algorithms

MDPI

Article

Pediatric Ischemic Stroke: Clinical and Paraclinical Manifestations—Algorithms for Diagnosis and Treatment

Niels Wessel [1,2], Mariana Sprincean [3,4,*], Ludmila Sidorenko [3], Ninel Revenco [4] and Svetlana Hadjiu [4]

1 Department of Human Medicine, MSB Medical School Berlin GmbH, 12247 Berlin, Germany; niels.wessel@medicalschool-berlin.de or wessel@physik.hu-berlin.de
2 Department of Physics, Humboldt-Universität zu Berlin, 12489 Berlin, Germany
3 Department of Molecular Biology and Human Genetics, "Nicolae Testemitanu" State University of Medicine and Pharmacy, 2004 Chisinau, Moldova; ludmila.sidorenco@usmf.md
4 Public Health Medical Institution Mother and Child Institute, MD 2062 Chisinau, Moldova; ninel.revenco@usmf.md (N.R.)
* Correspondence: mariana.sprincean@usmf.md; Tel.: +373-698-898-00

Abstract: Childhood stroke can lead to lifelong disability. Developing algorithms for timely recognition of clinical and paraclinical signs is crucial to ensure prompt stroke diagnosis and minimize decision-making time. This study aimed to characterize clinical and paraclinical symptoms of childhood and neonatal stroke as relevant diagnostic criteria encountered in clinical practice, in order to develop algorithms for prompt stroke diagnosis. The analysis included data from 402 pediatric case histories from 2010 to 2016 and 108 prospective stroke cases from 2017 to 2020. Stroke cases were predominantly diagnosed in newborns, with 362 (71%, 95% CI 68.99–73.01) cases occurring within the first 28 days of birth, and 148 (29%, 95% CI 26.99–31.01) cases occurring after 28 days. The findings of the study enable the development of algorithms for timely stroke recognition, facilitating the selection of optimal treatment options for newborns and children of various age groups. Logistic regression serves as the basis for deriving these algorithms, aiming to initiate early treatment and reduce lifelong morbidity and mortality in children. The study outcomes include the formulation of algorithms for timely recognition of newborn stroke, with plans to adopt these algorithms and train a fuzzy classifier-based diagnostic model using machine learning techniques for efficient stroke recognition.

Keywords: cerebral stroke; ischemic stroke; childhood stroke; neonatal stroke; clinical signs; paraclinical manifestations; algorithms; early intervention

Citation: Wessel, N.; Sprincean, M.; Sidorenko, L.; Revenco, N.; Hadjiu, S. Pediatric Ischemic Stroke: Clinical and Paraclinical Manifestations—Algorithms for Diagnosis and Treatment. *Algorithms* **2024**, *17*, 171. https://doi.org/10.3390/a17040171

Academic Editor: Francesc Pozo

Received: 9 February 2024
Revised: 8 April 2024
Accepted: 17 April 2024
Published: 22 April 2024

1. Introduction

Stroke has a significant impact on morbidity and mortality rates in children [1]. Ischemic stroke (IS) most often occurs in the prenatal period and the first 28 days after birth with a frequency of 1:4000 live newborns [2]. Risk factors and clinical manifestations of stroke in children and adolescents differ from those in adults. The etiological factors of pediatric stroke involve neonatal encephalopathies, anomalies in the development of cerebral vessels (most often, arteriovenous anomalies), hereditary or acquired prothrombotic conditions, hereditary abnormalities of blood vessels in the frame of several genetic syndromes, etc. [3]. In young children, stroke is accompanied by motor, speech, and sensory disorders. In addition, stroke can occur during pregnancy or immediately after childbirth, without any severe symptoms. Sometimes, newborns who suffer stroke present mild or no clinical symptoms until the age of 4–8 months, whereas seizures or paralysis are recorded in some cases. As a result, many children are at risk of not receiving adequate treatment. The pathology leads to a high degree of disability, even resulting in death in 12% of cases, and in 70% of cases, it causes a persistent neurological deficit [4].

Pediatric stroke includes three subtypes: ischemic stroke (defined as sudden focal infarction, diagnosed by neuroimaging or autopsy, which can lead to arterial stroke, the most common type of stroke, after sudden arterial occlusion—50% of cases), cavernous sinus thrombosis (CVST, which is a venous infarction following a superficial and deep venous thrombosis, associated with severe complications in 1:4 cases) and hemorrhagic stroke (characterized by a spontaneous rupture of a cerebral vessel, commonly in small arteries, cerebral aneurysm, or cerebral arteriovenous malformations) [5]. Some clinicians report that stroke in children occurs in about 50% of cases, others describe a higher incidence of stroke with up to 67–85% of cases [6]. Rapid and accurate diagnosis of stroke is vital, and the therapeutic approach differs depending on the type of pediatric stroke.

Children present different clinical manifestations of ischemic stroke compared with those of adults, since they are not clear, showing a variable clinical polymorphism depending on the child's age. Thus, it is difficult to diagnose stroke, especially in the first six hours after the onset of the disease. Only 30% of children with cardiovascular disease will present any of the clinical manifestations confirmed by imaging findings during the effective therapeutic time [7]. Young children may have atypical manifestations, while older children have neurological symptoms similar to those found in adults. Older children, besides the neurological symptoms of hemiparesis, aphasia, and hemianopia, might experience headaches and convulsive seizures in 30% of cases, recorded in 20–48% of patients. The presence of nonspecific and variable neurological symptoms requires an investigation of all acute onset cases in young children to exclude the risk of possible ischemic stroke; thus, brain imaging should be recommended in each case [8]. Regarding all those facts mentioned above, the necessity of elaboration of algorithms which would include all signs, even minor signs, emerges to aid in the right indication for prompt imaging, aiming to define the diagnosis of IS as early as possible.

The planned outcome of this study is the elaboration of algorithms for timely newborn stroke recognition and algorithms for predicting stroke in children. The algorithm's elaboration is based on the results of the given study.

2. The Objective of the Study

The main goal was to develop and validate algorithms that can accurately predict the onset of ischemic stroke in newborns and children. Additionally, we aimed to create algorithms that can help recognize ischemic stroke in newborns promptly.

3. Materials and Methods

The study on childhood clinical manifestations was conducted by retrospectively analyzing data from 402 medical records of children hospitalized with stroke in the Neurology Departments of the Institute of Mother and Child PHMI (IMSP IMC) and the Clinical Hospital No. 1 PHMI (IMSP SCM) from 2010 to 2016. Additionally, prospective data from 108 children with stroke collected from 2017 to 2020 were included. A comprehensive analysis of clinical manifestations from both retrospective and prospective data was performed to obtain reliable statistical results. The analysis aimed to evaluate symptoms indicative of ischemic stroke in children of different ages using a logistic regression analysis, chosen to determine the relationship between triggering symptoms and stroke and establish algorithms for timely recognition and prediction of stroke.

This study employed a prognostic cohort design to estimate the incidence of pediatric stroke and assess its prognostic outcomes. The sample size was calculated based on the estimated incidence rate of pediatric stroke ($p = 0.0075$) and the desired confidence level and margin of error. With adjustments for design effect and non-response rate, a representative sample of 53 children with IS was included in the study. The research was conducted in consecutive stages, with the first stage comprising the full descriptive study, focusing on analyzing incidence, morbidity, and mortality rates, as well as the distribution of IS cases by various factors. The second stage was a prognostic cohort study, which aimed to assess the incidence of pediatric stroke and its prognostic outcomes.

The following types of studies were conducted:

1. Full descriptive study—to analyze the incidence, prevalence, disability, and mortality rates in children who experienced acute stroke between 2010 and February 2020
2. Prognostic cohort study:

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

where

p is the incidence of pediatric stroke, estimated by the statistical frequency of IS in children and newborns in the population 2–13/100,000; it is on average p = 0.0075;
Z = 1.96 for the 95.0% confidence interval;
e = 0.03 is the accepted error;
n = 0.0075 × 0.9925 (1.96/0.03)2 = 31.74; n × design effect (1.5) = 47.6 and with a 10.0% non-response rate, so a representative sample size has to include 53 children with IS.

The scientific research was carried out consecutively in several stages.

Stage I included the full descriptive study (2010–2020). Data were assessed by the IBM SPSS Statistics 26 program. This study involved a comprehensive examination of the evolutionary aspects and structure of neonatal and pediatric ischemic stroke (IS) in the Republic of Moldova from 2010 to 2020. It included retrospective and prospective observational analytical studies on incidence, morbidity, and mortality, conducted at the Pediatric Neurology Clinic of the Department of Pediatrics of the PI USMF Nicolae Testemițanu, along with relevant sections within IMSP IMC and IMSP SCM No. 1. The analysis covered the distribution of IS cases across different regions of the Republic of Moldova, as well as by age and gender. Furthermore, the study analyzed the profile of determinants involved in initiating IS in the pediatric population of the Republic of Moldova, categorized by age category. The estimation of cases diagnosed with neonatal IS and pediatric IS from 2010 to 2020 (totaling 510 children) was conducted, considering evolving clinical and paraclinical manifestations.

In stage II, the prognostic study was conducted in two directions: (1) on pregnant women at risk of giving birth to children with IS, involving 153 pregnant women, and (2) on a group of children who suffered acute IS, totaling 108 children.

The first study aimed to analyze the results of examinations of pregnant women using both non-invasive (fetal ultrasonography and biochemical screening: double/triple test) and invasive (amniocentesis with fetal karyotype study) prenatal diagnosis methods. These examinations were performed at the Center for Reproductive Health and Medical Genetics under the National Program for the Evaluation of Pregnant Women and Prophylaxis of Hereditary Pathologies. The results from 153 pregnant women who underwent medico-genetic counseling were evaluated to prevent and predict cerebral pathology in children.

Additionally, within the prospective study, children who suffered acute neonatal IS (NIS) or acute pediatric IS (PIS) between 2017 and 2020 (108 children) were identified. This study allowed for the highlighting and specification of the clinical–paraclinical manifestations of NIS and PIS based on the determinants involved (perinatal and postnatal) and the age of the patient. A detailed analysis of prenatal factors associated with the risk of NIS was conducted, estimating the importance of the medical-genetic consultation in such cases. Furthermore, clinical symptoms characteristic of the studied age were elucidated through neurological examination, utilizing the PedNIHSS scale to assess the severity of CNS involvement in IS.

In stage III, an assessment of the prognosis of neurological complications in patients with stroke was conducted. This involved assessing the relationship between determinants involved in stroke, the age of the child, clinical features at the stage of confirming the diagnosis, and the risk of occurrence using mathematical analysis methods for neurological complications. Predictive methods were proposed for the prevention of IS risk and neurological complications in children. Statistical processing of the obtained data was carried out

by researching correlations and conducting a multivariate analysis of the causes involved in the development of IS, considering clinical and imaging factors depending on the child's age to calculate the risk of neurological complications.

Stage IV included the development of algorithms for managing women/families at risk of giving birth to a child with IS and algorithms for the diagnosis and management of newborns and children with IS. Additionally, the National Clinical Protocol for cerebral vascular accidents in children was developed, aiming at prophylaxis, early diagnosis, and definitive treatment of stroke in pediatric patients, for healthcare professionals and the population of the Republic of Moldova.

In the context of the study, the following criteria for inclusion/exclusion of patients served as conceptual and methodological benchmarks:

Criteria for including patients in the study:

1. Children diagnosed with acute ischemic stroke of various types.
2. Newborn infants aged between 0 and 28 days.
3. Children aged between 28 days and 18 years.
4. Pregnant women.
5. Availability of informed consent from parents or guardians.

Exclusion criteria from the study:

1. Children diagnosed with hemorrhagic stroke.
2. Children diagnosed with venous sinus thrombosis.
3. Children older than 18 years.
4. Children with acute craniocerebral trauma.
5. Premature infants.
6. Lack of informed consent from parents or guardians.

The research was made possible by the project "Evaluation of incidence, prevalence, risk factors, research of clinical, neuroimaging, neurophysiological, and neurotrophic remedial aspects of cerebrovascular accidents in children" within the state program "Systemogenesis of risk factors, optimization of the medical assistance service, evaluation sustainable and mathematical modeling of Stroke", considering the cost and methodological difficulties (exceptionally used for scientific purposes) of the method. The project was conducted in the Department of Pediatrics of SUMP "Nicolae Testemițanu".

Patients underwent examinations in departments specializing in neurological care, the resuscitation department, and neonatal neurology. A periodic observation of patients was conducted as necessary, depending on established diagnoses and the child's age. Data were recorded in a questionnaire which included information on risk factors, determinants, clinical outcomes following the Amiel-Tison test (for newborns and children up to 3 months), and the pedNIHSS scale (for children over 3 months). Additional examinations such as CT and MRI of the brain, as well as EEG, were utilized to assess functional and structural changes in the brain. These investigations were conducted in inpatient settings. EEGs were performed based on existing indications, and imaging examinations were conducted in 108 children with acute neonatal or pediatric stroke in the prospective study group. The results of these additional investigations facilitated the confirmation of acute stroke diagnosis in children, the assessment of the dimensions of the cerebral ischemic focus, and the evaluation of the disease prognosis.

The participants included in the study, namely, the parents of children with IS, had to complete the Informed Agreement prior to the study. Confidentiality and protection of personal data were ensured by coding all the names and any personal data of the participants, before transferring data into Excel tables. Prior to conducting the study, it was approved by the favorable opinion of the ethics committee no. 69, dated 21 March 2017.

4. Results

The results of the descriptive statistics characterize both studied cohorts, including the retrospectively and the prospectively analyzed patients, as follows: (1) a ret-

rospective analysis of 402 medical records of newborn children (291 children, 57.1%; 95% CI [54.91–59.29]) and those aged between 28 days and 18 years (111 children, 21.8%; 95% CI [19.97–23.63]), diagnosed with neonatal or pediatric ischemic stroke between 2010 and 2016 in the neurology departments of IMSP IMC and IMSP SCM No. 1; and (2) a prospective study from 2017 to 2020 within the same medical institutions, with a sample of 108 children aged 0 to 18 years, distributed by age categories: newborn—71 (65.7%; 95% CI [61.13–70.27]), children aged between 28 days and 18 years (meeting pediatric ischemic stroke criteria)—37 (28.7%; 95% CI [24.35–33.05]), all diagnosed with acute ischemic stroke. To analyze epidemiological aspects, clinical manifestations, and neurological outcomes in both retrospective and prospective studies, data from 510 medical records of childhood acute stroke cases were examined, distributed by age categories: newborn—362 (71%, 95% CI [68.99–73.01]), child—148 (29%, 95% CI [26.99–31.01]). Imaging, neurofunctional, and immunological manifestations were analyzed based on results obtained from the 108 patients with ischemic stroke in the prospective study.

The study of the clinical manifestations of IS in children across different age groups is crucial in this field. IS cases were predominantly diagnosed in newborns, with 362 cases (71%, 95% CI 68.99–73.01), while 148 cases (29%, 95% CI 26.99–31.01) occurred after 28 days of birth. Among newborns with IS, 242 (66.9%, 95% CI 64.43–69.37) were boys and 120 (33.1%, 95% CI 30.63–35.57) were girls.

Perinatal IS is defined in the specialized literature as an acute neurological syndrome of vascular origin, occurring between 20 weeks of gestation and 28 days after birth, confirmed by neuroimaging or neuropathological studies, and leading to neurological outcomes. Clinical manifestations in this group of children are less specific, with seizures, apnea, and impaired consciousness being the most common. In the pediatric population, perinatal IS accounts for 25% of IS cases and 43% of cavernous sinus thrombosis cases.

The analysis of IS clinical manifestations revealed differences compared to other age groups, characterized by several generalized symptoms (refer to Table 1), associated with age-specific nervous system development.

Table 1. Clinical manifestations of ischemic stroke in newborns (Number of cases = 362), abs., %.

Clinical Symptoms	Abs.	P ES (%)	95% CI
Epileptic seizures: focal motor seizures involving a limb	321 211	88.7 65.7	87.03–90.37 63.05–68.35
Apnea attacks	185	51.1	48.47–53.73
Impaired consciousness	269	74.3	72.0–76.6
Generalized movement disorders (hypotonia)	243	67.1	64.63–69.57
Tremors	169	46.7	44.08–49.32
Resuscitation required	142	39.2	36.63–41.77
Pathologic irritability	99	27.3	24.96–29.64
Convergent strabismus	93	25.7	23.4–28.0

Table 1 illustrates that 88.7% of newborns with ischemic stroke experienced convulsive seizures, with 65.7% exhibiting focal manifestations. The most prevalent clinical symptoms were apnea attacks, impaired consciousness, and movement disorders, while tremors, pathologic irritability, and converging strabismus were less frequent. However, it is important to include pathologic irritability in the algorithm for decision-making, as it represents an alarming sign. To interpret that, a brief difference to physiologic irritability is emphasized: Physiological irritability typically increases in the early weeks of life, peaks around 6–8 weeks of age, and generally improves by 3–4 months of age. In contrast, pathological irritability is characterized by excessive and relentless crying, which may lead to hypoxia and even epileptic seizures. This is a significant risk factor for abusive

head trauma (previously known as shaken baby syndrome) and may indicate intense pain [7]. Some infants also displayed additional manifestations such as rotatory nystagmus (6.07%) and leg clonus (5%). Consequently, newborns present clinical signs reminiscent of various central nervous system disorders, necessitating a thorough differential diagnosis. These events, documented in the neonatal period, are closely linked to cognitive and/or motor outcomes in childhood, often resulting in varying degrees of disability. The logistic regression analysis revealed a significant association between clinical symptoms and the child's age. Specifically, epileptic seizures ($p < 0.001$; RR = 5.118), impaired consciousness ($p = 0.006$; RR = 2.909), generalized movement disorders ($p = 0.004$; RR = 3.963), and apnea attacks ($p = 0.002$; RR = 2.861) were identified as the most significant suggestive symptoms for diagnosing ischemic strokes in newborns.

The clinical presentation of childhood stroke varies depending on factors such as age, developmental characteristics of the central nervous system, affected artery, and the underlying cause of the disease. To account for these variations, the clinical manifestations of IS were evaluated in 148 children aged between 28 days and 18 years. They were categorized according to the stages of child development: infants (28 days–1 year), young children (1–3 years), preschoolers (4 years–6 years), schoolchildren (7–12 years), and adolescents (13–18 years), with grouping based on similarities of IS clinical symptoms to those observed in adults (Figure 1).

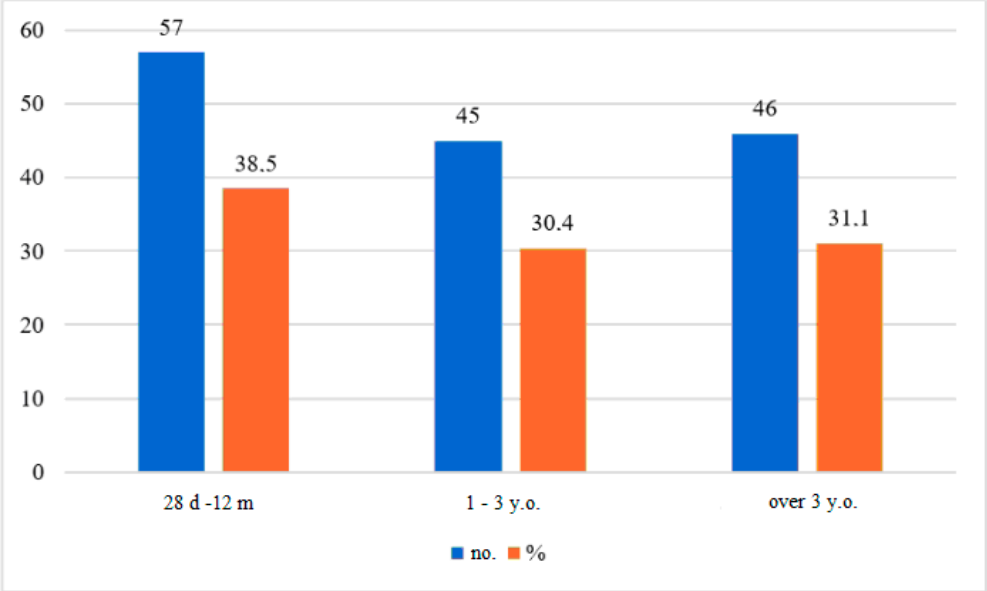

Figure 1. Age–related distribution of children with IS according to their age (abs., %).

1. Children aged between 28 days and 1 year old presented one-sided body weakness ($p < 0.001$; OR = 4.324), one-hand preferential use ($p = 0.004$; RR = 8.588), focal epileptic seizures ($p = 0.006$; RR = 3.377), and impaired consciousness ($p = 0.003$; RR = 1.143).
2. Children aged between 1 and 3 years old presented one-sided body weakness ($p = 0.003$; RR = 3.438), focal movement disorder ($p = 0.002$; RR = 1.178); focal epileptic seizures ($p < 0.001$; RR = 3.348), speech disorders ($p = 0.004$; RR = 4.163), psychomotor agitation ($p = 0.003$; RR = 1.114), and impaired consciousness ($p = 0.001$; RR = 1.043).
3. Children older than 3 years old presented hemiparesis ($p = 0.004$; RR = 1.153), headaches ($p = 0.001$; RR = 3.159), sensory disturbances ($p = 0.003$; RR = 3.156), psychomotor agitation ($p = 0.002$; RR = 2.341), and focal epileptic seizures ($p < 0.001$; RR = 4.365).

Following the analysis of ischemic stroke (IS) symptoms in children older than 28 days, it was found that the clinical presentation correlated with the children's early age. The symptoms of stroke in infants (28 days–1 year) are often described as subtle focal neuro-

logical deficits that may go unnoticed by parents and doctors, such as reduced one-sided body strength, preferential use of one hand, fist clenching or leg clonus, psychomotor agitation, mainly focal epileptic seizures, as well as respiratory and consciousness disorders in severe cases. The clinical symptoms in young children (from 1 to 3 years old) are characterized by slight focal neurological deficits such as hemiparesis, focal movement disorders, and one-sided body weakness. Motor deficits often manifest on one side of the body, more commonly on the right, followed by injury to the left cerebral hemisphere. Other predominant symptoms include focal epileptic seizures, impaired consciousness, psychomotor agitation, and less commonly, coordination disorders, tremor, nystagmus, impaired eyesight, and vomiting. Children over three years of age may present the following clinical manifestations: focal neurological deficit, commonly followed by hemiparesis, less often by hemiplegia, focal epileptic seizures, mental disorders, headaches, and agitation. Less common symptoms observed are ataxia, nystagmus, dizziness, hemianopia, and speech disorder.

Based on the child's age, disease onset, clinical symptoms, and imaging findings, neurological examination results suggested significant logistic regression outcomes. Moreover, the data analysis, modeling the relationship between a series of independent variables and a dichotomous dependent variable, identified the most important suggestive symptoms for diagnosing IS, depending on the child's age.

Therefore, mathematical calculations on clinical IS symptoms in children of different ages are crucial for confirming the disease and initiating early treatment. Table 2 illustrates the clinical manifestations of stroke according to age.

Table 2. Clinical manifestations of IS in newborns and children (Number of cases = 148), abs., %.

Clinical Symptoms	Abs.	P ES (%)	95% CI
Age: 28 days–1 year old (Number of cases = 57)			
Focal neurological deficits:	41	71.9	65.95–77.85
- One-sided body weakness;	15	36.6	29.08–44.12
- One hand preference;	11	26.8	19.88–33.72
- Fist clenching;	8	19.5	13.31–25.69
- Leg clonus.	7	17.1	11.22–22.98
- Epileptic seizures:	39	68.4	62.24–74.56
- Focal;	31	79.5	73.03–85.97
- Generalized.	8	20.5	14.03–26.97
Impaired consciousness	37	64.9	58.58–71.22
Psychomotor agitation	20	35.1	28.78–41.42
Respiratory disorders	18	31.6	25.44–37.76
Age: 1–3 years (Number of cases = 52)			
- Focal neurological deficits:	43	82.7	77.45–87.95
- Hemiparesis;	4	9.3	4.87–13.73
- Focal movement disorder;	15	34.9	27.63–42.14
- One-sided body weakness.	24	55.8	48.23–63.37
- Epileptic seizures:	34	65.4	58.8–72.0
- Focal;	27	79.4	72.47–86.33
- Generalized.	7	20.6	13.67–27.53

Table 2. *Cont.*

Clinical Symptoms	Abs.	P ES (%)	95% CI
Speech disorder	33	63.5	56.82–70.18
Psychomotor agitation	27	51.9	44.97–58.83
Impaired consciousness	25	48.1	41.17–55.03
Impaired coordination	17	32.3	26.19–39.21
Tremor	16	30.8	24.4–37.2
Nystagmus	11	21.2	15.54–26.86
Impaired eyesight	7	13.5	8.77–18.23
Respiratory disorder	6	11.5	7.07–15.93
Vomiting	4	7.7	4.0–11.4
Age: children older than 3 years (Number of cases = 39)			
Focal neurological deficit:	37	94.9	91.37–98.43
- Hemiplegia;	6	16.2	10.14–22.26
- Hemiparesis.	31	83.8	77.74–89.86
Headaches	25	64.1	56.42–71.78
Psychomotor agitation	20	51.3	43.3–59.3
Focal epileptic seizures	18	46.2	38.22–54.18
Impaired consciousness	16	41.0	33.12–48.88
Ataxia	11	28.2	20.99–35.41
Nystagmus	10	25.6	18.61–32.59
Vertigo	8	20.5	14.03–26.97
Full or partial hemianopia	7	17.9	11.75–24.05
Impaired speech (dysarthria, aphasia)	7	17.9	11.75–24.05

Further studies are required to confirm the diagnosis of stroke. Imaging findings, including brain CT scans, often do not reveal the presence of brain injury, largely depending on the timing of the examination. MRI scanning of the brain allows an assessment of the pathological focus topography and volume. During the study, it was observed that in newborns, the anterior cerebral artery and the middle cerebral artery were primarily affected, accounting for 228 cases (63.0%; 95% CI 60.46–65.54), along with the left cerebral hemisphere in 245 cases (67.7%; 95% CI 65.24–70.16). Multifocal brain injuries were identified in one-third of the children, totaling 119 cases (32.9%; 95% CI 30.43–35.37).

Throughout the study, a wide range of outcomes was observed among patients in the acute phase of the disease, reflecting varying degrees of severity from mild to severe symptoms, often resulting in severe neuro-psychomotor impairment (Table 3).

Of the 108 children examined, 82 (75.9%; 95% CI [71.79–80.01]) presented motor deficits, 45 (41.7%; 95% CI [36.96–46.44]) had convulsions, and 19 (17.6%; 95% CI [13.94–21.26]) experienced impaired consciousness. Additionally, among these children, 87 (80.6%; 95% CI [76.79–84.41]) had a unilateral stroke, and 77 (71.3%; 95% CI [66.95–75.65]) showed signs of middle cerebral artery injuries. The degree of neurological manifestations was assessed using the Amiel-Tison and Gosselin summary tables (classified as shown in Table 3) and the PedNIHSS scale. The mean value of the PedNIHSS scale was 7.8 points, with the scale ranging from 0 to 17 points. The statistical results of the calculated tests ($\chi^2 = 13.923$, df = 4, and $p < 0.01$) were significant. The majority of children with IS exhibited a mild to moderate IS severity, with 89 cases (82.4%; 95% CI [78.74–86.06]) falling within this range. The results obtained from the assessment of the Amiel-Tison, Gosselin, and PedNIHSS

scale confirmed the clinical neurological manifestations, enabling the recognition of mild and moderate forms of IS in most patients.

Table 3. The results of the Amiel-Tison and Gosselin assessments, based on the PedNIHSS scale in the acute period of stroke in children (abs., *p*, χ^2).

The Degree of IS Severity	IS Acute Period		
	Abs.	*P*, %	CI 95%
Mild severity	22	20.4	16.54–24.28
Mild-to-moderate severity	34	31.5	27.03–35.97
Moderate severity	33	30.6	26.17–35.03
Severe form	10	9.3	6.51–12.09
Extremely severe form	9	8.3	5.64–10.96

Children presenting with sudden onset of general neurologic symptoms should undergo an immediate neurological examination to identify the following neurological symptoms: focal neurological symptoms, seizures associated with neurological symptoms, visual or speech disorders, mental disorders, impaired coordination or ataxia, headaches, and signs of intracranial tension. Urgent neuroimaging studies are essential in such cases, as these symptoms have a high significance as predictors for IS. Regarding the imaging aspects of IS, in addition to cerebral hypodensities observed through CT examination in neonates, other cerebral changes were also identified. These included myelination deficiency (n = 11; 15.5%; 95% CI [11.21–19.79]), congenital dilatation of the ventricular system (n = 9; 12.7%; 95% CI [8.75–16.65]), cortical atrophy with various localizations (n = 7; 9.9%; 95% CI [6.36–13.44]), dilatation of the subarachnoid spaces (n = 6; 8.5%; 95% CI [5.2–11.8]), nonspecific glioependymal foci (n = 4; 5.6%; 95% CI [2.86–8.32]), intracerebral foci with subcortical extension (n = 5; 7.0%; 95% CI [3.96–10.04]), intracerebral cystic formations (n = 3; 4.2%; 95% CI [1.81–6.59]), and anomalies of brain development, among others (see Figure 2).

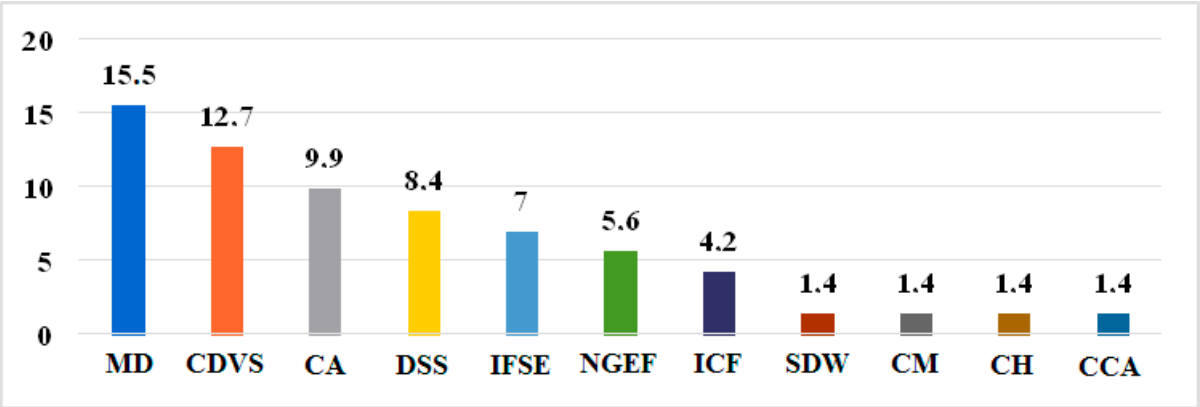

Figure 2. Changes detected in brain CT examination in newborns included in the study (excluding hypodensities), (%). Note. MD—myelination deficiency, CDVS—congenital dilatation of the ventricular system, CA—cortical atrophy, DSS—dilatation of subarachnoid spaces, IFSE—intracerebral foci with subcortical extension, NGEF—nonspecific glioependymal foci, ICF—intracerebral cystic formations, SDW—Sm Dandy–Walker, CM—congenital microcephaly, CH—congenital hydrocephalus, CCA—corpus callosum agenesis.

Next, the imaging changes detected during cerebral MRI examination are presented, depending on the size of the ischemic focus. In newborns, the initial imaging examination

was performed, in most cases, within the first week, during the onset of disease symptoms (Table 4).

Table 4. Changes detected in brain MRI examination during the acute period of IS in neonates (abs., %).

Imaging Changes	Acute IS			
	Abs.	P, %	ÎI 95%	
Acute millimeter ischemic lesions (0.5 × 1.0 cm)	4	5.6	2.86–8.34	χ^2 = 15.895; gl = 4
Small acute ischemic lesions (1.0 × 3.0 cm)	18	25.4	20.24–30.56	
Medium-sized ischemic lesions (3 × 5.0 cm)	37	52.1	46.17–58.03	
Large ischemic lesions (encephalomalacia or porencephaly)	8	11.3	7.55–15.05	
Large ischemic lesions with diffuse encephalomalacia and ischemic destructive-necrotic lesions	4	5.6	2.86–8.34	

The cerebral CT examination was not sufficient to establish the diagnosis, but it was helpful to clear concerns regarding the presence of a hemorrhagic stroke, tumor process, etc., and a brain MRI evaluation followed. This evaluation was performed in all 37 children (34.3%; 95% CI [29.73–38.87]) with suspected IS during the acute period of the disease. In all examined cases, ischemic lesions of various sizes were detected, characterized by a hypointense signal in T1 and a hyperintense signal in T2 (Table 5). Medium-sized ischemic lesions predominated in 46% of cases, while small or large lesions were observed in a smaller number of cases (24.3% and 29.7%, respectively).

Table 5. Changes detected during brain MRI examination during the acute period of IS in children aged 28 days–18 years (abs., %).

Imaging Changes	Acute IS			
	Abs.	P, %	ÎI 95%	
Acute millimeter ischemic lesions (0.5 × 1.0 cm)	1	2.7	0.03–5.37	χ^2 = 13.685; gl = 4
Small acute ischemic lesions (1.0 × 3.0 cm)	8	21.6	14.83–28.37	
Medium-sized ischemic lesions (3 × 5.0 cm)	17	46	37.71–54.09	
Large ischemic lesions (encephalomalacia or porencephaly)	7	18.9	12.46–25.34	
Large ischemic lesions with diffuse encephalomalacia and ischemic destructive-necrotic lesions	4	10.8	5.7–15.9	

The distribution of ischemic foci according to size in the total study group, within the prospective study, is depicted in Figure 3. It is observed that medium-sized ischemic lesions were the most frequent type detected, with a slight predominance in the infant group. However, large-sized foci prevailed in the group of children older than 28 days, particularly in infants and those of young age. This trend was influenced by the characteristic etiologies associated with these age groups, often determined by infectious causes.

In the cerebral MRI examination, in addition to the ischemic foci, other types of changes were also detected in some children, which possibly constituted a cause of IS or worsened the evolution of this disease. Among such changes were myelination deficiency (n = 19; 26.8%; 95% CI [21.55–32.05]), congenital dilatation of the ventricular system (n = 9; 12.7%; 95% CI [8.75–16.65]), cortical atrophy with various locations and degrees (n = 10; 14.1%; 95% CI [9.97–18.23]), dilatation of the subarachnoid spaces (n = 7; 9.9%;

95% CI [6.36–13.44]), nonspecific glioependymal foci (n = 6; 8.5%; 95% CI [5.2–11.8]), nonspecific intracerebral foci with subcortical extension (n = 5; 7.0%; 95% CI [3.96–10.04]), intracerebral cystic formations (n = 3; 4.2%; 95% CI [1.81–6.59]), etc. (Figure 4).

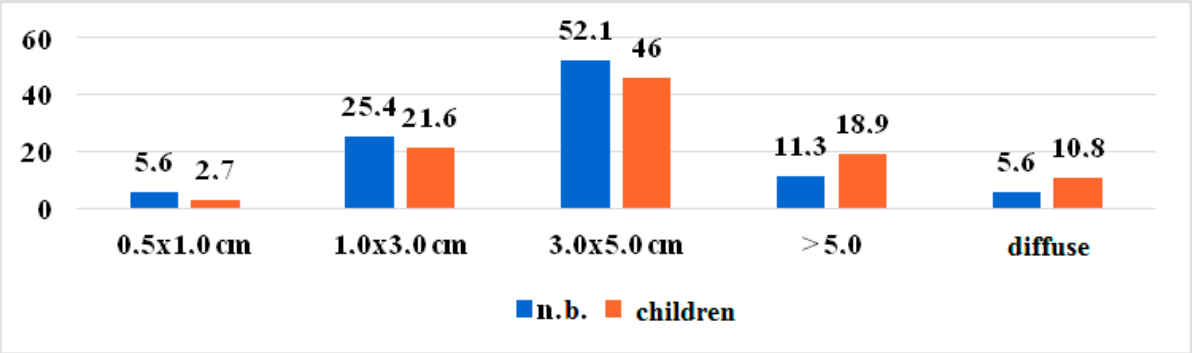

Figure 3. Distribution of ischemic lesions detected during cerebral MRI examination depending on the size of the focus in newborns and children (in absolute numbers and %). *Note.* N.b.—newborn, 0.5 × 1.0 cm—millimeter ischemic foci, 1.0 × 3.0 cm—small-sized ischemic foci, 3.0 × 5.0 cm—medium-sized ischemic foci, >5.0 cm—ischemic foci of large size, diffuse—large ischemic lesions with diffuse encephalomalacia and ischemic destructive-necrotic lesions.

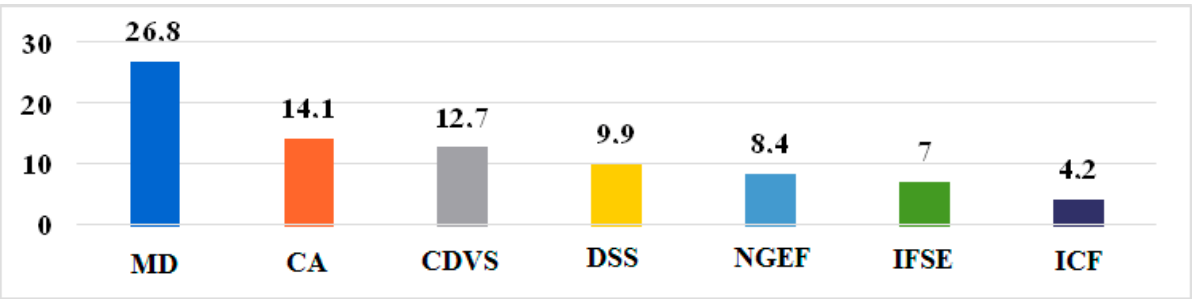

Figure 4. Other changes detected during cerebral MRI examination, associated with AVCI in newborns and children (in absolute numbers and %). *Note:* MD—myelination deficiency, CA—cortical atrophy, CDVS—congenital dilation of the ventricular system, DSS—dilation of the subarachnoid spaces, NGEF—nonspecific glioependymal foci, IFSE—intracerebral foci with nonspecific subcortical extension, ICF—intracerebral cystic formations.

Such changes, in some cases combined, were mainly detected in the group of infants and young children. In some children, besides ischemic foci, other types of changes were observed, which might have been present before the stroke or contributed to its onset. These included: myelination deficiency (n = 5; 13.5%; 95% CI [7.88–19.12]), ventricular system dilatation (n = 9; 24.3%; 95% CI [17.25–31.35]), cortical atrophy of varying degrees and locations (n = 6; 16.2%; 95% CI [10.14–22.26]), subarachnoid space dilatation (n = 5; 13.5%; 95% CI [7.88–19.12]), nonspecific glioependymal foci of various sizes (n = 7; 18.9%; 95% CI [12.46–25.34]), nonspecific intracerebral foci with subcortical extension (n = 2; 5.4%; 95% CI [1.68–9.12]), intracerebral cystic formations (n = 3; 8.1%; 95% CI [3.61–12.59]), and other anomalies of brain development (Figure 5). These changes, sometimes occurring together, were predominantly observed in infants and young children.

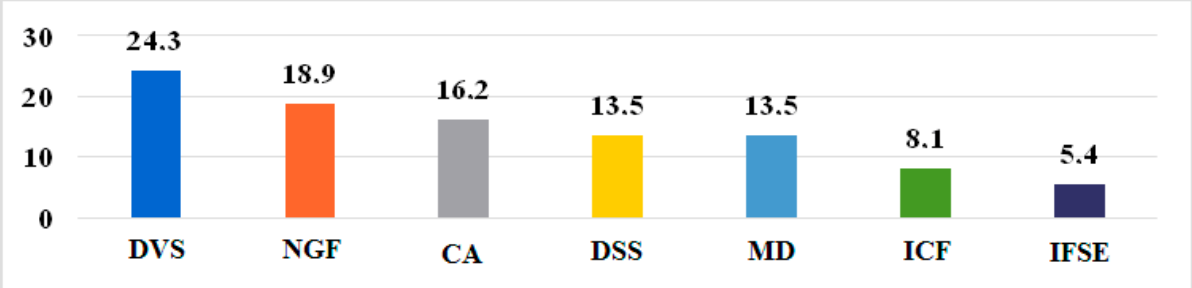

Figure 5. Other changes detected in cerebral MRI examination associated with IS in children aged 28 days to 18 years (%). *Note.* DVS—dilatation of the ventricular system, NGF—nonspecific glioependymal foci, CA—cortical atrophy, DSS—dilation of subarachnoid spaces, MD—myelination deficiency, ICF—intracerebral cystic formations, IFSE—intracerebral foci with nonspecific subcortical extension.

According to the results of MRI in children and newborns, the most frequent additional stroke-associated cerebral MRI changes in children were dilatation of the ventricular system and nonspecific glioependymal foci (Figure 6). Comparing with newborns, the results of MRI showed that the most common additional stroke-associated cerebral changes in newborns are represented by myelination deficiency, on first place and on the second place by the cortical atrophy (Figure 6).

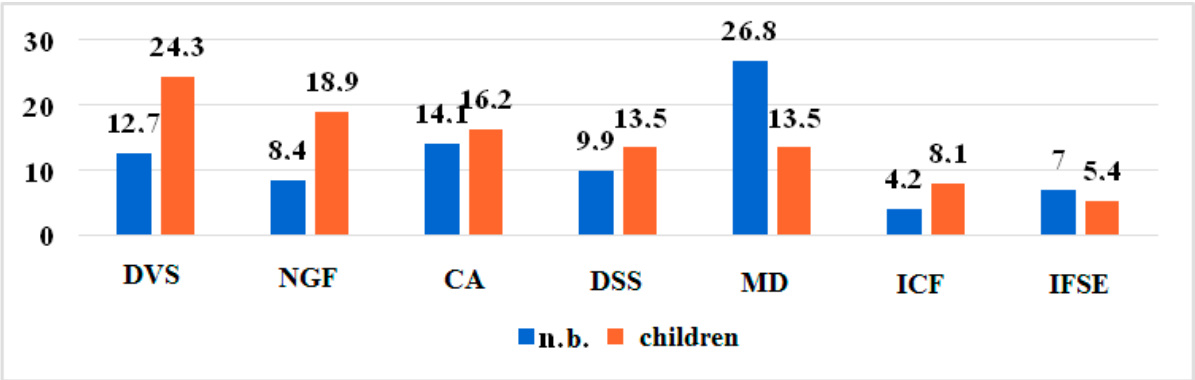

Figure 6. Comparison of the most commonly encountered additional stroke-associated cerebral MRI changes in newborns and children (%). Here, the results of the comparison of cerebral structural changes according to age are shown. *Note.* DVS—dilatation of the ventricular system, NGF—nonspecific glioependymal foci, CA—cortical atrophy, DSS—dilation of subarachnoid spaces, MD—myelination deficiency, ICF—intracerebral cystic formations, IFSE—intracerebral foci with nonspecific subcortical extension.

Below are some developmental anomalies of the brain found in children with IS, such as a developmental anomaly of the ventricular system (n = 3; 8.1%; 95% CI [3.61–12.59]), hypogenesis of the corpus callosum (n = 2; 5.4%; 95% CI [1.68–9.12]), hypogenesis of the cerebellar vermis, retrocerebellar cyst, Arnold Chiari malformation, and hypogenesis of the cerebellar hemispheres, each one case (2.7%; 95% CI [0.03–5.37]). Thus, brain developmental abnormalities detected in children with stroke were present in nine (n = 9; 24.3%; 95% CI [17.25–31.35]) cases (Figure 7).

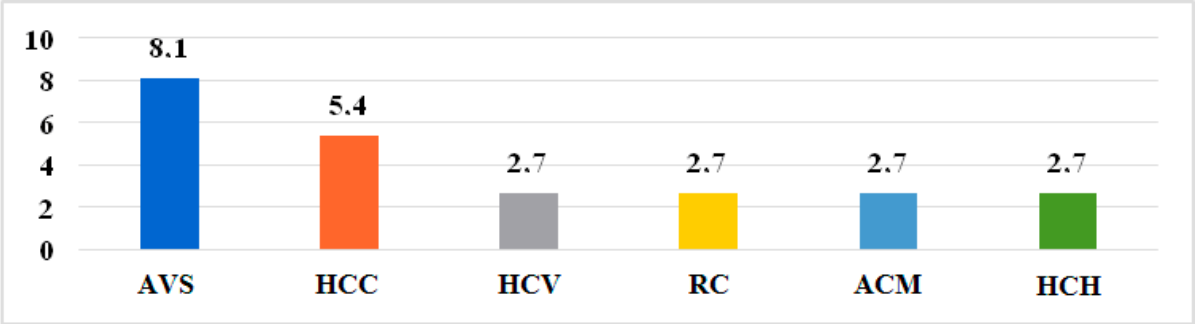

Figure 7. Developmental abnormalities of the brain in children with stroke (brain MRI examination %). *Note.* AVS—developmental abnormality of the ventricular system, HCC—hypogenesis of the corpus callosum, HCV—hypogenesis of the cerebellar vermis, RC—retrocerebellar cyst, ACM—Arnold Chiari malformation, HCH—hypogenesis of the cerebellar hemispheres.

Brain MRI results associated with the age of the child and the topographic location of the ischemic focus were analyzed (Figure 8).

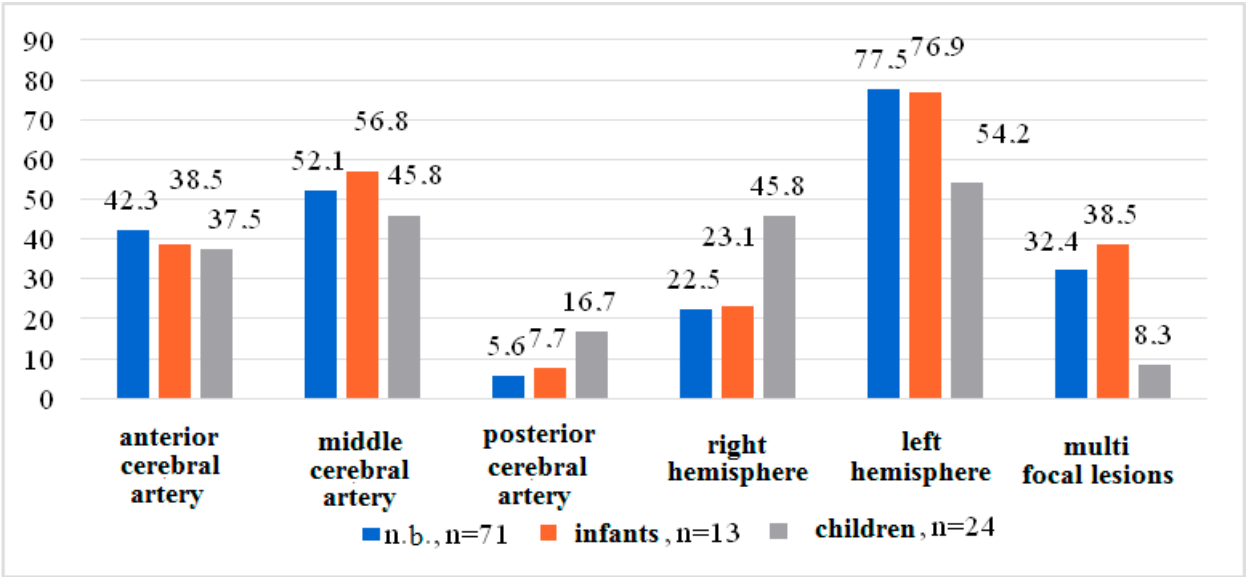

Figure 8. The results of the cerebral MRI examination regarding the location of the ischemic focus according to age and the involved artery in newborns and children with IS (%).

Brain MRI was performed in the acute period of the stroke and at six months after the disease in all children included in the prospective study group. In contrast to CT, MRI images were much more informative and allowed for the assessment of the dimensions of the pathological focus at a distance compared to the acute period of the disease. It was found that the ischemic changes in the brain tissue detected during the acute period evolved into gliotic foci or cysts of various sizes, with a statistically significant difference being attested in that case (Table 6).

Evolution towards normality was found only in the case of very small ischemic foci (3.7%). Additionally, a slight reduction in medium-sized ischemic foci was observed in 17 (31.5%) cases, possibly due to tissue recovery from the ischemic penumbra. Large lesions underwent cystic transformation. Angio-CT and angio-MRI were applied in exceptional cases to eight children with suspected vascular malformations (Figure 9).

Table 6. Evolution of the sizes of the ischemic foci detected by MRI in the acute period and six months after IS (abs., %).

Ischemic Foci	Acute Period			6 Months Apart		
	Abs.	P, %	ÎI 95%	Abs.	P, %	CI 95%
Norm	-	-	-	4	3.7	1.88–5.52
0.5 × 1.0 cm	5	4.6	2.58–6.62	13	12.0	8.87–15.13
1.0 × 3.0 cm	26	24.1	19.99–28.21	31	28.7	24.35–33.05
3.0 × 5.0 cm	54	50.0	45.19–54.81	37	34.3	29.73–38.87
Porencephaly or encephalomalacia	15	13.9	10.57–17.23	15	13.9	10.57–17.23
Diffuse encephalomalacia	8	7.4	4.88–9.92	8	7.4	4.88–9.92

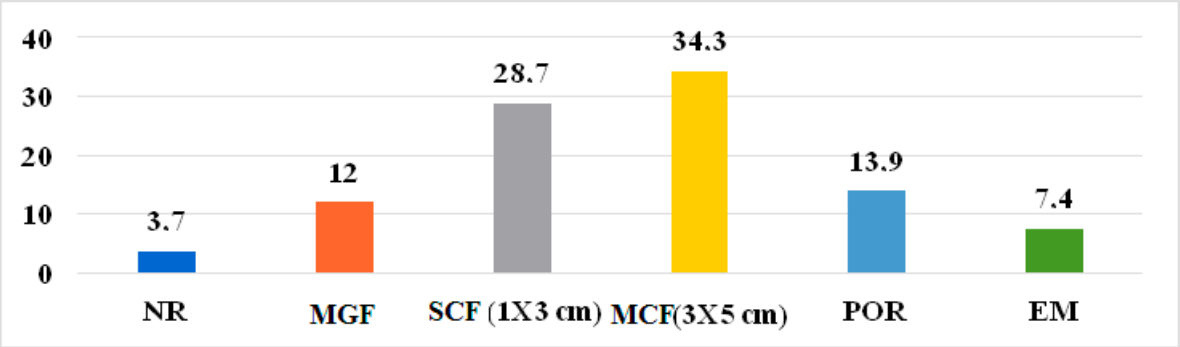

Figure 9. Percentage rate of the evolution of the sizes of the ischemic foci on MRI six months after IS (%). *Note.* NR—norm, MGF—millimeter gliotic foci (0.5 × 1.0 cm), SCF (1 × 3 cm)—small cystic formations (1.0 × 3.0 cm), MCF (3 × 5 cm)—cystic formations of medium size (3.0 × 5.0 cm), POR—porencephalic cysts larger than 5.0 cm, EM—encephalomalacia with bilateral cystic transformation.

5. Discussion

IS in children is specified as a major neurological emergency, being a primary cause of morbidity and mortality. In the neonatal period, one in 2500–4000 live-born children presents with a stroke, and in children over one month old, 1.2–8 per 100,000 [7]. The data of the given study showed the following distribution: A 24.5% decrease in the primary disability indicator was observed in 2020 (2.1 cases per 100,000 children) compared to 2016 (2.8/100,000). The highest values were recorded in 2017 and 2018 (3.7/100,000), and the trends for the repeated disability indicator were similar. Cases certified in 2020 (11.6/100,000 children) were 23.9% less than in 2016 (15.3/100,000), with the highest level recorded in 2017 (16.9/100,000).

Clinical manifestations of IS in children, unlike those in adults, are varied depending on age, and are often obscure, with a variable clinical polymorphism. Also, IS can occur during pregnancy or immediately after birth, without significant symptoms. The mortality rate from pediatric stroke is between 5% and 10%. More than half of survivors have long-term neurological sequelae, and 10–20% suffer from stroke recurrences [7,9]. These arguments condition the creation of emergency care and rehabilitation centers for pediatric stroke patients, a multidisciplinary approach, highly specialized evaluation and treatment, with significant input from the health care system, families, and the community.

According to the WHO classification, stroke can be of several types: transient stroke (TS), which represents ischemia in a localized area of the brain, with motor deficit up to 24 h (from a few minutes to a few hours), without neurological sequelae; involutive stroke, characterized by acute cerebral ischemia with motor deficit for more than 24 h, with its complete involution for 21 days; lacunar stroke—a type of stroke in which blood flow is blocked in a group of very small arteries inside the brain, mainly those that supply blood to

deep areas of the brain. In these types of infarctions, cerebral ischemic lesions range from 2 to 20 mm in diameter; IS in evolution is characterized by a slow-progressive evolution, from a few hours to a few days. Clinical symptoms persist for more than three weeks and motor deficit evolves/regresses in about 30 days. In progressive evolution, it can evolve towards established IS—this is a consequence of the neuronal destruction in the damaged vascular territory, which will manifest itself clinically with an installed motor deficit [10]. Each type of stroke requires its specific approach to diagnostics and treatment. For that reason, the study design of this research work included only one type of stroke, ischemic stroke.

According to several researchers [11] ischemic stroke is defined when a focal neurological deficit occurs that lasts more than 24 h, with neuroimaging evidence of cerebral infarction. In the case of a neurological deficit that recovers before 24 h and there are no neuroradiological changes, the event is called a transient ischemic attack. If the clinical manifestations last less than 24 h, but there are neuroradiological signs of infarction, it is considered an IS [11]. According to the authors G. Jeong et al., stroke in children is defined as a sudden focal infarction of brain tissue, diagnosed by neuroimaging or at autopsy, which may lead to arterial stroke or venous infarction. An IS occurs when there is a sudden occlusion of one or more cerebral arteries. In children, arterial ischemic stroke is the most common subtype, accounting for just over half of all cerebrovascular accidents [12]. Some authors mention in their papers [13] that IS in children can present with subtle symptoms, especially among newborns and small children. According to researchers, the clinical manifestations and risk factors of IS in children are different from those of adults; therefore, the disease can be considered an independent nosological entity [13,14]. To address the issue of uncertain clinical symptoms of IS in children and newborns, a significant aspect of the study involved evaluating the clinical signs of IS in that population. Consequently, all signs exhibited by patients were considered potential diagnostic and prognostic features and were statistically analyzed. The most relevant signs, which demonstrated a significant association with IS, were then incorporated into the algorithms. The following standardized measures served as the basis for characterizing all clinical signs assessed in the study. Stroke symptoms in early childhood are usually nonspecific, and in older children, they often manifest as focal neurological deficits, such as acute hemiplegia. The neurological examination should highlight the most subtle symptoms suggestive of a stroke, including monitoring of vital parameters, identifying neurological damage and suggesting the presumptive diagnosis and brain topography involved. As a rule, some systemic diseases that increase the risk of stroke must be excluded. The suggestive symptoms for damage to a cerebral vascular territory are the following: (1) internal carotid artery—hemiparesis, aphasia, and hemianopsia; (2) anterior cerebral artery—hemiparesis, especially in the lower limbs; (3) middle cerebral artery—hemiparesis of the upper limbs, hemianopsia, and aphasia; (4) posterior cerebral artery—hemiparesis, hemianopsia, ataxia, and dizziness; (5) basilar artery—difficulty breathing, sensory or balance disturbances, ataxia, nystagmus, opisthotonus, tremors, and vomiting; (6) cerebellar artery—sensory deficit, headache, fever, vomiting, and cerebellar signs [6]. The clinical manifestation of IS in children varies depending on the age, the involved artery and the cause [3]. Focal symptoms, especially hemiplegia, are most frequently present in hemorrhagic stroke and vary according to different authors. The clinical presentation of IS is diverse, and common IS symptoms such as altered consciousness, convulsions, etc., may be encountered. The diagnosis of pediatric ischemic stroke is based on the recognition of clinical manifestations depending on the age and the cerebral vascular system involved.

The statistical analysis in this study revealed distinct clinical symptom patterns as the most relevant for IS in children of different age groups:

1. Children aged between 28 days and 1 year old presented one-sided body weakness, one-hand preferential use, focal epileptic seizures, and impaired consciousness. These symptoms were significant indicators of ischemic stroke in that age group.

2. Children aged between 1 and 3 years old exhibited one-sided body weakness, focal movement disorder, focal epileptic seizures, speech disorders, psychomotor agitation, and impaired consciousness. These symptoms were more pronounced compared to infants, indicating a clearer clinical picture.
3. Children older than 3 years old demonstrated hemiparesis, headaches, sensory disturbances, psychomotor agitation, and focal epileptic seizures. These symptoms were more akin to those observed in adults, highlighting a closer resemblance in clinical presentation.

The most common disabilities found in children older than 3 years, who had suffered a stroke were motor disability—74.9%, including hemiparesis—63.7%, tetraparesis—25.8%, tetraplegia—10.4%, epilepsy—28%, disorders of speech—17.8%, cognitive and behavioral problems—53.9%.

IS represents a clinical syndrome with rapid evolution, manifested by the global or focal disturbance of cerebral function, lasting more than 24 h or leading to death without any obvious nonvascular reason [7]. The importance of developing algorithms to reduce decision-making time is obvious. A clear correlation between the clinical and imaging aspects of ischemic stroke is evident, as it is a clinical syndrome characterized by a neurological deficit related to the perfusion territory of a cerebral artery and neuroradiological evidence of an ischemic lesion" [7]. For that obvious reason, in the recently developed algorithms, the paraclinical signs were also included. The diagnosis of IS in children is often delayed because signs and symptoms can be subtle and nonspecific, and thus treatment is often delayed and limited.

Several authors mention that even the definitive causes in the majority of pediatric, especially neonatal, strokes have not been established, and large case–control studies are needed to understand the early clinical manifestations and pathogenesis if treatment outcomes are to be improved [6]. The authors DeLaroche A.M. and Sivaswamy L. consider that IS in children are some of the most frequent complications of hypoxia and ischemia in the first week of life [2]. Lee J et al. describe how those complications following perinatal stroke vary according to the type of accident and that some children may have a normal neurological outcome, while others develop cerebral palsy (CP) (58%), language (25%), and behavioral disorders (22%). In other cases, motor symptoms can be observed later after birth [14]. The authors of another study consider that in children, unlike young children or adolescents, there are no clinical signs suggestive of a presumptive diagnosis of arterial IS, and the recognition of the condition is based on imaging data [3]. Authors Lai M.C. and Yan S.N. found that among children with perinatal stroke, the specific radiological findings and the lack of symptoms in newborns were associated with a high risk of CP [15], especially the hemiparetic forms. Taking into consideration the above-mentioned problem of unspecific imaging signs, a delayed or lack of indication for imaging lengthens the diagnostic and treatment time. Thus, the important applicative value of this study is that some clinical and paraclinical signs that were not previously considered pathognomonic for ischemic stroke in newborns and children have now been included in the new algorithms of national protocols as direct and urgent signs for MRI and CT and for appropriate treatment. In the past, these signs were not indications for CT and MRI, leading to delayed diagnosis and treatment, resulting in long-lasting complications and consequences in children. According to the study, only CT and MRI can confirm the diagnosis of stroke, so it is crucial to recognize these signs for timely intervention. These new paraclinical signs, included in the algorithm, belong to the clinical presentation of ischemic stroke (IS) in children and vary depending on their age. Younger children tend to have more subtle and nonspecific symptoms, which are often initially attributed to other causes. This can lead to a delay in diagnosing IS and result in further complications. The study results suggest that imaging should be considered for all children, even those with minimal suspicion of IS. In fact, in all cases where there was minimal suspicion of stroke, IS was diagnosed using CT and MRI. Identifying the minimal but relevant clinical signs for IS based on the age of the children can serve as the right indications for CT and MRI. The mathematical analysis yielded the following results:

(1) newborns: epileptic seizures, disturbance of consciousness, generalized motor disorders, and apnea attacks; (2) infants: decreased strength in one half of the body, preferential use of one hand, focal epileptic seizures, and impaired consciousness; (3) young children: decreased strength in one side of the body, focal movement impairment, focal epileptic seizures, speech disorder, and disorder of consciousness; (4) children older than three years: weakness on one side of the body, headache, sensory disturbances, and psychomotor agitation, and focal epileptic seizures.

IS in both the middle cerebral artery system and the posterior cerebral artery system may manifest as seizures of one half of the body, whereas stroke in the middle cerebral artery system may manifest as seizures of the hand and face only. Seizures isolated to one leg can be found in neonatal IS with localization in the anterior cerebral artery system, and those isolated to the upper extremities are characteristic of the involvement of the posterior part of the middle cerebral artery. Authors Gelfand A.A. and Glass H.C. mention that in cases of an involvement of the middle cerebral artery, atypical convulsions are observed (hiccupping, eye blinking, gaze fixation, chewing, sucking, vertical nystagmus, and thumb adduction) [16], such convulsions being rarely isolated. Apnea attacks or cyanotic attacks, probably of an epileptic nature, have been reported. Strokes, regardless of age of onset, can be hemorrhagic (subarachnoid or intraparenchymal) or ischemic. The type of stroke varies depending on the age of the patient and the etiology, which is different in the child than in the adult. More than 70 potential risk factors for stroke in children and adults are described. Often, however, ischemia is the result of nonatherosclerotic vasculopathy, cardiac embolisms, or coagulability disorders. In children, stroke can occur as a result of congenital heart diseases, acquired heart diseases, infectious or inflammatory diseases, vascular disorders, hematological diseases, cerebrovascular malformations, or brain trauma; however, for a third of strokes, the etiology remains undetermined [17,18].

The incidence of ischemic stroke (IS) in children is increasing due to the advancement of imaging techniques for diagnosing the disease. Imaging studies help in identifying the type and location of IS, as well as in making a differential diagnosis. According to the data from a specific study, medium-sized ischemic areas are more common in neonates (52.1%) compared to pediatric patients (46%), while larger areas are predominant in the pediatric group (29.7%), especially in infants and young children. The middle cerebral artery (51.0%) and the anterior cerebral artery (40.7%) are the main arteries involved in the ischemic process across all age groups, with a higher prevalence in neonates and infants. The posterior cerebral artery (8.3%) is more frequently involved in older children (16.7%). The left hemisphere is more commonly affected (72.2%) compared to the right (27.8%), and a diffuse distribution of the pathological focus was found in 27.8% of cases, with a higher prevalence in infants (38.5%) and newborns (32.4%). These findings align with existing literature data. The study's strength lies in its correlation of clinical signs relevant to IS prognosis with paraclinical results. Strong correlations were found between imaging and clinical data (rxy = 0.983), which facilitated the development of a clinical-etiological classification of IS in children based on age. This formed the basis for the algorithm development and its inclusion in protocols. These newly developed algorithms led to the standardization of imaging protocols in pediatric centers for stroke patients. An international study of clinical and imaging analyses of symptomatic IS summarized various clinical presentations, risk factors, types of investigations, treatments, and early outcomes in IS. The most important clinical symptoms reported were seizures (72%) and nonfocal neurological signs (63%) [19]. However, some studies mention that about 40% of children do not show specific symptoms in the neonatal period; they are recognized later, with the appearance of motor disorders, developmental delays, cognitive impairment, or seizures [20]. Notably, pediatric IS (PIS) leads to significant morbidity and mortality. Of all cases, approximately 10–25% will be fatal, up to 25% of patients will have a recurrence, and up to 66% will have persistent neurological deficits or develop epilepsy, learning problems, or developmental problems. Up to one-third of children who have had a stroke have a history of recent events compatible with transient stroke. Neurological impairment

during childhood will have a major impact on the quality of life of the child and the family, but also on the economic and emotional costs of society [21]. Early recognition of PIS requires emergency neurological consultation and hospitalization to provide coherent etiological/pathogenetic diagnostic and treatment management and improve outcomes.

The diagnosis of PIS is based on the recognition of symptoms according to age and the vessel involved. Signs of stroke in early childhood are usually nonspecific, and in older children, focal neurological deficits are often noted, such as acute hemiplegia. The neurological examination should highlight the most subtle symptoms of a possible stroke, including monitoring of vital parameters, identifying neurological damage, and assuming the presumptive diagnosis and topography of the involved vessel. As a rule, some systemic diseases that increase the risk of IS must be excluded. Neuroimaging is crucial in defining the diagnosis, other tests being necessary depending on the clinical picture. Thus, PIS is better recognized among practitioners as a clinically significant entity [22]. It is known that the diagnosis of stroke in children can often be delayed, and sometimes missed due to mild and nonspecific clinical symptoms and since they are initially related to other causes than stroke. The suggestive stroke symptoms characteristic of a certain age category may improve diagnosis in 66–99.7% of cases [23] if using the mathematical calculations proposed for the prevalence of certain symptoms of the disease. In this context, the results of the study reveal that children with sudden onset of the following clinical symptoms are at high risk of developing IS: focal neurological symptoms, seizures, accompanied by neurological symptoms, visual or speech disorders, mental disorders, impaired coordination or ataxia, headaches, and signs of intracranial tension. For that reason, these clinical signs have to be regarded as predictors of IS, and the patients should undergo an immediate neurological examination for the detection of IS. At the same time, urgent neuroimaging studies are required. Children with suspected ischemic stroke should undergo MRI, as a method of early diagnosis. If an urgent MRI examination is not possible, a brain CT scan should be considered as an alternative, especially in adolescents [24]. Brain MRI or brain CT scanning should be performed in children with suspected hemorrhagic stroke [25]. Based on the symptoms that had a significant relationship with the following stroke event, the data-driven statistical analysis makes it possible for the first time to establish algorithms that enable a clinical plan for fast, time-saving recognition of the stroke diagnosis; thus, it allows the choice of the best, time-dependent treatment options of stroke events in newborns and children of different age groups. Logistic regression was used to derive the algorithms for decision-making regarding stroke diagnosis and its early treatment, to decrease life-long morbidity and mortality of children. Based on the results of this study, algorithms for timely newborn stroke recognition were elaborated. Furthermore, it is planned that to adopt these newly elaborated algorithms and train a fuzzy classifier-based diagnostic model using these algorithms for developing machine learning algorithms for decision-making regarding prompt, time-saving stroke recognition. This is an important step towards a new generation of algorithm formation based on machine learning techniques [18]. The advantage of such an approach to diagnosis and prediction, especially in neurology, when a time-dependent recognition of trigger symptoms is critical, is described in the literature [14–17,23,24]. In the study conducted by Shkilniak L. et al., relevant results in prognostic modeling in pathological conditions regarding edema of soft tissue with the implementation of vessels and blood clotting abnormalities, realized via a fuzzy classifier, were shown [26]. From the literature data, it can be assumed that the fuzzy classifier is an appropriate method for the future conversion of the developed algorithms into automatized algorithms. The basics for its realization will be implemented based on the fundamental principles of neural network circuits, regarding their potential possibilities for application in biosciences and medicine [27]. It is known that machine learning algorithms have to be trained with high-quality data [18]. The clinical algorithms developed in this study for valid, timely IS detection are therefore promising results for further training the fuzzy classifier with this validated and high-quality data, which is planned as the next step of the study.

Clinical impact of the developed algorithms

In the current research, the solved scientific problem consists in the elucidation of the evolutionary clinical–paraclinical peculiarities of IS in children, which will improve the early diagnosis of the disease and the prophylaxis of neurological disorders in the future. The diagnosis and treatment of strokes can be optimized by applying the diagnostic and therapeutic algorithms elaborated in this study. They involve a combination of clinical, neuroimaging, neurofunctional assessment methods, and laboratory tests. Implementing these algorithms in clinical settings will help recognize and prevent childhood strokes, reduce treatment delays for ischemic stroke, and provide real-time decision support. These algorithms include clinical and paraclinical signs that were not previously considered for stroke diagnosis but are now included in newly developed national protocols as pathognomonic signs. They are now considered urgent signs for MRI and CT to facilitate real-time decision support. Analyzing the risk factors for ischemic stroke has also allowed for the development of an algorithm to identify and manage newborns and children at risk for this disease, along with recommendations for its prevention in children.

The generalizability of the results to various populations and healthcare settings

The study involved evaluating children and newborns from across the country based on specific criteria and signs that were identified in advance as potential predictors and diagnostic signs of ischemic stroke. The findings of the study can be applied to the general population of Moldova, particularly to children and newborns with ischemic stroke. Additionally, these findings can be useful in various healthcare settings, as three distinct algorithms have been developed for specialized medical care, preclinical medical assistance, and management of relatives' behavior.

Future outlook

Furthermore, the developed algorithms will also be included in training machine learning algorithms, as it was shown in a series of studies that the training of machine learning algorithms using neuroimaging findings with a certain aim revealed promising results [15–17,28].

The presented algorithms will allow specialists in the field to timely diagnose stroke in children and to correctly apply their diagnostic and treatment methods. Therefore, a logistic regression was applied to recognize which symptoms were related to the triggering and prediction of stroke. Further machine learning methods will have to prove how well these correlations work in automatic algorithms. However, this study is an important tool to develop further machine learning tools for clinical and paraclinical symptom-based recognition and prediction of IS.

The need for external validation is important, however, to obtain additional data, and it must be carried out in future studies.

Similar studies are also required for children with hemorrhagic stroke; thus, in the future, we will also investigate the relevant diagnostic and predictive signs for timely hemorrhagic stroke recognition.

The results of the study convinced the Medical Society of the Republic of Moldova of the importance of early diagnosis of IS not only in adults but also in children. Until recently it was considered that IS was only a condition in adults; we demonstrated through concrete studies that the number of children with IS in the Republic of Moldova was high, and these studies can also be replicated in other countries of the world. It may be necessary to join some international IS research studies.

Limitations of the study and potential bias

Parents provided information about the clinical and anamnestic data because newborns and children were unable to express verbally their symptoms and the circumstances when the signs appeared. We were reliant on the reports of the relatives, which may lead to some missing data and paraclinical information. The retrospective analysis may also be biased due to the quality of the data collection from the parents being reflected in the documentation, which depended on the subjective human factor. Another limitation is that the study design only focused on newborns and children with ischemic stroke, not hemorrhagic stroke, so the study results are limited to ischemic stroke. Therefore, any

conclusions about the broader population should be limited to what can be supported by the sample studied.

6. Conclusions

The present study revealed the challenges in differentiating the conditions that characterize a perinatal stroke in newborns and children, as well as in providing a clinical picture of this disease, since a stroke in children differs from age to age, whereas the clinical manifestations are related to the age-specific developmental features of the nervous system, the artery involved, and the causes of the disease onset. In the acute period of the disease, patients had a wide range of clinical symptoms of IS, reflecting the patient's condition, from mild symptoms to severe forms of neuropsychomotor disorders, with predominantly mild or moderate forms in most patients—89 (82.4%) cases. The PedNIHSS clinical score summary was used to evaluate correlations with other variables. The presence of nonspecific and variable neurological symptoms requires the investigation of all acute onset cases in children, especially in young children, to exclude any suspected stroke, and additional imaging investigations should be carried out as soon as possible to confirm this diagnosis. The study enabled the elucidation of epidemiological peculiarities and stratification of clinical–paraclinical manifestations of ischemic stroke in children of different ages, as well as the determination of predictive clinical and paraclinical signs for this disease in newborns and children, and served as the basis for the development of prognostic algorithms for IS in newborns and children. These diagnostic algorithms will facilitate the correct approach of specialists in the field, which will contribute to the early diagnosis of stroke in children and newborns. Furthermore, it is planned to adopt the newly elaborated algorithms and train a fuzzy classifier-based diagnostic model using these algorithms for developing machine learning algorithms for decision-making regarding prompt, time-saving stroke recognition.

Author Contributions: Conceptualization, M.S. and S.H.; methodology, N.W.; software, validation, S.H.; formal analysis, L.S.; investigation, M.S. and S.H.; resources, N.W. and L.S.; writing—original draft preparation, M.S.; writing—review and editing, M.S. and S.H.; visualization, L.S. and M.S.; supervision, N.W.; project administration, N.R. All authors have read and agreed to the published version of the manuscript.

Funding: The research was founded by [17.000418.80.07A] the project "Evaluation of incidence, prevalence, risk factors, research of clinical, neuroimaging, neurophysiological, and neurotrophic remedial aspects of cerebrovascular accidents in children" within the state program "Systemogenesis of risk factors, optimization of the medical assistance service, evaluation sustainable and mathematical modeling of Stroke".

Data Availability Statement: http://www.cnaa.md/files/theses/2022/58352/mariana_sprincean_thesis.pdf (accessed on 8 April 2024).

Conflicts of Interest: The authors declare no conflicts of interest regarding this article. The authors declare that all the procedures and experiments of this study respected the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law.

List of Abbreviations

Public Health Medical Institution—PHMI, cavernous sinus thrombosis—CVST, ischemic stroke—IS, Pediatric NIH Stroke Scale—PedNIHSS, computerized tomography—CT, magnetic resonance imaging—MRI.

References

1. Guiraut, C.; Cauchon, N.; Lepage, M.; Sébire, G. Perinatal Arterial Ischemic Stroke Is Associated to Materno-Fetal Immune Activation and Intracranial Arteritis. *Int. J. Mol. Sci.* **2016**, *17*, 1980. [CrossRef]
2. DeLaroche, A.M.; Sivaswamy, L.; Farooqi, A.; Kannikeswaran, N. Pediatric Stroke Clinical Pathway Improves the Time to Diagnosis in an Emergency Department. *Pediatr. Neurol.* **2016**, *65*, 39–44. [CrossRef] [PubMed]

3. Murray, K.N.; Girard, S.; Holmes, W.M.; Parkes, L.M.; Williams, S.R.; Parry-Jones, A.R.; Allan, S.M. Systemic inflammation impairs tissue reperfusion through endothelin-dependent mechanisms in cerebral ischemia. *Stroke* **2014**, *45*, 3412–3419. [CrossRef] [PubMed]
4. Sprincean, M.; Hadjiu, S.; Calcii, C.; Lupusor, N.; Crivceanscaia, E.; Groppa, S.; Revenco, N. Dynamics of some enzyme immunoassay parameters in ischemic stroke in children. *Arch. Balk. Med. Union* **2020**, *55*, 548–563. [CrossRef]
5. Ruksakulpiwat, S.; Thongking, W.; Zhou, W.; Benjasirisan, C.; Phianhasin, L.; Schiltz, N.K.; Brahmbhatt, S. Machine learning-based patient classification system for adults with stroke: A systematic review. *Chronic Illn.* **2023**, *19*, 26–39. [CrossRef] [PubMed]
6. Sarker, I.H. Machine Learning: Algorithms, Real-World Applications and Research Directions. *SN Comput. Sci.* **2021**, *2*, 160. [CrossRef] [PubMed]
7. Elbers, J.; Wainwright, M.S.; Amlie-Lefond, C. The Pediatric Stroke Code: Early Management of the Child with Stroke. *J. Pediatr.* **2015**, *167*, 19–24.e4. [CrossRef] [PubMed]
8. Sfaihi, L.; Elloumi, S.; Fourati, H.; Kamoun, T.; Mnif, Z.; Hachicha, M. Arterial ischemic stroke in children: 22 cases from southern Tunisia. *Fetal Pediatr. Pathol.* **2013**, *32*, 271–275. [CrossRef] [PubMed]
9. Stacey, A.; Toolis, C.; Ganesan, V. Rates and Risk Factors for Arterial Ischemic Stroke Recurrence in Children. *Stroke* **2018**, *49*, 842–847. [CrossRef]
10. *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modifications (ICD-10-AM)*, Australian Classification of Health Interventions (ACHI). 1 July 2010.
11. Mallick, A.A.; Ganesan, V.; Kirkham, F.J.; Fallon, P.; Hedderly, T.; McShane, T.; Parker, A.P.; Wassmer, E.; Wraige, E.; Amin, S.; et al. Childhood arterial ischaemic stroke incidence, presenting features, and risk factors: A prospective population-based study. *Lancet Neurol.* **2014**, *13*, 35–43. [CrossRef]
12. Jeong, G.; Limb, C.; Chae, J.H. Pediatric Stroke. *J. Korean Neurosurg. Soc.* **2015**, *57*, 396–400. [CrossRef]
13. Rosa, M.; De Lucia, S.; Rinaldi, V.E.; Le Gal, J.; Desmarest, M.; Veropalumbo, C.; Romanello, S.; Titomanlio, L. Pediatric arterial ischemic stroke: Acute management, recent advances and remaining issues. *Talian J. Pediatr.* **2015**, *41*, 95. [CrossRef] [PubMed]
14. Lee, J.; Croen, L.A.; Lindan, C.; Nash, K.B.; Yoshida, C.K.; Ferriero, D.M.; Barkovich, A.J.; Wu, Y.W. Predictors of outcome in perinatal arterial stroke: A population-based study. *Ann. Neurol.* **2005**, *58*, 303–308. [CrossRef] [PubMed]
15. Lai, M.C.; Van, S.N. Perinatal Hypoxic-Ischemic Encephalopathy. *J. Biomed. Biotechnol.* **2011**, *8*, 103–120. [CrossRef] [PubMed]
16. Gelfand, A.A.; Glass, H.C.; Elysa, J.; Ferriero, D.M. Focal clonic seizures suggest stroke in a newborn. *Neurosci. Bull.* **2010**, *2*, 7–11.
17. Revenco, N.; Hadjiu, S.; Crivceanscaia, L.; Calcii, C.; Sprincean, M.; Lupusor, N. *Stroke in Children: National Clinical Protocol (I Edition) PCN-404*; Chisinau, Moldova, 2022; 83p.
18. Tuckuviene, R.; Christensen, A.; Helgestad, J.; Johnsen, S.; Kristensen, S. Paediatric arterial ischaemic stroke and cerebral sinovenous thrombosis in Denmark 1994–2006: A nationwide population-based study. *Acta Paediatr.* **2011**, *100*, 543–549. [CrossRef] [PubMed]
19. Pezzini, A.; Grassi, M.; Del Zotto, E.; Lodigiani, C.; Ferrazzi, P.; Spalloni, A.; Patella, R.; Giossi, A.; Volonghi, I.; Iacoviello, L.; et al. Common genetic markers and prediction of recurrent events after ischemic stroke in young adults. *Neurology* **2009**, *73*, 717–723. [CrossRef] [PubMed]
20. Li, M.; Guo, R.; Zhang, K.; Lin, Z.; Yang, F.; Xu, S.; Chen, X.; Massa, A.; Abubakar, A. Machine Learning in Electromagnetics With Applications to Biomedical Imaging: A Review. *IEEE Antennas Propag. Mag.* **2021**, *63*, 39–51. [CrossRef]
21. Brankovic, A.; Zamani, A.; Trakic, A.; Bialkowski, K.; Mohammed, B.; Cook, D.; Walsham, J.; Abbosh, A.M. Unsupervised Algorithm for Brain Anomalies Localization in Electromagnetic Imaging. *IEEE Trans. Comput. Imaging* **2020**, *6*, 1595–1606. [CrossRef]
22. Mariano, V.; Vasquez, J.A.T.; Casu, M.R.; Vipiana, F. Model-Based Data Generation for Support Vector Machine Stroke Classification. In Proceedings of the 2021 IEEE International Symposium on Antennas and Propagation and USNC-URSI Radio Science Meeting (APS/URSI), Singapore, 4–10 December 2021; pp. 1685–1686.
23. Mariano, V.; Casu, M.R.; Vipiana, F. Simulation-based Machine Learning Training for Brain Anomalies Localization at Microwaves. In Proceedings of the 2022 16th European Conference on Antennas and Propagation (EuCAP), Madrid, Spain, 27 March–1 April 2022; pp. 1–3.
24. Taunk, K.; De, S.; Verma, S.; Swetapadma, A. A Brief Review of Nearest Neighbor Algorithm for Learning and Classification. In Proceedings of the 2019 International Conference on Intelligent Computing and Control Systems (ICCS), Madurai, India, 15–17 May 2019; pp. 1255–1260.
25. Masri, A.; Al-Ammouri, I. Clinical presentation, etiology, and outcome of stroke in children: A hospital-based study. *Brain Dev.* **2016**, *38*, 204–208. [CrossRef]
26. Shkilniak, L.; Wójcik, W.; Pavlov, S.; Vlasenko, O.; Kanishyna, T.; Khomyuk, I.; Bezverkhyi, O.; Dembitska, S.; Mamyrbayev, O.; Iskakova, A. Expert fuzzy systems for evaluation of intensity of reactive edema of soft tissues in patients with diabetes. *Inform. Autom. Pomiary W Gospod. I Ochr. Sr.* **2022**, *12*, 59–63. [CrossRef]

27. Sidorenko, A.; Klenov, N.; Soloviev, I.; Bakurskiy, S.; Boian, V.; Morari, R.; Savva, Y.; Lomakin, A.; Sidorenko, L.; Sidorenko, S.; et al. Base Elements for Artificial Neural Network: Structure Modeling, Production, Properties. *Int. J. Circuits Syst. Signal Process.* **2023**, *17*, 177–183. [CrossRef]
28. Daidone, M.; Ferrantelli, S.; Tuttolomondo, A. Machine learning applications in stroke medicine: Advancements, challenges, and future prospectives. *Neural Regen. Res.* **2024**, *19*, 769–773. [CrossRef]