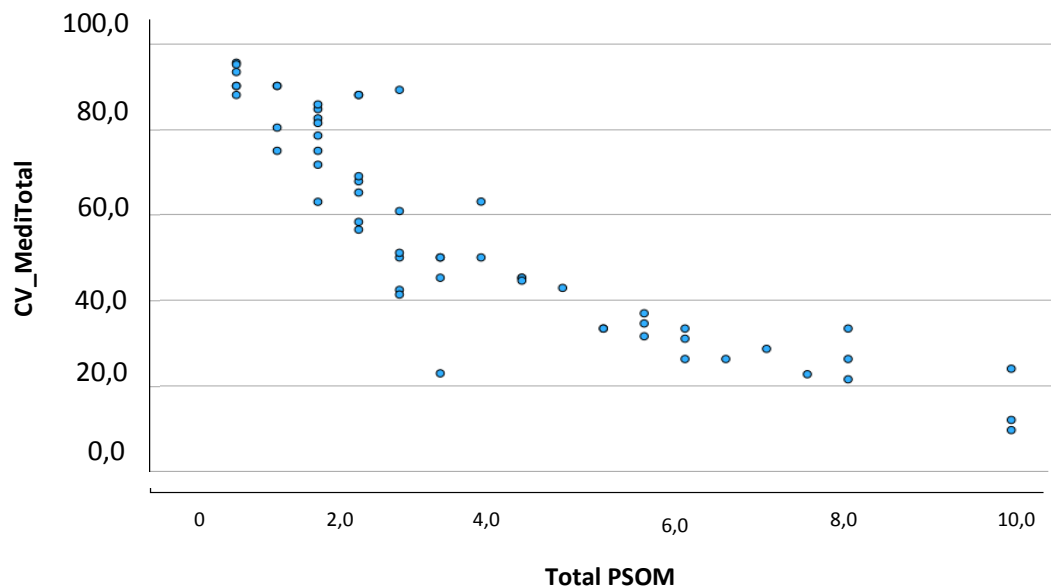


Figure 9. Scatter plot of correlation between PSOM and quality of life score

We notice that the points were distributed on the graph in a general ascending manner. This indicates that as the neurological deficits were more severe, the quality of life was lower.

The influence of sleep disorders on the quality of life of post-stroke children

In children who did not have sleep disorders, the average value of the total quality of life score was 86.6 ± 8.1 points, being statistically significantly higher compared to the one recorded in children with sleep disorders – 45.7 ± 20.0 points ($p < 0.001$).

The graphs from the Mann-Whitney Statistical Analysis of the quality of life scores between the group of children without sleep disturbances and the group of children with sleep disturbances suggested visualizing the differences in the quality of life scores between the two groups. It was visually observed that the quality of life scores in the group of children with sleep disorders was lower, thus sleep disorders represented a significant negative factor in the quality of life of children with ischemic stroke (figure 10).

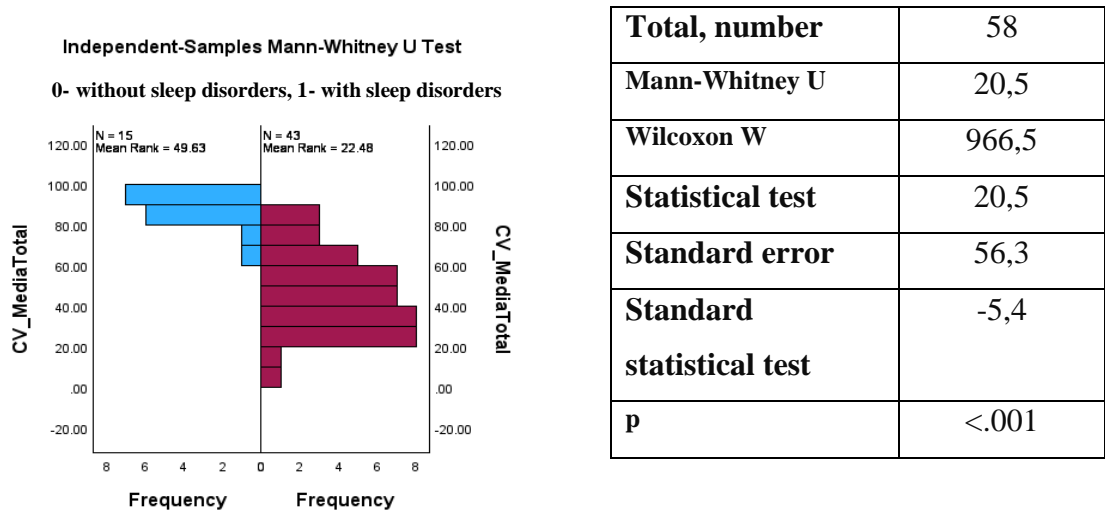


Figure 10. Mann-Whitney analysis of quality of life scores between the group of children without/with sleep disorders

The result of the Mann-Whitney U test, which measured the difference between the two groups (children with/without sleep disorders), was 20.5. This result suggested that there was a significant difference between the mean quality of life score of the two compared groups. Also, the Wilcoxon W value had a higher value (966.5) and thus indicated a difference between the 2 groups.

The analysis of quality of life on all PedsQL scales indicated statistically significant differences between subjects without sleep disorders and those with sleep disorders: on the physical health scale the mean value was 90.8 ± 7.5 points vs 37.5 ± 23.9 points ($p < 0.001$), on the emotional health scale the average value 86.7 ± 10.5 points vs 66.9 ± 16.5 points) ($p < 0.001$), on the social scale, the average value was 85.0 ± 16.7 points vs 44.6 ± 25.6 ($p < 0.001$) and on the preschool and school activities scale the average value was 81.4 ± 11.6 points vs 35.1 ± 30.2 points ($p < 0.001$).

The Spearman correlation coefficient between SDSC and QL score was -0.9 ($p < 0.0001$) (figure 11).

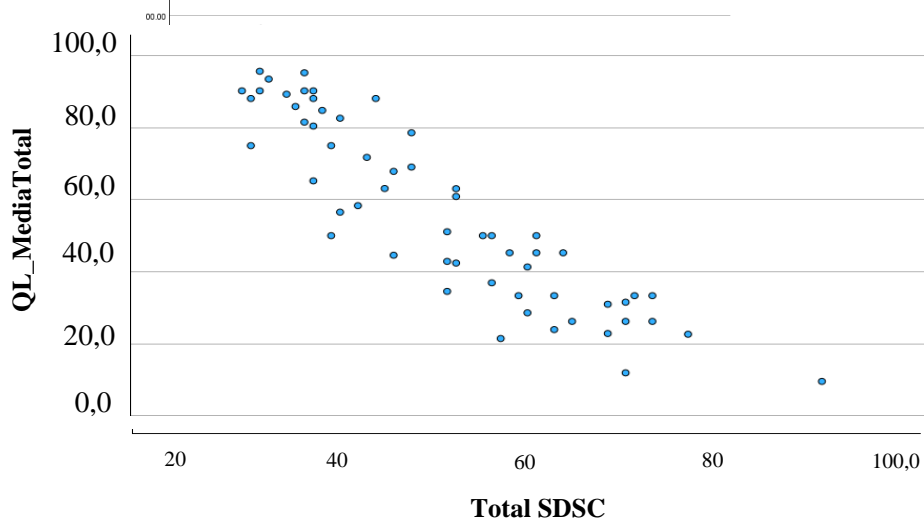


Figure 11. Scatter plot of correlation between sleep disturbance and quality of life score

Thus, it was observed that as the severity of sleep disturbances increased (the higher the score), the quality of life scores were lower. Thus, the association of sleep disorders after a stroke leads to a series of negative consequences, which influence both the physical state (and thus precarious of the post-stroke subjects), as well as the psychological and emotional state, all of which amplify the social integration disorders.

Influence of epilepsy on quality of life in post-stroke children

We analyzed the relationship between epilepsy as a post-stroke complication and the PedsQL quality of life score. The average value of the total quality of life score in children without this diagnosis was 67.1 ± 21.7 points and was higher compared to children with epilepsy – 37.0 ± 19.1 points ($p < 0.005$).

The graphs from the Mann-Whitney statistical analysis of the quality of life scores between the group of children without epilepsy and the one with epilepsy suggested the visualization of the differences in scores between the two groups, in the group of children with epilepsy the average score of the quality of life was lower (figure 12).

The result of the Mann-Whitney U test, which measured the difference between the two groups (children with/without epilepsy), was 114,000. and suggested that there was a significant difference between the mean quality of life score of the two compared groups. Also, the Wilcoxon W value had a higher value (345,500) and thus indicated a greater difference between the 2 groups.

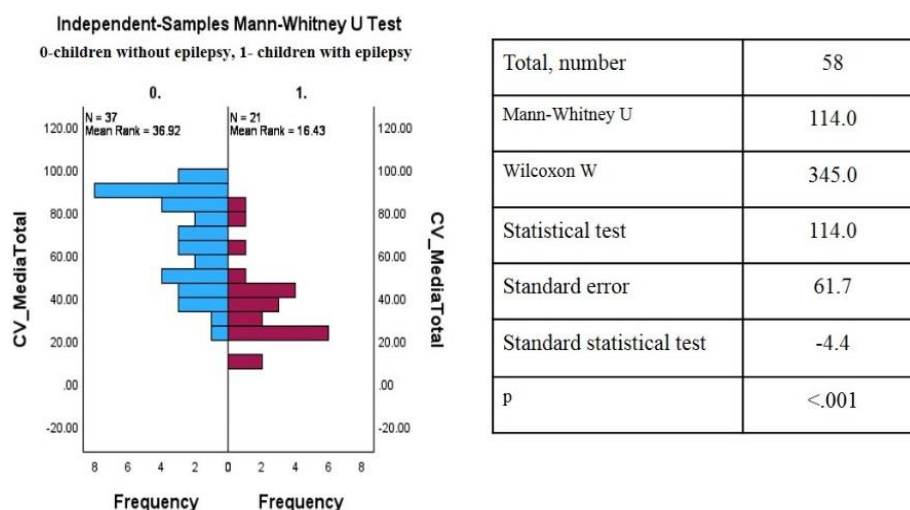


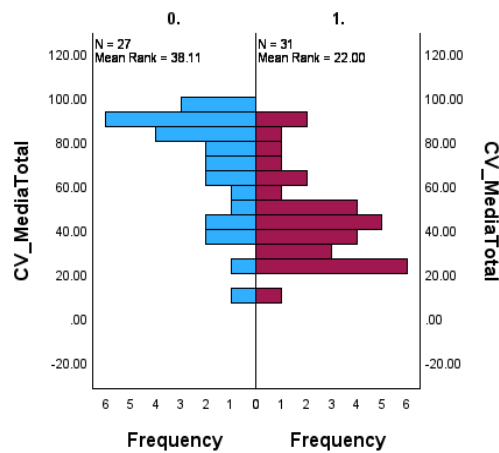
Figure 12. Mann-Whitney analysis of the mean score of Quality of Life between the group of children without/with epilepsy

Influence of continuous or quarterly rehabilitation programs on quality of life in children post-ischemic stroke

In children who followed continuous rehabilitation treatment, the average value of the total quality of life score was 69.2 ± 24.3 points, being significantly higher compared to children with quarterly rehabilitation treatment - 45.0 ± 20.4 points ($p < 0.001$).

The graphs from the Mann-Whitney statistical analysis of the quality of life scores between the group of children with quarterly or continuous rehabilitation treatment suggested the visualization of the differences in the quality of life scores between the two groups, in the group of children with quarterly treatment it was lower, thus the diagnosis of epileptic disease representing a significant negative factor on the quality of life of children with ischemic stroke (figure 13).

Indepent Samples Mann-Whitney U Test
 0- children with continuous rehabilitation treatment.
 1- children with quarterly rehabilitation treatment



Total, number	58
Mann-Whitney U	186.0
Wilcoxon W	682.0
Statistical test	186.0
Standard error	64.1
Standard statistical test	-3.6
p	<.001

Figure 13. Mann-Whitney analysis of mean Quality of Life score among children with continuous/quarterly rehabilitation treatment

The result of the Mann-Whitney U test, which measured the difference between the two groups (children continuous or quarterly rehabilitation treatment), was 186,000 suggesting that there was a significant difference between the average score of the quality of life of the two compared groups. Also, the Wilcoxon W value had a higher value (682,000) and thus indicated a greater difference between the 2 groups.

Stroke rehabilitation treatment is important, both in its type and duration, as well as in its continuity. Therefore, these children require a continuous rehabilitation program that facilitates positive progress in the child's motor, cognitive and social functions.

The analysis of the quality of life on all PedsQL scales indicated statistically significant differences between subjects with continuous rehabilitation treatment and those with quarterly rehabilitation treatment: on the physical health scale the mean value was 68.2 ± 30.2 points vs 36.6 ± 24.7 points ($p < 0.001$), on the emotional health scale the mean value 68.3 ± 28.5 points vs 43.5 ± 25.6 points) ($p < 0.001$), on the social scale the mean value was 61.8 ± 31.3 points vs 34.2 ± 30.4 ($p < 0.001$), on the scale of preschool and school activities the average value was 81.4 ± 11.6 points vs 35.1 ± 30.2 points) ($p < 0.05$).

Consequently, it was determined that neurological deficits with a more severe degree, the presence of sleep disorders, epilepsy and discontinuous rehabilitation treatment had a negative impact (possible also of mutual aggravation, with bidirectional influence) on all the average scores of the quality of life scales.

5. POTENTIAL PROGNOSTIC FACTORS OF QUALITY OF LIFE IN CHILDREN WITH ISCHEMIC STROKE

In our study, to evaluate the prognostic factors of poor quality of life in children with ischemic stroke, we studied the mean quality of life scores and used univariate analysis depending on the child's sex, age at stroke onset, time since the onset of the stroke until the examination of the child included in the study group, the aetiology of the ischemic stroke, the results of the PSOM neurological deficits,

the presence or absence of sleep disorders, the presence or absence of the diagnosis of epilepsy, as well as the serum level of protein S-100B. These characteristics and assessed parameters were included as prognostic factors of low quality of life.

At the same time, we also studied the relationship between the protein S-100B biomarker level (serum concentration at least 6 months after suffering an ischemic stroke) with long-term neurological outcomes and the quality of life of children with ischemic stroke. The Pearson correlation coefficient between serum Protein S-100B values and the PedsQL quality of life score indicated a strong negative correlation (rho coefficient -0.64 ($p < 0.0001$)) (figure 14), meaning that there is an inverse association between the two variables, that is, when serum levels of Protein S-100B are higher, the quality of life score (assessed with PedsQL) tends to be lower (and thus a poor quality of life).

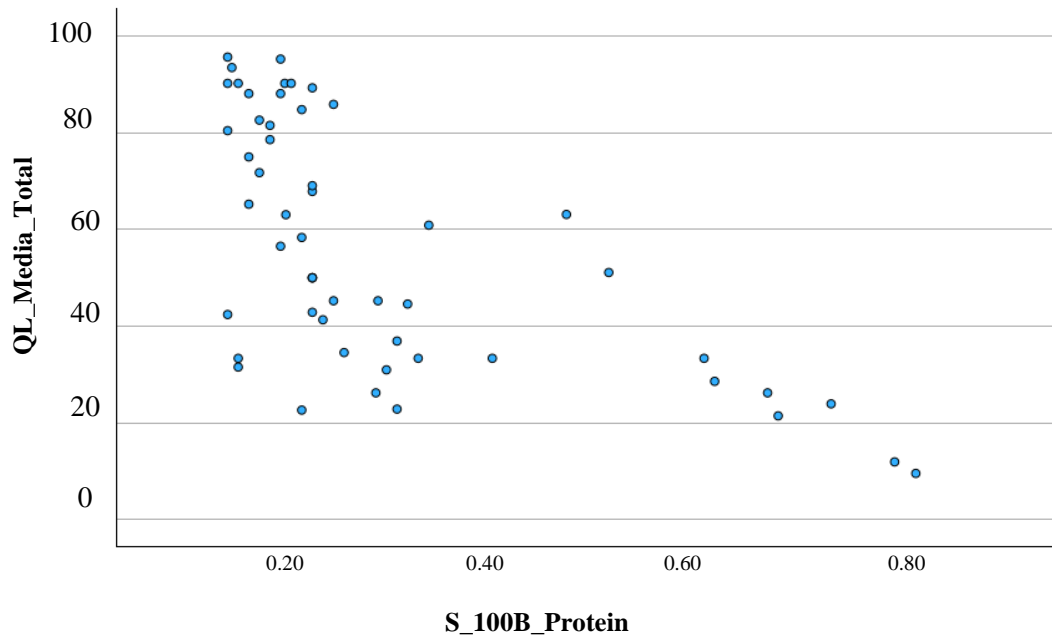


Figure 14. **Scatter Plot of Correlation Between Serum Protein S-100B Values and Quality of Life Score, Pearson Correlation Coefficient -0.64**

In this context, we could interpret the fact that the levels of increase of S100 B protein could be associated with a greater severity of ischemic stroke or the presence of complications affecting quality of life. These results allow us to support the hypothesis that Protein S-100B is a biomarker that can serve as a prognostic factor of poor quality of life in children who have had an antecedent of ischemic stroke.

Analyzing the results of the quality of life depending on the gender of the child, we established lower scores in female patients. At the same time, we evaluated the influence of age on neurological outcomes and quality of life and observed that quality of life was lower in children with stroke onset at a younger age (infancy), supporting the argument that neurons are more vulnerable in the brain than in the development process. At once, the presence of sleep disorders and/or epilepsy in children with stroke was associated with a more severe prognosis and a very low quality of life. Etiological factors leading to ischemic stroke were also analyzed, thus, congenital heart malformations, CNS infections, coagulability disorders and arterio-venous malformations were negative prognostic factors for a low quality of life. Higher levels of protein S-100 B above normal limits were also associated with lower quality of life, thus increasing the potential of this biomarker as a negative prognostic factor in pediatric ischemic stroke (Table 5).

Table 5. Predictors of poor quality of life in children with ischemic stroke

Prognostic factors	Regression coefficient, Exp (B)	Logistic regression	
		95 % CI	p
Female	-0,073	-0,13-0,2	<0.05
Age			
3-4 years	29.855	2,9-301,5	<0.001
5-7 years	13.383	1,2-14,7	<0.05
Moderate or severe neurological deficits, PSOM	0,879	0,7-1,01	<0.001
The presence of sleep disorders	0,674	0,4-0,9	<0.001
The presence of epilepsy	0,055	0,009-0,3	<0.005
Quarterly rehabilitation treatment	0,037	0,005-0,2	<0.001
Risk factors			
MCC	0,356	0,2-0,8	<0.001
Coagulability disorders	0,186	0,4-0,9	<0.005
Protein S-100B	-0,94	-125,4 - -62,5	<0.001

Understanding and knowing the prognostic factors of ischemic stroke can contribute to the development of more effective approaches to improve the quality of life.

THE MAIN CONCLUSIONS OF THE THESIS

1. Pediatric ischemic stroke predominated in male children (62%), its onset was predominantly in children under 1 year of age (48%), being associated with the following etiological factors: cardiac pathology (17%) and infectious neurological pathology (13%). In most cases the etiology of the ischemic stroke was not determined (44.8%).
2. Most of the children (84%) had motor deficits of varying degrees of severity, and the structures most often involved in ischemic stroke were the territory of the middle cerebral artery (71%) and the left hemisphere (46%).
3. The quality of life was significantly affected in children with an antecedent of ischemic stroke) 38 (65.5%) of the children included in the study scored less than 70 points (according to the average score of the PedsQL questionnaire), which counts as the quality of life at a very low level.
4. Three-quarters of children presented with sleep disorders (74%), in particular, sleep initiation and maintenance disorder (48%) and sleep-disordered breathing (38%), and more than half (53%) of the children did not benefit from continuous rehabilitation treatment.
5. The mean value of the total quality of life score correlated strongly negatively with the neurological deficits score (correlation coefficient - 0.7 (p < 0.0001)), highly negatively with the sleep disturbances score (correlation coefficient -0.906 (p < 0 .0001)) and strongly negative with S100B protein values (correlation coefficient -0.64 (p < 0.0001)).
6. Poor quality of life outcomes was determined by female gender (Exp (B) -0.073, p<0.05) of the child, younger age at stroke onset (Exp (B) 29.885, p<0.001), MCC (Exp (B) 0.356, p<0.001), coagulability disorders (Exp (B) 0.186, p<0.05), moderate or severe degree of PSOM neurological deficits (Exp (B) 0.879, p<0.001), presence of sleep disorders (Exp (B) 0.674, p<0.001), presence of epilepsy (Exp (B) 0.055, p<0.005), quarterly rehabilitation treatment (Exp (B) 0.037, p<0.001), higher serum levels of S-100B protein ((Exp (B) -94.0, p<0.001), and thus were included as negative prognostic factors of poor quality of life in children an antecedent of ischemic stroke.
7. In the current research, the solved scientific problem suggested the need to evaluate children in the post-stroke period, the assessment of the quality of life of these children to eliminate the

barriers in performing continuous rehabilitation treatment and social integration of these children oriented us towards the assessment of potential negative prognostic factors regarding the low quality of life of children with an antecedent of ischemic stroke.

RECOMMENDATIONS

We consider it necessary to mention some recommendations ((explained in the *Algorithm for the management of the pediatric post-ischemic stroke patient*) concerning the management of the quality of life of children who have suffered an ischemic stroke, which include questionnaires regarding the quality of life, the neurological clinical examination according to the PSOM, the sleep disorders questionnaire, and the evaluation of some markers, such as protein S -100B.

Thus, the recommendations for a child with an antecedent of ischemic stroke must be personalized and established in collaboration with a specialized medical team, including pediatric neurologists, rehabilitators, physical therapists, occupational therapists, and other professionals.

1. **Repeated medical examinations.** These regular visits to the pediatric neurologist will allow the child's health to be assessed and progress to be monitored. Parents (guardians) and children will be questioned regarding the quality of life and sleep disorders, the neurological clinical examination according to the PSOM will be performed, and some markers will be evaluated, such as S-100B protein for a prognosis of the disease. The treatment and recommendations will also be adapted according to the results of these investigations/examinations and the individual needs of the child. Because sleep is an indispensable process for the cognitive, physical, and psycho-emotional development of children, but also very important for the rehabilitation process, the identification of sleep disorders and their correct management should become a mandatory objective in the process of children's recovery in the post-stroke period. Especially since, in most cases, the identification of sleep disorders is possible by conducting a detailed survey of parents and/or children, and the resolution of these disorders is based on behavioural methods, which do not require expensive interventions and hospitalization. At the same time, it is opportune to train medical staff and parents to prevent, identify and resolve sleep disorders and other disorders in children after ischemic stroke.
2. **Continuous rehabilitation treatment** with a physical therapy program where parents of children with stroke will be trained. The exercise program will be tailored to the child's needs and will help improve muscle strength, coordination and mobility.
3. **Occupational Therapy.** It will help the child to develop practical skills needed for daily activities (such as personal hygiene, feeding, dressing, etc.), as well as improve coordination and motor control.
4. **Speech therapy and communication.** If the stroke has affected the child's speech or communication skills, a speech therapist and language and communication techniques are essential to improve verbal or other ways of communication.
5. **Emotional support.** It will be ensured that the child and family receive adequate emotional support, either through individual counselling or through support groups.
6. **Education and cognitive stimulation.** An educational program adapted to the child's needs will be carried out, which will include various games and activities that will develop thinking, concentration and memory.
7. **Pharmaceutical treatment.** Management of ischemic stroke symptoms and comorbidities (seizures, muscle spasticity) is essential.
8. **Healthy lifestyle.** It will necessarily include a balanced diet, regular, moderate physical exercise and individually adapted to each child. Also maintaining an optimal weight and identifying risk factors for another stroke.

Practical recommendations at different levels of the medical service:

1. At the level of primary medicine, we recommend the following:

- Evaluation of children who suffered an ischemic stroke by assessing the degree of functionality and impairment of various functions (motor, sensory, communication, behavioural, sleep quality, etc.)
- When identifying different types of disorders, patients with health problems are recommended to be referred to a medical specialist_(neurologist-pediatrician, psychologist, speech therapist, physiotherapist, specialist in sleep disorders) to confirm or deny complications arising after an accidental stroke.

2. At the level of specialized medicine, we propose:

Evaluation of the child through the following examinations: EEG, brain MRI imaging examination, the inclusion of the child in the recovery group with the application of a continuous rehabilitation treatment through the involvement of the family and guardians according to the child's needs.

3. At the research level, we recommend continuing the study of ischemic stroke with onset at the pediatric age with research at the cardiological, hematological, molecular-genetic level, etc. to identify the risk factors for this disease with onset in childhood and those to develop of long-term complications according to predisposing factors.

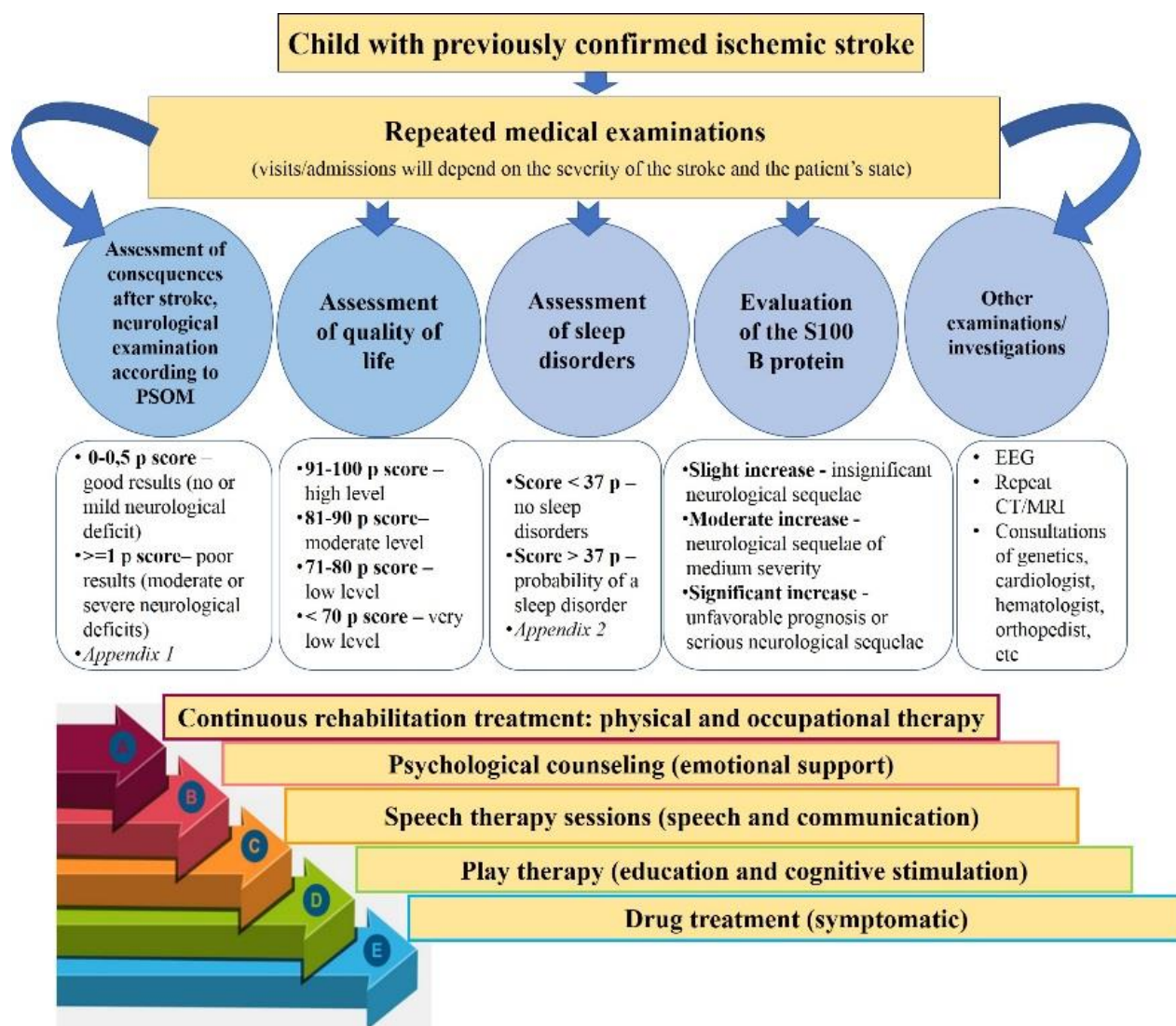


Figure 15. Algorithm for the management of the pediatric post-ischemic stroke patient

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” **Child’s quality of life after ischemic stroke: medical-social considerations**”, doctoral program
 321.05 – clinical neurology, "Nicolae Testemițanu" State University of Medicine and Pharmacy
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ADNOTARE

Lupușor Nadejda, „Calitatea vieții copilului după accidentul vascular cerebral ischemic: considerente medico-sociale”, teză de doctor în științe medicale, Chișinău, 2024

Structura tezei: Teza este expusă pe 148 pagini de text (100 pagini text de bază) și include: introducere, 5 capitole, sinteza rezultatelor obținute, concluzii generale, recomandări practice, indice bibliografic cu 164 de titluri și 11 anexe. Materialul ilustrativ conține 26 de tabele și 58 figuri.

Cuvinte cheie: accident vascular cerebral pediatic, calitatea vieții, deficit, tulburări, somn, reabilitare, proteina S100B, prognostic.

Scopul cercetării: evaluarea particularităților calității vieții copilului cu antecedente de accident vascular cerebral ischemic pediatic sub influența programelor de reabilitare pentru a aprecia prognosticul medical și social.

Obiectivele cercetării: 1) Analiza demografică, cauzală și clinico-paraclinică a copiilor care au suportat un accident vascular cerebral ischemic pediatic; (2) Evaluarea complexă a copiilor cu accident vascular cerebral ischemic în antecedente prin aprecierea calității vieții, specificului deficitelor neurologice, particularităților tulburărilor de somn și programului de reabilitare; (3) Estimarea relației dintre calitatea vieții copilului care a suportat accident vascular cerebral ischemic și gradul de deficit neurologic, tulburările de somn, nivelul seric al proteinei S100B și programul de recuperare; (4) Aprecierea factorilor potențiali de prognostic negativ al calității vieții la copiii care au suportat accident vascular cerebral ischemic, în funcție de parametrii studiați.

Noutatea și originalitatea științifică. În premieră în populația pediatică autohtonă a fost realizat un studiu de evaluare a calității vieții copiilor cu accident vascular cerebral ischemic în antecedente. Acest studiu ne-a permis să facem o analiză complexă a statutului medico-social prin utilizarea chestionarelor de apreciere a calității vieții, evaluarea clinică a deficitului neurologic, identificarea tulburărilor de somn și estimarea eficienței programului de reabilitare. În baza rezultatelor obținute a fost elaborat un algoritm de conduită și recomandări privind evaluarea copilului cu accident vascular cerebral ischemic în perioada de reabilitare, calitatea somnului și programul de recuperare recomandabil (terapie continuă/trimestrială). De asemenea, a fost elaborat un algoritm de prognostic la distanță al acestor copii pentru ameliorarea calității vieții lor, precum și a îngrijitorilor lor.

Rezultatele obținute care contribuie la soluționarea unei probleme științifice. Rezultatele obținute constă în elaborarea algoritmului de prognostic și recomandări al copilului în perioada post-accident vascular cerebral ischemic, fapt ce va avea ca efect ameliorarea calității vieții copilului și familiei acestuia.

Semnificația teoretică. Copiii cu accident vascular cerebral au calitatea vieții redusă, însă deseori nu sunt evaluați conform scalelor calității vieții și tulburărilor de somn. Rezultatele obținute în urma cercetării vor contribui la elaborarea unor activități de gestionare complexă a copiilor cu accident vascular cerebral ischemic.

Valoarea aplicativă. Recunoașterea timpurie a nevoilor acestor copii (fizice, emoționale și sociale), dar și a problemelor legate de tulburările de somn, precum și încurajarea părinților referitor la programul de recuperare recomandat, asigură un management corect al pacientului după un accident vascular cerebral ischemic. Studiul dat a facilitat formularea unor recomandări detaliate referitor la examinarea copiilor post-AVC ischemic pentru a crește calitatea vieții acestora și a îngrijitorilor lor.

Implementarea rezultatelor științifice. Rezultatele obținute în cadrul studiului, algoritmul de conduită a pacientului pediatic post-accident vascular cerebral ischemic au fost implementate în Clinica de Pediatrie și Neurologie pediatică a Departamentului Pediatrie, secția de reabilitare medicală pediatică, secția de neurologie și psihoneurologie vârstă fragedă a IMSP Institutul Mamei și Copilului.

ANNOTATION

**Lupușor Nadejda, "Child's quality of life after ischemic stroke: medico-social considerations",
PhD thesis in medical sciences, Chisinau, 2024**

Thesis structure. The thesis is presented on 148 pages (100 pages of basic text) and including an introduction, 5 chapters, synthesis of the obtained results, general conclusions, practical recommendations, bibliographic index with 164 titles and 11 appendices. The illustrative material contains 26 tables and 58 figures.

Keywords: pediatric stroke, quality of life, deficit, disorders, sleep, rehabilitation, S100B protein, prognosis.

The aim of the research: to evaluate the peculiarities of the quality of life of the child with a history of pediatric ischemic stroke under the influence of rehabilitation programs in order to assess the medical and social prognosis.

Research objectives: 1) Demographic, causal and clinical-paraclinical analysis of children who suffered a pediatric ischemic stroke; (2) Complex assessment of children with a history of ischemic stroke by assessing the quality of life, the specifics of neurological deficits, the particularities of sleep disorders and the rehabilitation program; (3) Estimation of the relationship between the quality of life of the child who suffered an ischemic stroke and the degree of neurological deficit, sleep disorders, the serum level of the S100B protein and the recovery program; (4) Appreciation of the potential negative prognostic factors of the quality of life in children who suffered ischemic stroke, according to the parameters studied.

Scientific novelty and originality of the research. For the first time in the native pediatric population, a study was conducted to evaluate the quality of life of children with a history of ischemic stroke. This study allowed us to make a complex analysis of the medico-social status by using quality of life assessment questionnaires, clinical assessment of neurological deficit, identification of sleep disorders and estimation of the effectiveness of the rehabilitation program. Based on the results obtained, a behavior algorithm and recommendations were developed regarding the evaluation of the child with ischemic stroke during the rehabilitation period, the quality of sleep and the recommended recovery program (continuous/quarterly therapy). A remote prognostic algorithm for these children was also developed to improve the quality of life for them as well as their caregivers.

The obtained results contribute to the solution of a scientific problem. The obtained results consist in the elaboration of the prognosis algorithm and recommendations for the child in the post-ischemic stroke period, which will have the effect of improving the quality of life of the child and his family.

Theoretical importance. Children with stroke have reduced quality of life, but are often not assessed according to quality of life and sleep disturbance scales. The results obtained from the research will contribute to the development of complex management activities for children with ischemic stroke.

Applicative value: Early recognition of the needs of these children (physical, emotional and social), but also of problems related to sleep disorders, as well as encouraging parents regarding the recommended recovery program, ensures correct management of the patient after an ischemic stroke. The given study facilitated the formulation of detailed recommendations regarding the examination of children post-ischemic stroke to increase the quality of life of them and their caregivers.

Implementation of the scientific results. The results obtained in the study, the algorithm for the behavior of the pediatric patient after ischemic stroke were implemented in the Clinic of Pediatrics and Pediatric Neurology of the Department of Pediatrics, the pediatric medical rehabilitation section, the neurology and early psychoneurology section of Mother and Child Institute.

АННОТАЦИЯ

Лупушор Надежда, «Качество жизни ребенка после ишемического инсульта: медико-социальные аспекты», диссертация доктора медицинских наук, Кишинев, 2024

Структура диссертации. Диссертация изложена на 148 страницах (100 страниц основного текста) и включает: введение, 5 глав, обобщение полученных результатов, общие выводы, практические рекомендации, библиографический указатель из 164 названий и 11 приложений. Иллюстративный материал содержит 26 таблиц и 58 рисунков.

Ключевые слова: детский инсульт, качество жизни, дефицит, нарушения, сон, реабилитация, белок S100B, прогноз.

Цель: оценить особенности качества жизни ребенка, перенесшего ишемический инсульт, под влиянием реабилитационных программ с целью оценки медико-социального прогноза.

Цель исследования: 1) Демографический, причинный и клиничко-параклинический анализ детей перенесших ишемический инсульт; (2) Комплексное обследование детей перенесших ишемический инсульт, путем оценки качества жизни, особенностей неврологического дефицита, особенностей нарушений сна и программы реабилитации; (3) Оценка связи качества жизни ребенка, перенесшего ишемический инсульт, со степенью неврологического дефицита, нарушений сна, сывороточного уровня белка S100B и программы реабилитации; (4) Оценка потенциальных негативных прогностических факторов качества жизни детей перенесших ишемический инсульт, по изученным параметрам.

Научная новизна и оригинальность. Впервые в отечественной педиатрической популяции проведено исследование по оценке качества жизни детей перенесших ишемический инсульт. Проведенное исследование позволило провести комплексный анализ медико-социального статуса путем использования опросников оценки качества жизни, клинической оценки неврологического дефицита, выявления нарушений сна и оценки эффективности программы реабилитации. На основании полученных результатов были разработаны алгоритм поведения и рекомендации по оценке ребенка с ишемическим инсультом в реабилитационном периоде, качеству сна и рекомендуемой программе восстановления (непрерывная/ежеквартальная терапия). Также был разработан алгоритм дистанционного прогнозирования этих детей с целью улучшения качества жизни их самих и их опекунов.

Полученные результаты способствуют решению научной задачи: Полученные результаты заключаются в разработке алгоритма прогноза и рекомендаций ребенка в период постишемического нарушения мозгового кровообращения, что будет иметь эффект улучшения качества жизни ребенка, ребенок и его семьи.

Теоретическая значимость. У детей с инсультом снижается качество жизни, но их часто не оценивают по шкалам качества жизни и нарушений сна. Результаты, полученные в результате исследования, будут способствовать разработке комплексных лечебных мероприятий у детей с ишемическим инсультом.

Прикладная ценность. Раннее признание потребностей этих детей (физических, эмоциональных и социальных), а также проблем, связанных с нарушениями сна, а также поощрение родителей к рекомендуемой программе реабилитации обеспечивает правильное ведение пациента после ишемического инсульта. Проведенное исследование способствовало формулированию детальных рекомендаций по обследованию детей, перенесших ишемический инсульт, с целью повышения качества жизни их самих и лиц, осуществляющих уход за ними.

Реализация результатов: Результаты, полученные в исследовании, алгоритм поведения пациента детского возраста после ишемического инсульта внедрены в Клинике педиатрии и детской неврологии кафедры педиатрии, отделения детской медицинской реабилитации, отделения неврологии, отделение ранней психоневрологии Института матери и ребенка.

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**QUALITY OF LIFE IN CHILDREN AFTER
AN ISCHEMIC STROKE:
MEDICAL-SOCIAL CONSIDERATIONS**

321.05 - CLINICAL NEUROLOGY

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