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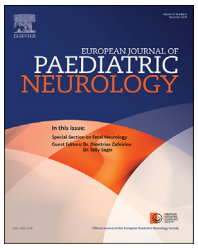

Original article

Long-term neurodevelopmental outcome after perinatal arterial ischemic stroke and periventricular venous infarction

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ABSTRACT

Background: Long-term follow-up data after different vascular types of ischemic perinatal stroke is sparse. Our aim was to study neurodevelopmental outcomes following neonatal and presumed perinatal ischemic middle cerebral artery territory stroke (arterial ischemic stroke, AIS) and periventricular venous infarction (PVI).

Methods: A prospective consecutive cohort of 40 term-born children with perinatal stroke (21 AIS, 19 PVI) was identified through the Estonian Paediatric Stroke Database. While 48% of the children with AIS were diagnosed during the neonatal period, all the children with PVI had presumed perinatal stroke. Outcomes based on the Paediatric Stroke Outcome Measure (PSOM) and Kaufman Assessment Battery for Children – Second Edition (K-ABC-II), in relation to extent and laterality of stroke, were defined.

Results: At a median age of 7 years 6 months (range 3.6–13y), there was a trend towards worse neurodevelopmental outcome in participants with AIS when compared to PVI (mean total PSOM scores 3.1 and 2.2, respectively; $p = 0.06$). Combined deficits of motor, language and cognitive/behavioural functions were significantly more common among children with AIS (90%) when compared to children with PVI (53%, $p = 0.007$). General cognitive ability (by K-ABC-II) was significantly lower in the AIS subgroup (mean 79.6; 95% CI 72.3–87.0), but children with PVI (91.6; 95% CI 85.5–97.8) also had poorer performance than the age-equivalent normative mean. Large extent of stroke was associated with poorer neurodevelopmental outcome and lower cognitive performance in children following AIS but not in PVI.

Conclusion: In this national cohort, poor long-term neurodevelopmental outcome after perinatal ischemic stroke was seen irrespective of the vascular type or time of diagnosis of

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stroke. However, the spectrum of neurological deficits is different after perinatal AIS and PVI, with combined deficits more common among children following AIS.

1. Introduction

With an incidence of 1 in 1600–5000 live births (including delayed presentations and haemorrhagic strokes),[1–3] perinatal stroke is an increasingly acknowledged cause of significant lifelong neurological morbidity including impairments of sensorimotor, cognitive and language functions, as well as behavioural problems and epilepsy.[4,5]

Ischemic perinatal stroke refers to focal disruption of cerebral blood flow secondary to arterial or venous thrombosis or embolization, between 20 weeks of fetal life through the 28th postnatal day, confirmed by neuroimaging or neuropathologic studies.[1] As the pathophysiology of perinatal stroke remains unclear, few disease-specific treatments and no prevention strategies are currently available.[6] With a distinct pattern of ischemic brain injury in an arterial distribution, arterial ischemic stroke (AIS) in the territory of middle cerebral artery (MCA) is the most common type of lesion.[1,7–9] Periventricular venous infarction (PVI), referring to a focal unilateral periventricular white matter medullary venous territory infarction secondary to germinal matrix haemorrhage, is an important comparative outcomes model among the perinatal stroke syndromes.[8]

Symptomatic neonatal strokes that present acutely (usually with focal seizures) during the neonatal period are relatively well-studied, though this only represents a fraction of all perinatal stroke cases.[10,11] Presumed perinatal stroke (PPS) defines a child with a normal perinatal neurological history with emerging neurological deficits later in infancy (usually hemiparesis or focal seizures) attributable to remote focal infarction on neuroimaging.[7,8,12] Among infants with PPS, PVI has been found to be the most common[13,14] or second most common type of brain injury after AIS.[8]

Long-term outcome studies of perinatal stroke are sparse, and results vary to a great extent, depending on the stroke subtypes included, duration of follow-up, and measures used for outcome evaluation. Asymmetric sensorimotor impairments (i.e., congenital hemiparesis/hemiplegia, unilateral spastic cerebral palsy) are the most common consequences, affecting up to half of children with neonatal AIS,[10,15–20] and >80% with PPS (for which retrospective diagnosis confers a selection bias).[8,14,17,18,21] While some studies report normal or near-normal cognitive ability following neonatal AIS,[22–24] others have revealed variable cognitive deficits.[25–30] There is lack of systematic studies about cognitive development of children with PPS (and especially PVI) who reach medical attention mainly due to motor deficits.

The purpose of this study was to determine long-term neurological and cognitive outcomes of a term-born national cohort of children following ischemic perinatal stroke. Our primary aim was to identify possible differences in outcomes after two vascular subtypes of ischemic perinatal stroke (AIS and PVI). We hypothesized that regardless of stroke subtype, children with stroke would perform worse than the normative population in standardized intelligence testing, and that cognitive performance would correlate with the level of neurological impairment. We also studied whether the extent and laterality of stroke accounted for differences in neurodevelopmental outcomes following ischemic perinatal stroke. Our hypothesis was that large extension of lesion would be associated with more severe neurological impairment and lower cognitive performance. As delayed diagnosis creates considerable bias towards severe outcomes, we also aimed to study the possible differences in outcomes of neonatal and presumed perinatal arterial ischemic stroke.

2. Materials and methods

2.1. *Participants*

Participants were identified from the Estonian Paediatric Stroke Database, which contains the data of children with perinatal stroke collected on the basis of an epidemiological study (1994–2003)[3] and prospectively thereafter. Estonia has two tertiary neonatal intensive care units and two child neurology departments to where all paediatric stroke cases are referred. All patients in the Estonian Paediatric Stroke Database have radiologically proven diagnosis of stroke: with magnetic resonance imaging (MRI) or computed tomography (CT). All brain images in Estonia are archived in the all-Estonian Picture Archiving System.

Since the epidemiological study, Estonian primary care physicians and paediatric neurologists have been trained to recognise perinatal stroke, to enable consecutive patient inclusion into the database. After the diagnosis of perinatal stroke, children are annually followed at the Children's Clinic of Tartu University Hospital or Tallinn Children's Hospital.

For the outcome study, patients were consecutively selected according to the following inclusion criteria: (1) children with neonatal AIS in the MCA territory or PVI, diagnosed between birth and 28 days of life on the basis of MRI revealing an acute ischemic stroke; (2) children with presumed AIS in the MCA territory or PVI, diagnosed after 28 days of life with MRI revealing a lesion consistent with remote stroke; (3) gestational age of at least 36 weeks; (4) aged $\geq$ 3 years at the time of outcome assessment. The exclusion criteria were: (a) more global brain injuries (e.g. hypoxic-ischemic encephalopathy, watershed infarction, periventricular leukomalacia); (b) other documented diseases

with central nervous system involvement; (c) acute stroke after the neonatal period; (d) AIS in the territories of anterior cerebral artery (ACA) and posterior cerebral artery (PCA) for a more homogeneous patient population.

Eligible patients were evaluated by a multidisciplinary team at the Children's Clinic of Tartu University Hospital between 1st June 2010 and 31st December 2015. The study was approved by the Medical Research Ethics Committee of the University of Tartu (decisions 170/T-6, 28.4.2008; 233/T-10, 2.1.2014). Written informed consent for participation in the study was obtained from the parents and children aged seven years or over.

2.2. Background clinical data

All available hospital charts were reviewed for background clinical information, including gestational age, delivery, birthweight, Apgar scores, presenting symptoms, epilepsy, and received treatments and (re)habilitation services. The parents of children with delayed diagnosis were interviewed on the first concerns or potential abnormal signs.

2.3. Neurodevelopmental assessments

Structured neurological examination was performed according to the Pediatric Stroke Outcome Measure (PSOM; see Appendix), a disease-specific measure of neurological recovery after stroke in children. PSOM has shown good inter-rater agreement and construct validity.[31,32] Each evaluation was done by at least two paediatric neurologists who were blinded to the neuro-radiological findings and results of the cognitive assessment. PSOM contains 115 test items and yields a deficit severity score on a Likert-type scale for five subscales, including sensorimotor, expressive and comprehensive language, and cognitive/behavioural performance. Based on the combination of scores in the individual subscales, the overall outcome was classified as good (normal or mild deficit) or poor (moderate or severe impairment). Normal outcome was defined as a score of 0 in all five subscales, mild deficit as a score of 0.5 in one subscale only, moderate deficit as an overall score of 1–1.5, and severe deficit as an overall score of 2–10.[31,32]

The neurological motor outcome was evaluated by PSOM and defined according to Surveillance of Cerebral Palsy in Europe (SCPE) criteria. The severity of motor impairment was rated according to the PSOM sensorimotor subscales. Children who had persisting increased tone and pathological reflexes resulting in abnormal pattern of movement and posture were considered to have unilateral spastic cerebral palsy (i.e., hemiplegic CP).[33] Mild motor abnormalities were defined as slight abnormalities of tone or reflexes that did not interfere with function.

Cognitive performance was evaluated using the Kaufman Assessment Battery for Children, Second Edition (K-ABC-II; see Appendix).[34] Three measures, including: (1) the Fluid-Crystallized Index (FCI), a general measure of cognitive ability that includes acquired knowledge; (2) the Mental-Processing Index (MPI), mental processing ability that excludes measures of acquired knowledge; and (3) the Nonverbal Index (NVI), a general measure of nonverbal abilities, were estimated. In addition, the standard scores of five subscales (sequential and simultaneous processing, learning, planning and knowledge) were provided. The range of possible scores is from 40 to 160 (mean 100, SD 15). Based on the standard scores, cognitive performance was rated as above average (> + 1 SD; >116 points), average (−1 SD to 1 SD; 85–115 points), below average (borderline) (−1 SD to −2 SD; 70–84 points), and lower extreme (<−2 SD; <69 points). The scoring system of K-ABC-II is described in detail in the Appendix. Cognitive performance of children with perinatal stroke was compared to age-equivalent results of the normative sample of K-ABC-II.[34]

2.4. Neuroimaging analysis

Participants were imaged on the magnetic resonance scanners of Siemens Medical Solutions (1.5 T Magnetom Symphony) or Philips Medical Systems (1.5T Philips Ingenia or 3.0T Philips Achieva) using conventional T1-, T2-weighted sequences, fluid-attenuated inversion recovery (FLAIR) and susceptibility weighted imaging in order to confirm the diagnosis. The neuroimaging findings were independently re-reviewed by three radiologists (P.I., D.L., T.T.) and consensus regarding the diagnosis of stroke subtype was achieved. In the case of disagreement, consensus was reached after discussion of the case between the radiologists. According to the vascular syndrome, ischemic stroke was classified as AIS or PVI.[8] AIS included only occlusions in the territory of MCA. Periventricular venous infarction was defined as unilateral periventricular white matter (PVWM) medullary venous territory infarction with focal PVWM encephalomalacia, posterior limb of the internal capsule (PLIC) T2 prolongation, spared cortex, and basal ganglia relatively spared with the bulk of lesion involving more rostral portions of the PVWM.[8] The extent of the affected areas was graded in a similar fashion to previous studies of early focal brain injury. AIS was considered small if there was cortical damage involving one cerebral lobe only and large if multiple lobes were affected. PVI was rated as small if there was focal ventricular dilatation or periventricular damage involving one cerebral lobe only, and large if multiple lobes were affected.[28,35] In case of bilateral asymmetric infarctions, the evaluation of the extent of the lesion was done based on the larger lesion (dominant lesion side).

2.5. Statistical analysis

Percentages were used to describe the clinical features and outcomes of the two study groups. Relative risk was estimated by Odds Ratios (OR) and a 95% confidence interval (CI). To compare proportions between subgroups, χ^2 or Fisher exact tests for dichotomous variables were used. The Kolmogorov–Smirnov criterion was used for assessment of parametric/non-parametric distribution. Statistical comparisons between normally distributed continuous and categorical variables were performed with the Student's t-test. In the case of asymmetric continuous variables, the tested hypotheses were based on the calculations of nonparametric tests, such as the Mann–Whitney U-test. Regression analysis (linear and logistic regression) was used to examine relations between subtype and extent of stroke, and outcomes.

Spearman's (or Pearson's) correlations were calculated to explore correlations between the two outcome measures. Correlations of 0.50 were considered large in magnitude, 0.30 moderate, and 0.10 small. All probability values were two-sided, and differences were considered statistically significant if the probability values were less than 0.05. Analysis was performed with the SAS Version 8.02 statistical package.

3. Results

3.1. *Patient population*

A total of 40 children with confirmed diagnosis of ischemic perinatal stroke (19 males, 21 females) were enrolled, and divided into two subgroups according to the vascular aetiology: (1) AIS (n = 21), and (2) PVI (n = 19). While males outnumbered females in the AIS subgroup (57%), there were more females in the PVI group (63%; $p = 0.15$). The two stroke subgroups did not differ in terms of age at follow-up. The main patient characteristics are shown in Table 1.

3.2. *Symptoms at presentation*

The most common symptoms of neonatal presentation were seizures (55%), muscle tone abnormalities (36%; asymmetric limb tone, hypotonia, or spasticity), abnormal level of consciousness (27%), apneas (27%) and feeding difficulties (10%).

There was substantial delay from first parental concern to diagnosis in children with PPS. Median age at parental concern, ranging from asymmetric muscle tone at birth to asymmetric walking at 18 months, was 4 months. Median age at diagnosis of PPS, based on the time when the first neuroimaging was performed, was 19 months (range 2 months–7 years). Median age at diagnosis of presumed AIS and PVI did not differ significantly.

The majority of infants with PPS (93%) reached medical attention due to asymmetrical motor deficits. Asymmetrical hand function (fisted hand, early hand preference in reaching and grasping, difficulties with releasing objects) was the cause of referral in 38% of the children with PPS. The parents also reported stiffness of one arm when dressing, difficulties with rolling over, crawling and sitting due to asymmetric posture or hand function. Four children (14%, three PVI) presented with hemiparesis affecting mainly the lower extremity, with parents describing clumsiness and stumbling or abnormal positioning of the foot when learning independent walking.

3.3. *Neuroimaging findings*

Thirty-nine participants (98%) had a single unilateral stroke. Bilateral asymmetric infarctions were detected in one patient with neonatal AIS. In both study groups, left hemisphere lesions of large extent were predominant. The proportion of large MCA infarctions was similar among children with

Table 1 – Main patient characteristics.

Characteristic	Arterial Ischemic Stroke (AIS) n (%)	Periventricular Venous Infarction (PVI) n (%)	*p* value	OR (95% CI)
Sex				
Male	12 (57)	7 (37)	0.20	2.5 (0.7–8.7)
Female	9 (43)	12 (63)		
Type of presentation				
Neonatal	11 (52)	0 (0)	0.0002*	
Presumed perinatal	10 (48)	19 (100)		
Age at diagnosis in PPS# (months)				
Median (quartiles)	14.5 (12.0;34.0)	22.0 (9.0;36.0)	0.68	
Range	2.0–84.0	6.0–84.0		
Age at testing (months)				
Mean (95% CI)	94.1 (78.0–110.2)	87.6 (76.3–101.7)	0.53	
Birth-weight (grams)				
Mean (95% CI)	3384 (3139–3629)	3360 (3145–3574)	0.88	
Delivery				
Normal vaginal	7 (33)	13 (68)	0.03*	4.3 (1.2–16)
Emergency SC	8 (38)	2 (11)	0.07	5.3 (0.9–29)
Apgar score (≤7)				
At 1 min	8 (38)	1 (5)	0.02*	11 (1.2–100)
At 5 min	3 (14)	0 (0)	0.23	
Lesion laterality				
Left	16 (76)	13 (68)	0.58	1.5 (0.4–6.0)
Right	5 (24)	7 (32)		
Extent of the affected areas				
Small##	6 (29)	8 (42)	0.37	1.8 (0.5–6.8)
Large###	15 (71)	11 (58)		
Epilepsy at outcome	12 (57)	0 (0)	<0.0001*	

PPS stands for Presumed Perinatal Stroke.
Small = involving one cerebral lobe.
Large = involving more than one cerebral lobe.
* $p < 0.05$.

neonatal and presumed AIS. Main lesion characteristics are shown in Table 1, and examples of lesions and associated outcomes in Fig. 1.

3.4. *Neurological outcome according to PSOM*

The primary outcome based on PSOM revealed moderate to severe neurological impairment in 95% of children with AIS and 94% with PVI (Table 2). There was a trend towards worse overall neurodevelopmental outcome in the AIS subgroup when compared to children with PVI (mean PSOM overall scores 3.1 and 2.2, respectively; $p = 0.06$). All children with neonatal AIS had poor neurological outcome. Mean PSOM overall deficit scores of children with neonatal and presumed AIS did not differ significantly (3.6 vs. 2.5, respectively; $p = 0.14$).

The spectrum of neurological deficits in the two stroke subgroups is shown in Table 3. Combined deficits of motor, language and cognitive/behavioural functions were significantly more common among children with AIS (90%) when compared to children with PVI (53%, $p = 0.007$). Isolated spastic hemiplegia without language or cognitive deficits occurred in 9 (47%) children with PVI and 2 (10%) with AIS

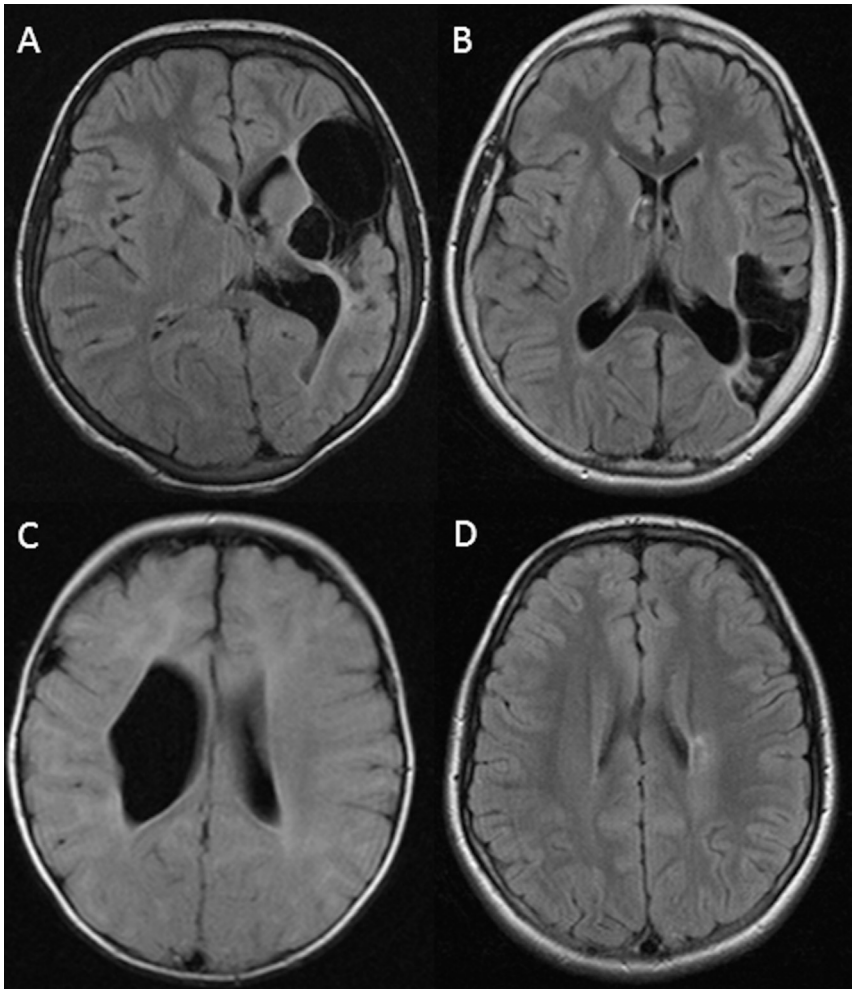

Fig. 1 – Examples of imaging features (Axial T2-weighted FLAIR) and outcomes in arterial ischemic stroke (AIS) and periventricular venous infarction (PVI). (A) Large left middle MCA proximal M1 segment infarction with basal ganglia involvement in a 4-year-old girl who presented on the third day of life with an abnormal level of consciousness and asymmetric grasp reflex. At the age of 11 years, she had a total PSOM score of 3, with borderline cognitive ability, moderate right-sided hemiplegia, and epilepsy; (B) Large left inferior MCA division infarction involving parietal and posterior temporal lobes in a 1-year-old boy with neonatal stroke who presented with focal seizures during the first day of life. At the age of 7 years, he had a total PSOM score of 2, with borderline cognitive ability, mixed specific developmental disorder, specific speech articulation disorder, mild right-sided sensorimotor deficits, and epilepsy; (C) Large right PVI in a 2-year-old girl with PPS who reached medical attention due to a fisted left hand at the age of 4 months. At the age of 4 years, she had a total PSOM score of 3, with severe left-sided hemiplegia, comprehension and behavioural problems according to PSOM but average cognitive ability by K-ABC-II; (D) A small left PVI in a 3-year-old boy with PPS who reached medical attention at the age of 18 months due to asymmetric walking and a clumsy right hand. At the age of 10 years, he had a total PSOM score of 1.5 with moderate right-sided lower limb dominant hemiplegia and borderline cognitive ability.

Table 2 – Outcomes by pediatric stroke outcome measure (PSOM).

Outcome Classification*		All N = 40 (%)	AIS N = 21 (%)	PVI N = 19 (%)	P value
Good	Normal	0	0	0	NS
	Mild deficit	2 (5)	1 (5)	1 (6)	NS
Poor	Moderate deficit	9 (22)	4 (19)	5 (26)	NS
	Severe deficit	29 (73)	16 (76)	13 (68)	NS

* Scoring criteria according to PSOM: Normal = score 0 in all five subscales; Mild deficit = score 0.5 in one subscale only; Moderate deficit = score 0.5 in more than one subscale, or score 1 in one subscale, or score 1 in one subscale and 0.5 in another subscale; Severe deficit = score 0.5 in all five subscales, or score 1 in one subscale plus 0.5 in two subscales, or score 1 or 2 in at least two subscales.[30]

(p = 0.007; OR = 8.6; 95% CI 1.5–47). All children who had isolated hemiplegia lacked neonatal symptoms and were diagnosed with PPS.

From the AIS subgroup, 12/21 (57%, 7 with neonatal stroke) had epilepsy at outcome assessment (92% receiving antiepileptic treatment). The overall neurological outcome of children with epilepsy was poorer than in children with AIS who did not have epilepsy, but the difference was not statistically significant (mean PSOM overall scores 3.6 and 2.4, respectively; p = 0.09). While incidence of expressive or receptive language deficits did not differ in children with or without epilepsy, cognitive/behavioural impairments affecting function were more frequent in the AIS subgroup of children with epilepsy (5/12, 42% vs. 1/9, 11%, respectively), but the difference was not statistically significant (p = 0.18).

3.5. *Cognitive outcome according to K-ABC-II*

Thirty–nine (21 AIS, 18 PVI) of the 40 children enrolled completed age–appropriate K–ABC–II at a mean age of 7.6 years (range 3.6–13.1). One child moved abroad and cognitive evaluation could not be completed. 38% of the studied children were at preschool age (3.6–6.8 years). Both stroke subgroups showed significantly lower FCI scores (i.e., IQ) than the age–equivalent normative mean (Fig. 2). 12/21 (57%) of the tested children with AIS and 6/18 (33%) with PVI had poorer performance than −1SD of the age–equivalent normative mean. From the AIS subgroup, 4/21 (19%, all neonatal AIS) of the studied children had lower extreme (IQ ≤ 69) and 8/21 (38%, 5 neonatal AIS) showed below average/borderline (IQ 70–84) cognitive ability. In children with PVI, cognitive performance was rated as borderline in 6/18 (33%). However, nobody had lower extreme cognitive ability.

The performance of participants who had epilepsy at follow–up was a mean 9.3 points lower on K–ABC–II index scores when compared to children with AIS who did not have epilepsy, and performance was 15.3 points lower when compared to all participants (including PVI) who did not have epilepsy.

3.6. *Association of outcomes with extent and laterality of stroke*

Large extent of stroke predicted poorer overall neurological outcome in children with AIS (mean PSOM overall score 3.8 vs. 1.3; p = 0.0001) but not in PVI (mean PSOM 2.4 vs. 1.9; p = 0.40). Epilepsy occurred significantly more frequently among children with large AIS (11/15, 73% vs. 1/6, 17%; p = 0.03; OR = 9.5; 95% CI 1.1–84.1). Regardless of stroke subtype, moderate to severe expressive language impairment was seen only among children who suffered extensive strokes (8/26; 31% vs. 0/14; p = 0.03).

Large extent of lesion predicted weaker cognitive performance in children with AIS, but not with PVI. There were no significant differences between the cognitive performance of children with left– vs. right–sided lesions.

The overall neurological outcome did not differ in left– versus right–sided lesion groups. The two lesion laterality groups did not differ in prevalence of moderate to severe language or cognitive/behavioural impairments.

Table 3 – Spectrum of neurological deficits in children with arterial ischemic stroke (AIS) and periventricular venous infarction (PVI) by Pediatric Stroke Outcome Measure (PSOM).

Type of deficit	All N = 40 (%)	AIS N = 21 (%)	PVI N = 19 (%)	P value	OR (95% CI)
Sensorimotor (score 0.5–2)	39 (98)	20 (95)	19 (100)	NS	
Moderate or severe motor impairment (score 1–2)#	33 (83)	16 (76)	17 (90)	NS	
Speech–language (score 0.5–2)	27 (68)	17 (81)	10 (53)	NS	
Expressive language (score 0.5–2)	26 (65)	17 (81)	9 (47)	NS	
Receptive language (score 0.5–2)	17 (43)	11 (52)	6 (32)	NS	
Moderate or severe language impairment (1–2)	11 (28)	8 (38)	3 (16)	NS	
Cognitive/behavioural (score 0.5–2)	23 (58)	17 (81)	6 (32)	0.002*	9.2 (2.1–40)
Moderate or severe (score 1–2)	8 (20)	6 (29)	2 (11)	NS	
With expressive or receptive language deficit	21 (53)	15 (71)	6 (32)	0.011*	5.4 (1.4–21)
Combined neurological deficit (score 0.5–1 in >1 subscale)	29 (73)	19 (90)	10 (53)	0.007*	8.6 (1.5–47)

Unilateral spastic CP according to SCPE.[33]

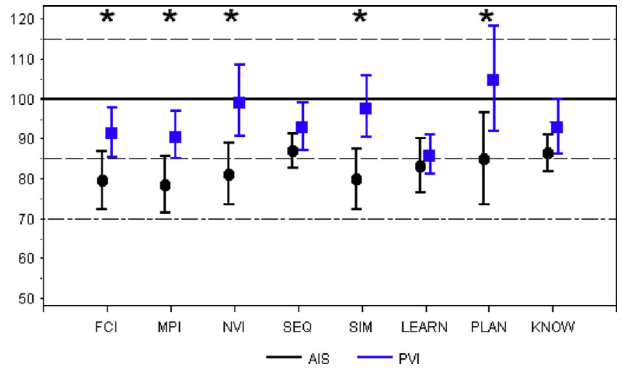

Fig. 2 – Mean (95% CI) K-ABC-II index and subscale scores of children with arterial ischemic stroke (AIS, n = 21) and periventricular venous infarction (PVI, n = 18). K-ABC-II normative mean is 100 and SD 15. FCI stands for Global Fluid-Crystallized Index (includes all subscales); MPI for Mental Processing Index (excludes acquired knowledge); NVI for Non-Verbal Index; SEQ for Sequential Processing; SIM for Simultaneous Processing; LEARN for Learning; PLAN for Planning; KNOW for Knowledge; *$p < 0.05$.

3.7. *Correlations between PSOM and K-ABC-II results*

Total PSOM scores demonstrated significant negative correlations with the K–ABC–II index measures and subscale scores, with greater neurological deficits related to poorer cognitive performance (see Table 4 in Appendix). The FCI scores of K–ABC–II showed strong negative correlations with the expressive and comprehensive language as well as cognitive/behavioural deficit scores on PSOM. The strongest associations of the PSOM cognitive/behavioural deficit scores were observed with the scores of non-verbal abilities and planning on K–ABC–II. Cognitive ability according to K-ABC-II did not show significant correlations with motor deficit scores of the PSOM.

3.8. *Received interventions*

Twelve patients from the PVI and three from the AIS study group (60% vs. 14%, $p = 0.002$, OR = 9.0; 95% CI 1.9–40.9) had received *Botulinum* toxin–A injections to their upper and/or lower extremity muscles for treatment of spasticity and contractures (no one during 6 months prior to outcome evaluation). Seven children (six with PVI) had undergone lower limb orthopaedic surgery. Only 5/21 (24%) participants with AIS and 5/20 (25%) with PVI received regular physiotherapy (once–weekly in half of the children, and intensive one–week therapy twice a year at a rehabilitation clinic in the other half), and used assistive devices (e.g. foot orthoses) at the time of follow–up. 24% of the whole study population had received occupational therapy during the past year, which was regular in only six cases. Five children from each study group attended regular speech therapy as part of day–care or education. While most school–aged participants (78%) attended mainstream schools, 52% of them received supported education services (including speech therapy or individualized curricula).

4. Discussion

In a prospective study of term–born children with ischemic perinatal stroke in Estonia, we found poor long–term neurodevelopmental outcome in the majority of children regardless of the vascular subtype or time of diagnosis of stroke. This is the first comprehensive outcome report of children included in the Estonian Paediatric Stroke Database. The findings of the study revealed several clinically important differences in outcomes of children after perinatal AIS and PVI. At preschool to early school age, children with AIS presented combined deficits of sensorimotor, language and cognitive/behavioural functions significantly more frequently than children with PVI. Furthermore, cognitive performance was significantly weaker in children with AIS, but the performance of children with PVI was also lower than the age–equivalent normative population. Large extent of stroke was associated with poorer overall neurological outcome and lower cognitive ability in children following AIS but not in children with PVI.

Neurodevelopmental (including neurological motor and cognitive) outcomes after ischemic perinatal stroke have been previously described in some studies, but most have concentrated on symptomatic neonatal AIS.[8,14–16,18,20,29] Particularly for differences of timing and location, PVI provides an important comparative outcomes model among the perinatal stroke syndromes. Although the same foetal germinal matrix haemorrhage with secondary medullary venous infarction commonly occurs in delivered preterm infants, the extrapolation of outcome studies from this population is limited by the many confounders of preterm birth.[12,24]

The incidence of neurological morbidity after perinatal stroke in our study is among the highest reported so far. Longer follow-up time and structured neurological evaluation might contribute to higher detection rates. An important factor possibly affecting the high proportion of children with poor long–term outcome in our study, is the limited access to regular rehabilitation services for the majority of these children in Estonia. In addition, while median age at PPS presentation and symptoms leading to neuroimaging were similar in our cohort in comparison to earlier studies,[8,14,18] diagnosis was made significantly later. This causes substantial delays in interventions, which have a documented effect on function,[36,37] and indicates the need for improvement in awareness of PPS symptomatology among primary care physicians, and early diagnostics in Estonia.

In agreement to previous outcome studies, we found that spastic hemiplegia was the most common consequence after ischemic perinatal stroke, and is more likely to affect children with PPS (and especially PVI).[5,8,14,18,20,21] In addition to the inherent selection bias in the PPS population (only those with morbidity are detected) and the factors mentioned earlier, the high incidence of spastic hemiplegia in our AIS cohort might be influenced by the predominance of large branch infarctions with involvement of more than one cerebral lobe and basal ganglia/thalamus. Large-branch or mixed arterial ischemic strokes have been found to be predictive of hemiplegic CP.[18,19,29,38] Consistent with the isolated, subcortical location of PVI with possible selective damage to the corticospinal projections in this type of injury,[8,39,40] this subgroup most

often presented with unilateral motor deficits and nearly half showed isolated spastic hemiplegia with no other neurological deficits at follow–up. Studies exploring the associations between location and extent of the lesion and severity of motor impairment in PVI are pending.

The prevalence and severity of long–term cognitive disorders after perinatal stroke are unclear. The barriers to the study of neuropsychological outcomes include the complexity of the timing of the appearance of specific deficits, the use of variable outcome measures, and studies with modest mixed samples that only rarely use a prospective longitudinal design.[4,30] We chose K–ABC–II instead of the Wechsler Intelligence Scale for Children (WISC) because it allows a more valid assessment of children with suspected language impairment (with the possibility to interpret results by excluding verbal ability).[41] K–ABC–II index scores have been found to correlate strongly with WISC–IV,[34,41] which makes the results of our study easily comparable to other studies.[16,23,24,26,28]

Consistent with the existing literature,[26,28] children with AIS revealed significantly lower general cognitive ability than the age–equivalent normative sample. The predominance of males and large infarctions, as well as the high incidence of post–neonatal epilepsy, are among the factors possibly explaining the poorer cognitive outcome in the Estonian AIS subgroup in comparison to earlier studies.[23,24,26,28] In contrast to some earlier studies we did not exclude the most severely impaired participants.[20] Post–neonatal epilepsy has been reported in 15–67% of children after perinatal stroke, with higher incidence among children with arterial lesions.[8,23,42] In our cohort, 57% of participants following AIS had epilepsy at follow–up, the majority of whom were on antiepileptic treatment and showed poor overall outcome. The detrimental effect of seizures on cognitive and language outcomes of children after perinatal stroke has been demonstrated by some studies.[20,24,27,43] In our study, children with post-neonatal epilepsy had poorer cognitive ability than those who did not have epilepsy at follow-up but the differences were not statistically significant. Lesion size with predominance of large branch infarctions might be an important confounder. While most studies have found no correlation between lesion size and cognition in children with perinatal stroke,[18,27] we found significantly higher overall neurological deficit scores, incidence of language impairments and post–neonatal epilepsy, and lower general cognitive ability in participants with large infarctions. The majority of previous reports,[23,26,28,44–46] as well as our study, found no effect of lesion laterality on cognitive outcome regardless of stroke subtype. We hope to revisit the issue when the cohort is larger.

Compared to AIS, purely subcortical PVI has been shown to have a much lower risk of cognitive and behavioural disorders,[8] which is also supported by our findings. On the other hand, the fact that the cognitive performance of children with PVI was also significantly lower than the age–equivalent normative population and their verbal abilities were significantly weaker than non-verbal abilities, enables suspicion that these children might be at risk of specific developmental disorders (e.g. speech and language disorders, learning disabilities). The results highlight the importance of all children with perinatal stroke undergoing formal specific cognitive assessment to detect possible subtle or emerging difficulties in higher–level cognitive abilities.

To our knowledge, this is the first outcome study to report female predominance among children with PPS (AIS and PVI). There is some evidence that ischemic perinatal stroke is slightly more frequent in boys, but the reasons for these differential risks are not known.[1] It has been proposed that male foetuses' higher susceptibility to placental dysfunction, their larger size and hormonal status may partly explain the gender disparity in neonatal stroke patients, and that female foetuses might survive better an insult that has probably happened during pregnancy some time before birth.[13,47] More studies of larger PPS cohorts are needed to explore gender distribution in different vascular subtypes of stroke and possible associated risk factors.

4.1. *Limitations and strengths*

The current study is subject to several limitations, including cross–sectional design and moderate sample sizes. The cognitive performance of participants might have been influenced by socioeconomic and demographic factors, which we did not control for. Instead of the qualitative analysis of stroke size used in this study, involvement of cerebral structures and volumetric analysis would be more precise in estimating the extent of stroke.

It is possible that we did not reach full ascertainment of ischemic perinatal stroke, since the diagnosis can only be made with appropriate neuroimaging. Infants who are asymptomatic or have a more favourable/milder outcome, may not undergo neuroimaging and therefore would not be identified. Despite possible missed cases, according to the Estonian epidemiological study, incidence of perinatal stroke shows good coverage. Selection bias could not explain the poor outcomes.

The strengths of the study include a systematic national registry-based sample with up-to-date imaging classification, long follow-up time and application of multiple standardized outcome measures. The neuroradiological classification and qualitative analysis of the extent of stroke used in this study is easily reproducible and could be useful for paediatric neurologists in predicting outcomes and directing surveillance and therapy.

5. Conclusions

In conclusion, the spectrum of neurological morbidity is different after perinatal MCA territory AIS and PVI with combined deficits more common among children following AIS. Poor outcome in the whole cohort suggests that irrespective of the vascular type and time of diagnosis, all children who have suffered perinatal stroke are at risk of neurodevelopmental impairments and need long–term follow–up of motor, cognitive and speech–language functions. Standardized disease–specific outcome measures, such as

the PSOM, that cover all neurodevelopmental areas are valuable in revealing the spectrum of neurological morbidity, but domain–specific assessment methods (e.g. K–ABC–II) complement in estimation of impairment specificity and severity. High prevalence of spastic hemiplegia among children with PVI highlights the need to improve early diagnostics and interventions with rehabilitation aimed at the individual. In addition to parental concerns regarding early motor asymmetries, observations of behavioural changes or specific cognitive/language delays might help to reduce the substantial delay in diagnosis of PPS.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2018.07.005.

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