Perinatal stroke

Doctoral thesis

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1. Introduction

Perinatal stroke encompasses a heterogenous group of neurological syndromes caused by cerebrovascular events leading to chronic neurological sequelae in most of the cases. Recent advances in diagnostic tools and neuroimaging modalities have resulted in a more frequent establishment of the diagnosis of the condition. Based on pathophysiology, acute strokes are classified as *perinatal arterial ischemic stroke (PAIS)*, *cerebral sinovenous thrombosis (CSVT)* and *perinatal hemorrhagic stroke (PHS)*. Finally, in patients not diagnosed in the neonatal period, the condition usually presents with focal asymmetry between 4-8 months of age and is referred to as *presumed perinatal stroke*.

The overall incidence of perinatal stroke is ~1 in 1100 live births. Therefore, approximately 80 neonates with the diagnosis of stroke are born in Hungary each year.

Even though 40% of neonates with perinatal stroke develop normally, the rest of the patients develop long-term neurological sequalae presenting as cerebral palsy, epilepsy, cognitive impairment, behavioral problems, language delay, visual field defect and/or hearing loss. A better classification of the extent of the injury and more precise localization of the affected brain compartment have been suggested to aid the clinician in the long-term prognostication and initiation of early rehabilitation. Of note is that early prognostication and parental counseling bear true clinical relevance in patients with perinatal stroke.

2. Aims

2.1 To analyze the clinical characteristics of term neonates with the diagnosis of perinatal stroke in a case-series study (patient data

obtained from the database of the Neonatal Intensive Care Unit of Szent János Hospital for the years spanning from 2006 to 2017)

2.1.1. In this longitudinal case-series, patient data were obtained for the years from 2006 to 2017 and we analyzed the clinical presentation, the imaging methods used, the etiology and the clinical relevance of perinatal stroke.

2.1.2. To assess the long-term neurodevelopmental outcome of patients with perinatal stroke, we carried out a systematic neurodevelopmental follow-up study of these patients at 2 years of age or later.

2.2. To assess the long-term neurodevelopmental outcome of term neonates diagnosed with perinatal arterial ischemic stroke (PAIS) and to investigate the associations among stroke territorial involvement, clinical risk factors and neurodevelopmental outcomes

2.2.1. To investigate the clinical risk factors, magnetic resonance imaging (MRI) studies, EEG findings and long-term neurodevelopmental outcomes in patients diagnosed with PAIS in Central-Hungary between 2007 and 2017 using a population-based study approach.

2.2.2. To describe the possible associations among the clinical presentation, potential clinical risk factors, MRI and EEG findings *and* long-term neurodevelopmental outcome in these patients.

2.3. Long-term neurodevelopmental outcome of term neonates with perinatal hemorrhagic stroke (PHS): a population-based study

2.3.1. To assess the long-term neurodevelopmental outcome of patients with PHS born between 2007 and 2017 using a population-based study approach.

2.3.2. To describe the possible associations among the clinical risk factors, MRI findings and long-term outcome in the patients enrolled.

2.4. Mortality and long-term outcome of neonates with congenital heart disease (CHD) *and* acute perinatal stroke: a population-based case-control study

2.4.1. We conducted a population-based case-control study enrolling 28 term and near-term neonates (≥35 weeks' gestation) with *CHD and acute perinatal stroke* (Study Group) confirmed by MRI born between 2007-2017 in Central-Hungary. We compared their outcome to that of 56 subjects with *matching CHD without stroke* (Control-1) and 56 neonates with *matching perinatal stroke without CHD* (Control-2). The primary goal of the study was to investigate whether perinatal stroke in conjunction with CHD increases mortality and, if so, to identify the risk factors that might contribute to the suspected increase in mortality.

2.4.2. The secondary aim was to compare the long-term neurodevelopment outcome of the Study Group patients to infants in the two control groups.

2.5. Perinatal stroke – review of the literature and management guideline

2.5.1. To provide a detailed review of the literature on perinatal stroke and summarize the epidemiology, clinical presentation, most appropriate imaging modalities and the recommended management strategies along with the available data on long-term neurodevelopmental outcome.

2.5.2. To develop a management guideline for the diagnosis and management strategies of acute perinatal stroke.

2.6. Perinatal stroke in Central-Hungary using a population-based study design

2.6.1. To give an overview of our previously published results in Hungarian.

2.6.2. To assess the clinical risk factors, MRI findings and long-term outcome of neonates with cerebral sinovenous thrombosis (CSVT) and fetal stroke.

3. Methods

3.1. Patient selection

A total of 314,400 neonates were born between 2007 and 2017 in the Central-Hungarian region. We reviewed the imaging studies of 1400 term and late preterm (32-36 weeks' gestation) neonates who had a head MRI performed prior to 28 days after delivery in the Department of Neuroradiology of the Medical Imaging Center, Semmelweis University. We excluded neonates with kernicterus, encephalitis, border-zone injury secondary to birth asphyxia, tumor, non-accidental brain injury, mitochondrial disorders, and congenital syndromes with known adverse outcome. We also excluded neonates with exclusively intraventricular, subarachnoidal, subdural or epidural hemorrhage without intraparenchymal bleeding as well as neonates with periventricular hemorrhagic leukomalacia. Finally, to decrease the heterogeneity of the study population, we included term and near-term **(**≥36 weeks' gestation) neonates with PHS and ≥35 weeks' gestation neonates with CHD *and* stroke.

We obtained Institutional Review Board approval from the Hungarian Medical Research Council (19934-4/2018/EKU).

3.2. MR imaging

Due to the lack of diagnostic accuracy of head ultrasound for all forms of neonatal stroke, patients were only included if they also had a brain MRI confirming the diagnosis. The scanning protocol included diffusion-weighted imaging, apparent diffusion coefficient map, conventional T1- and T2-weighted imaging, T2*- and susceptibility-weighted imaging. In selected cases, MR angiography and/or MR spectroscopy was added.

Classification was according to the affected brain compartment supplied by the region-specific arteries in PAIS and was based on the affected parenchymal lobes in PHS. Since previous reports have described an association between the involvement of the corticospinal tract and the

development of cerebral palsy, we also investigated the involvement of the posterior limb of the internal capsule (PLIC) on the diffusion weighted MR imaging. Furthermore, we noted the involvement of the thalamus and/or basal ganglia. Therefore, we reevaluated the MR images using the T1-, T2*- and diffusion weighted imaging. To assess the volume of the stroke, we measured the extent of the PHS by drawing a region of interest around the area judged to have abnormally high signal intensity on T2*-weighted images using the 3D image analysis package of the MRIcron program. Lesion volumes were expressed as total volume (cm^3) as well as, after excluding ventricular volume, the percentage of the supratentorial brain volume. The ratio of PHS to the supratentorial brain volume was further subcategorized as small (<5%), moderate (5%-10%) or large (>10%) based on the relative volume of the stroke.

Due to the relatively small number of patients involved in the study on patients with CHD *and* stroke, PAIS was dichotomized to be localized within the territory of the middle cerebral artery (MCA) or the anterior cerebral artery/posterior cerebral artery. Based on their largest diameter, strokes were also subcategorized as small (<3 cm) or large ($\geq$3 cm) strokes in this study.

3.3. Clinical data

Perinatal and postnatal clinical information was collected from chart reviews. Gestational age, birthweight, sex, modes of delivery, evidence of fetal distress during labor, Apgar scores, seizures, hypoglycemia (defined as blood glucose level <2.6 mmol/L), need for resuscitation and/or mechanical ventilation and/or cardiovascular support, abnormal muscle tone and level of consciousness (irritability/lethargy) along with other neonatal neurological symptoms were recorded. Risk factors during pregnancy, such as gestational diabetes (GDM), preeclampsia and placental abruption were also collected. We also identified neonates with possible birth injury (vacuum extraction, prolonged second stage labor and shoulder dystocia). We collected the test results in patients investigating suspected

coagulopathies and bleeding diatheses. Finally, we also collected data on electroencephalogram (EEG) and echocardiography (ECHO) studies.

3.4. Neurodevelopmental outcome

We prospectively performed a systematic neurodevelopmental follow-up assessment in all children that were diagnosed with perinatal stroke and were available for follow-up in 2018. Normal outcome was defined as symptom-free survival. Adverse outcome was noted if one or more of the following sequelae occurred: cerebral palsy (CP), fine motor impairment, cognitive impairment, behavioral problems, epilepsy, language delay, visual field defect and/or hearing loss. Neurodevelopmental outcome until up to three (3) years of age was assessed using the Bayley Scales of Infant Development, Second Edition or by the revised Brunet-Lézine scale. Beyond three (3) years of age, the Stanford-Binet Intelligence Scale was used to assess cognitive development. We used data from after 18 months until 12 years of age. Long-term neurodevelopmental assessment was feasible in 90% of the patients enrolled at a median age of 60 months [IQR: 35-88].

3.5 Statistical analysis

Descriptive statistics were expressed as absolute numbers and percentages in the population studied. Mean and standard deviation (SD) or median and interquartile range (IQR) were determined as appropriate. Neonatal clinical characteristics, the types of strokes and long-term neurodevelopmental outcome were compared with Fisher's exact test. Univariate logistic regression model was used to describe relationships between clinical predictors of interest and neurodevelopmental outcome. Multivariable logistic regression model was applied to ascertain the effect of significant predictors on the notion that a patient would likely have an adverse outcome, while controlling for other clinically relevant factors based on the results of the univariate analysis and previous research. Multivariable logistic regression model was used to assess the effect of stroke and other clinically significant variables in patient with congenital heart disease on

the notion that a patient would likely die. All statistical tests were two-sided, where p values of <0.05 were considered to indicate statistical significance. Statistical analyses were performed using IBM SPSS Statistics (Version 25, IBM Corp. Armonk, NY, USA).

4. Results

We identified 225 subjects with MR-evidence of perinatal stroke in the study period in the Central-Hungarian Region. We recruited 79 patients with PAIS, 55 subjects with PHS and 28 infants with CSVT in the study meeting inclusion criteria. Therefore, consistent with the available data in the literature, the disease incidence of PAIS over the study period in Central-Hungary was 1 per 3800 live births, the incidence of PHS was 1 per 5300 live births, while the incidence of CSVT was 1 per 11000 live births.

4.1. Perinatal stroke – from symptoms to follow-up

We recruited 18 patients with MRI-documented perinatal stroke into this longitudinal study. All patients were born in good condition with normal Apgar scores (9 ±1). In agreement with the data described in the literature, patients most frequently presented with seizures (77%). Three of the patients had been diagnosed with in-utero stroke.

Underlying pathology having likely contributed to the development of perinatal stroke included thrombophilia (n=14), infection (n=14), vascular malformation (n=2), mild asphyxia (n=2), and pre-eclampsia (n=2). Provision of early childhood developmental support was associated with normal development all patients except for those with in-utero stroke. These latter patients were diagnosed with severe neurodevelopmental impairment despite receiving appropriate early developmental support.

4.2. Role of brain territorial involvement and infection/ inflammation in the long-term outcome of neonates with PAIS: a population-based cohort study

Similar to the findings in the literature, we detected a male predominance (58%) in neonates with PAIS. Among the risk factors, infection/inflammation (>10 mg/L CRP) (19%) and CHD (15%) were associated with adverse long-term outcome, while seizure detected at the time of the first clinical admission was associated with the development of epilepsy. Data of the study population are summarized in Table 1.

Table 1.: Clinical characteristics, risk factors and presenting symptoms of neonates with PAIS in the study population.

	Patients with PAIS (n=79)
Gestational age [weeks], *mean (SD)*	38.8 (1.4)
Birthweight [g], *mean (SD)*	3312 (592)
Male, *n (%)*	50 (58)
Apgar score at 1 min, *mean (SD)*	7 (3)
Apgar score at 5 min, *mean (SD)*	9 (2)
Gestational diabetes mellitus, *n (%)*	8 (11)
Preeclampsia, *n (%)*	13 (16)
Placental abruption, *n (%)*	17 (22)
C-section, *n (%)*	42 (53)
5 minute Apgar score <7, *n (%)*	9 (11)
Possible birth trauma, *n (%)*	6 (8)
Congenital heart disease, *n (%)*	12 (15)
Cranial vasculopathy, *n (%)*	9 (11)
Infection/Inflammation, *n (%)*	15 (19)

CRP in patients with infection, *median [IQR]*	36 [13.5-5.5]
Clinical seizure, *n (%)*	59 (75)
Postnatal day at first seizure, *median [IQR]*	2 [1-3]
Hypoglycemia‡, *n (%)*	20 (25)
Altered consciousness, *n (%)*	10 (13)
Muscle tone abnormalities, *n (%)*	13 (16)
Respiratory distress, *n (%)*	29 (37)
Need for complex resuscitation / mechanical ventilation / cardiovascular support, *n (%)*	7 (9)

‡ Hypoglycaemia defined as blood glucose level <2.6 mmol/L, CRP: C-reactive protein

The most common presenting symptom of PAIS was seizure activity, occurring in 75% of patients, at a median age of 2 days [IQR 1-3]. Respiratory distress necessitating invasive or non-invasive ventillation was also frequent (37%). The rate of hypoglycemia, detected in 25% of the patients, was higher than that in the general neonatal population. The most commonly affected brain regions were the areas supplied by the main (20%), the anterior (22%) and the posterior branches of the MCA (19%). The involvement of the PLIC was detected in 28 neonates (35%).

Thirty of the 70 patients (43%) in this group with longitudinal follow-up had normal neurodevelopmental outcome. In patients with PAIS presenting with adverse neurodevelopmental outcomes, CP was the most frequent finding (29%). Language delay (23%), behavioral problems (21%), cognitive impairment (17%) and epilepsy (13%) were also commonly detected.

Using a multivariable logistic regression analysis, infants with main MCA stroke had 9,1 times higher odds (95% CI: 1,7-48,0) for overall adverse

outcome, and a particularly high risk for CP (OR: 55,9, 95% CI: 7,8-339,2). After excluding patients with main MCA branch stroke, the involvement of the PLIC was also associated with an increased risk for overall adverse outcome (OR: 8,1; 95% CI: 2,2-29,3) and CP/fine motor impairment (OR: 15,5; 95% CI: 3,6-67,5). Multiple strokes were significantly associated with epilepsy (OR: 9,5; 95% CI: 1,0-88,9) and behavioral problems (OR: 4,4; 95% CI: 1,1-17,5). Finally, infection/inflammation was associated with adverse outcome only in certain neurodevelopmental domains, including a higher likelihood for CP (OR: 9,8, 95% CI: 1,4-66,9), cognitive deficit (OR: 9,2, 95% CI: 1,8-47,8) and epilepsy (OR: 10,3, 95% CI: 1,6-67,9).

4.3. Long-term neurodevelopmental outcome of term neonates with PHS: a population-based study

The most common presenting symptom of PHS was seizure activity occurring in 62% of patients. The rate of respiratory distress was also relatively high, detected in 39% of the neonates (Table 2).

Table 2.: Clinical characteristics, risk factors and presenting symptoms of PHS in the study population.

Clinical characteristics, risk factors and presenting symptoms	**Patients with PHS, *n*=55**
Gestational age [weeks], *mean (SD)*	38.5 (1.6)
Birthweight [g], *mean (SD)*	3317 (549)
Male, *n (%)*	34 (62)
Apgar score 1 min, *mean (SD)*	8 (2)
Apgar score 5 min, *mean (SD)*	9 (1)
Possible birth trauma, *n (%)*	9 (16)
Spontanous vaginal birth, *n (%)*	38 (69)
Elective C-section, *n (%)*	11 (20)

Emegrency C-section, *n (%)*	6 (11)
Congenital heart disease, *n (%)*	5 (9)
Cranial vasculopathy, *n (%)*	6 (11)
Infection/Inflammation, *n (%)*	11 (20)
CRP in patients with infection/inflammation, *median [IQR]*	36 [13.5, 85.5]
Clinical seizure, *n (%)*	34 (62)
Postnatal day at first seizure, *median [IQR]*	2 [1,3]
Hypoglycemia‡, *n (%)*	10 (18)
Irritability/lethargy, *n (%)*	8 (15)
Muscle tone abnormalities, *n (%)*	8 (15)
Respiratory distress, *n (%)*	20 (36)
Complex resuscitation , *n (%)*	4 (7)

‡ Hypoglycaemia defined as blood glucose level <2.6 mmol/L, CRP: C-reactive protein

Hemorrhagic stroke occurred in the frontal (24%), temporal (24%), parietal (18%) and occipital lobes (18%), as well as in the basal ganglia and/or thalamus (22%). Eight patients (15%) developed hydrocephalus. Most of the PHS were subcategorized as small (62%), with the minority as moderate (27%) or large (11%).

Twenty (20) of the 50 infants (40%) with longitudinal follow-up had developed according to the population norms. Unexpectedly, CP was not as frequent finding in patient with PHS (8 patients (16%)) as in neonates with PAIS. Yet, in patients with PHS and CP, the condition was more severe as 75% of the affected infants (6/8) presented with tetraparesis. In individuals with chronic neurodevelopmental sequelae, the most common findings

were behavioral problems (24%), epilepsy (22%), language disorders (18%) and cognitive impairment (14%).

Using multivariable logistic regression analysis, parietal lobe PHS was a significant independent predictor of CP (OR: 6.7 95% CI: 1.1-41.4) and cognitive deficit (OR: 23.6 95% CI: 2.9-194.9). Infants with basal ganglia and/or thalamus involvement had seven times higher odds (95% CI: 1.3-37.7) for epilepsy. Strokes involving multiple lobes were independent predictors of impairment in several neurodevelopmental domains including CP (OR: 6.7 95% CI: 1.0-40.5), epilepsy (OR: 10.8 95% CI: 1.8-64.3) and the need for ventriculoperitoneal (VP) shunt placement (OR: 5.7 95% CI: 1.0-30.7). Finally, among the clinical risk factors, clinical seizure on admission was associated with the risk of later developing epilepsy (OR: 8.8 95% CI: 1.0-81.7).

Interestingly, none of the neonates with frontal lobe PHS developed later CP, cognitive impairment, or epilepsy during the follow-up period and the overall rate of impaired neurodevelopmental outcome was also less in these neonates. Importantly, in our study, two-thirds of the children with frontal lobe PHS were followed-up until school age when neurodevelopmental domains can indeed be appropriately assessed. We speculate that the PHS stroke of the frontal lobe may affect behavior and cognition at a level of higher functional complexity such as problem solving, impulse control and social interactions. Thus, it may only result in an atypical pattern of behavioral problems and not in cognitive impairment and may be more readily detectable only at later ages.

4.4. Mortality and long-term outcome of neonates with congenital heart disease *and* acute perinatal stroke: a population-based case-control study

The mortality of neonates with CHD *and* perinatal stroke (Study Group) was significantly higher compared to the mortality of neonates with congenital heart disease only (Control-1 Group, 5%) and of neonates with stroke only (Control-2 Group, 2%, $p<0.001$). Adverse neurodevelopmental outcome was prevalent in the Study Group (53%) and in neonates with

perinatal stroke without heart disease (Control-2 Group, 52%, p=0.03). Comparison of the baseline characteristics of the Study and of the Control Groups resulted in several statistically significant differences including the Apgar scores, the rate of Caesarean section, gestational age, cardiac interventions and multiple pregnancies. Using multivariable logistic regression analysis while adjusting for all clinically relevant parameters, the odds for mortality were still increased 6.5 times for patients in the Study Group compared to the patients with CHD without stroke (Control-1 Group, aOR: 6.5 95% CI: 1.1-39.4) (Table 3).

Table 3: Results of logistic regression analysis predicting the likelihood of death based on clinically relevant risk factors in the Study Group and in neonates with perinatal stroke without CHD (Control-2 Group). Neonates with CHD without stroke (Control-1 Group) were selected as a reference variable.

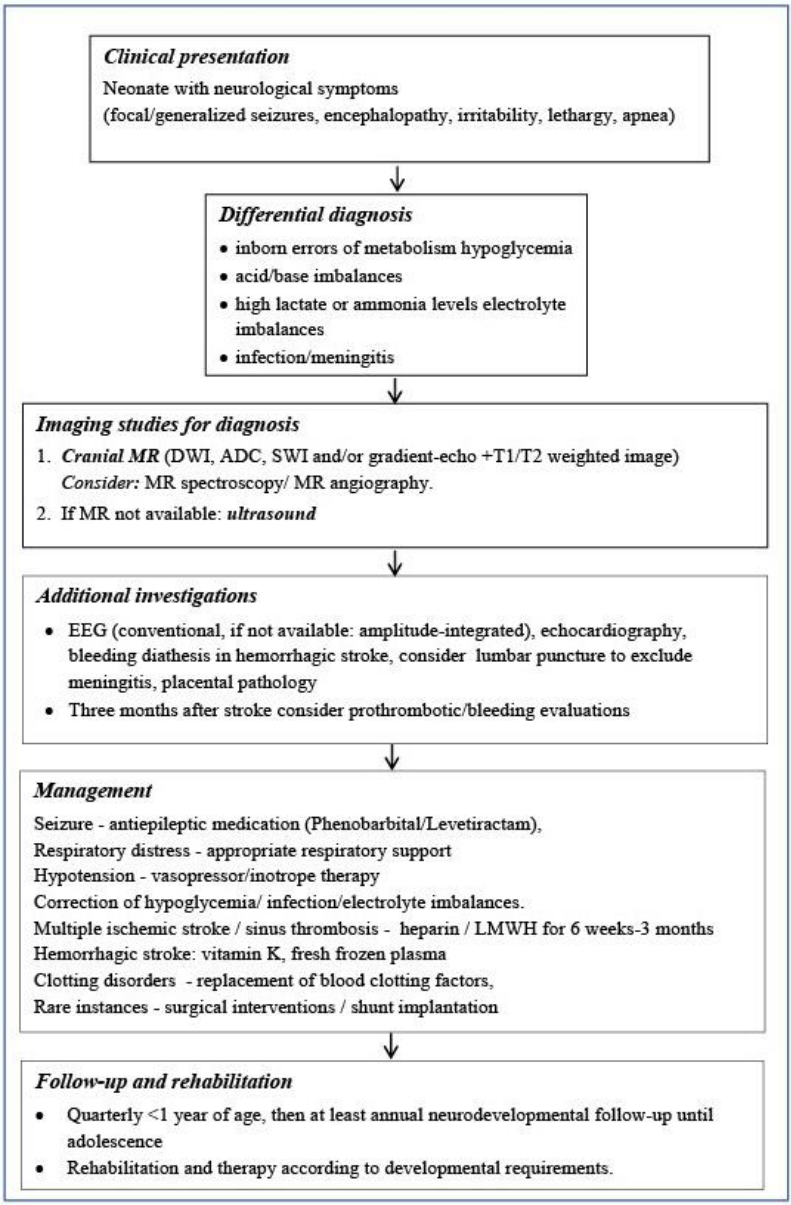
	Adjusted	
	aOR (95% CI)	***P* value**
Control-1 Group	NA	0.1
Control-2 Group	3.1 (0.2-42.3)	0.4
Study Group	6.5 (1.1-39.4)	0.04*
Vaginal birth	0.3 (0.06-1.6)	0.2
Gestational age at birth	1.4 (0.8-2.5)	0.3
Twin pregnancy	1.6 (0.08-33.1)	0.8
Apgar 1	1.1 (0.7-1.8)	0.7
Cardiac interventions	8.1 (0.9-73.5)	0.06

aOR: adjusted odds ratio, CI: confidence interval, NA: not available , *p < 0.05

4.5. Perinatal stroke: Investigation and management guideline

After reviewing the recommendations published in a recent review, we have designed a guideline to aid the clinician in establishing the diagnosis and the management plan in neonates with acute perinatal stroke (Figure 1).

Figure 1: Proposed management guideline for the diagnosis and care of neonates with acute perinatal stroke


Clinical presentation
Neonate with neurological symptoms
(focal/generalized seizures, encephalopathy, irritability, lethargy, apnea)
Differential diagnosis
• inborn errors of metabolism hypoglycemia
• acid/base imbalances
• high lactate or ammonia levels electrolyte imbalances
• infection/meningitis
Imaging studies for diagnosis
1. Cranial MR (DWI, ADC, SWI and/or gradient-echo +T1/T2 weighted image)
Consider: MR spectroscopy/ MR angiography.
2. If MR not available: ultrasound
Additional investigations
• EEG (conventional, if not available: amplitude-integrated), echocardiography, bleeding diathesis in hemorrhagic stroke, consider lumbar puncture to exclude meningitis, placental pathology
• Three months after stroke consider prothrombotic/bleeding evaluations
Management
Seizure - antiepileptic medication (Phenobarbital/Levetiractam),
Respiratory distress - appropriate respiratory support
Hypotension - vasopressor/inotrope therapy
Correction of hypoglycemia/ infection/electrolyte imbalances.
Multiple ischemic stroke / sinus thrombosis - heparin / LMWH for 6 weeks-3 months
Hemorrhagic stroke: vitamin K, fresh frozen plasma
Clotting disorders - replacement of blood clotting factors,
Rare instances - surgical interventions / shunt implantation
Follow-up and rehabilitation
• Quarterly <1 year of age, then at least annual neurodevelopmental follow-up until adolescence
• Rehabilitation and therapy according to developmental requirements.

4.6. Perinatal stroke in the Central-Hungarian Region: a retrospective, population-based study on patients with CSVT and fetal strokes

Neonates with CSVT had a poor prognosis as 18% of these patients died in the neonatal period. Among the survivors who were followed for at least 18 months of age, 70% of the patients had adverse long-term neurodevelopmental outcome. Three-quarters of the neonates with CSVT had thrombosis in multiple cerebral sinuses.

Stroke developed in fetal life in 20 neonates. None of them died in the neonatal period. However, long-term neurodevelopmental outcome was adverse in 67% of the neonates with fetal stroke.

5. Conclusions

This is the first population-based study on patients born in the Central Hungarian region with the aim to investigate the long-term neurodevelopmental outcome of neonates diagnosed with acute perinatal stroke and to describe the associations among clinical risk factors, MRI findings and long-term neurodevelopmental outcome of this condition.

In agreement with the findings in the literature, the incidence of acute PAIS, PHS and CSVT in our study was 1 per 3800, 1 per 5300 and 1 per 11000 live births, respectively.

Although 40% of the infants with acute perinatal stroke developed according to the population norms, the majority of the patients developed chronic neurodevelopmental sequelae. The sequelae included cerebral palsy, cognitive impairment, epilepsy, language delay, behavioral problems, visual field defect and/or hearing loss. We have found that stroke territorial involvement and clinical risk factors do influence the long-term outcome of patients with perinatal stroke.

In patients with PAIS, main MCA stroke, multiple strokes, and the involvement of the CST as well as infection/inflammation were independent predictors of adverse outcome. *In children with PHS*, parietal

lobe PHS, the involvement of the thalamus and/or basal ganglia, strokes affecting multiple lobes, and clinical seizures on admission were associated with poor outcome. *Patients with CHD and perinatal stroke* were at higher risk of dying compared to infants with CHD or perinatal stroke *alone*. The rate of neurodevelopmental morbidity was higher in neonates with CHD complicated by stroke than in neonates with CHD *only*. Of note is that surviving patients with CSVT had an increased rate of mortality and severely impaired neurodevelopmental outcome, while patients with in-utero stroke were at high risk for poor neurodevelopmental outcome. Finally, we designed a guideline to aid the clinician in establishing the diagnosis and managing the care of neonates with perinatal stroke.

In conclusion, determining the localization and volume of perinatal stroke may aid in the prognostication and individualized rehabilitation of neonates diagnosed with stroke.

Finally, in the future we plan to develop a national registry. The registry will enable us to collect statistically robust data, assess long-term outcome and test for treatment efficacy of neonates with stroke.

6. Candidate's publications

6.1 Publications related to the thesis

Vojcek E, Gyarmathy A, Graf R, Laszlo AM, Ablonczy L, Prodan Zs, Seri I: Mortality and long-term outcome of neonates with congenital heart disease and acute perinatal stroke: a population-based case-control study. Cong Heart Dis, 17 (4), 447-461. **IF=2.419**

Vojcek E, Seri I: Perinatalis stroke: Vizsgálati irányelv. Orvosi Hetilap 2022, 163 (24), 952-960. **IF=0.707**

Vojcek E, Graf R, Laszlo MA, Gyebnar Gy, Seri I: Long-term neurodevelopmental outcome of term neonates with perinatal hemorrhagic stroke: a population-based study. Dev Med Child Neurol 2022; 64 (8), 971-978. **IF=4.864**

Vojcek E, Jermendy A, Laszlo AM, Graf R, Rudas G, Berényi M, Seri I: The role of brain territorial involvement and infection/inflammation in the long-term outcome of neonates with arterial ischemic stroke: A population-based cohort study. Early Hum Dev 2021; 158: 105393. **IF=2.699**

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Total impact factor: 10.609

6.2 Publications unrelated to the thesis

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