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ULVI VAHER

Epilepsy after ischemic perinatal stroke in term born children: neuroimaging predictors, clinical course and cognitive outcome

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Epilepsy after ischemic perinatal stroke in term born children: neuroimaging predictors, clinical course and cognitive outcome

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Department of Radiology, Institute of Clinical Medicine, University of Tartu, Tartu, Estonia.

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1 LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original publications that are referred to in the text by their Roman numerals

I. Ulvi Vaher, Norman Ilves, Nigul Ilves, Rael Laugesaar, Mairi Männamaa, Dagmar Loorits, Pille Kool, Pilvi Ilves. Vascular syndrome predicts the development and course of epilepsy after perinatal stroke. Epileptic Disord. 2024 Aug;26(4):471–483. doi: 10.1002/epd2.20239. Epub 2024 May 10. PMID: 38727601.

II. Ulvi Vaher, Norman Ilves, Nigul Ilves, Rael Laugesaar, Mairi Männamaa, Dagmar Loorits, Pille Kool, Pilvi Ilves. The thalamus and basal ganglia are smaller in children with epilepsy after perinatal stroke. Front Neurol. 2023 Sep 28;14:1252472. doi: 10.3389/fneur.2023.1252472. PMID: 37840930

III. Ulvi Vaher, Mairi Männamaa, Rael Laugesaar, Norman Ilves, Nigul Ilves, Dagmar Loorits, Pille Kool, Pilvi Ilves. General ability and specific cognitive functions are lower in children with epilepsy after perinatal ischemic stroke. Front Stroke – Stroke in the Young. Front. Stroke, 13 May 2024. doi: 10.3389/fstro.2024.1371093

Applicant's contributions to papers I–III: Ulvi Vaher was involved in the study design, global outcome assessment, reviewing epilepsy diagnosis and electro-encephalography investigations, data collection, data analysis, and writing of the manuscripts and publishing.

2 ABBREVIATIONS

AIS	arterial ischemic stroke
AT	anterior trunk
CI	confidence interval
CT	computed tomography
DMI	distal M1 middle cerebral artery infarction
EEG	electroencephalography
EPSD	Estonian Pediatric Stroke Database
FCI	Fluid Crystallized Index
HR	hazard ratio
IED	interictal epileptiform discharges
IQR	interquartile range
KABC-II	Kaufman Assessment Battery for Children, Second Edition
LLS	stroke of the lateral lenticulostriate arteries
MCA	middle cerebral artery
MPI	Mental Processing Index
MRI	magnetic resonance imaging
NVI	Nonverbal Index
OR	odds ratio
PMI	proximal M1 middle cerebral artery infarction
PSOM	Pediatric Stroke Outcome Measure
PT	posterior trunk
PVI	periventricular venous infarction

3 INTRODUCTION

Stroke ranked eighth and epilepsy ranked sixth among 37 neurological diseases, causing disability-adjusted life-years per 100,000 children under 5 years of age by The Global Burden of Diseases Study in 2021 (Steinmetz et al. 2024).

Stroke during lifespan is not a single entity. Ischemic perinatal stroke is a group of different conditions where a focal disruption of cerebral blood flow occurs; based on the time of diagnosis, it is classified as fetal, neonatal and presumed perinatal ischemic stroke (Raju et al. 2007). The two main vascular types of ischemic perinatal stroke are arterial ischemic stroke (AIS) and periventicular venous infarction (PVI) (Raju et al. 2007; Kirton et al. 2008). In most cases perinatal AIS occurs in the middle cerebral artery (MCA) territory and is divided into distinct vascular syndromes based on the branch of the artery occluded (Kirton et al. 2008; Wagenaar et al. 2018).

A Canadian population-based study of disease-specific perinatal stroke in 2020 found an overall birth prevalence of 1:1,100 for term-born perinatal stroke, but it was different for distinct stroke entities (Dunbar et al. 2020).

Perinatal stroke causes unfavorable long-term outcome in the majority of these children (deVeber et al. 2017; Lõo et al. 2018; Wagenaar et al. 2018). In a number of cases neurological deficit arises only during follow-up beyond neonatal age (deVeber et al. 2017). The most common complications after perinatal stroke are motor deficit, impaired language, behavior or learning difficulties and epilepsy, which are often combined (Chabrier et al. 2016; Lõo et al. 2018; Wagenaar et al. 2018; Laugesaar et al. 2018). Different neurodevelopmental disorders in children after perinatal stroke lead to parents' depression and family malfunctioning, as well as to the increased economic burden (Bemister et al. 2015; Gardner et al. 2010).

Epilepsy develops in 6–71% of patients with perinatal stroke and can be a key risk factor for impaired non-verbal intelligence after perinatal AIS and presumed perinatal PVI (Billinghurst et al. 2017; deVeber et al. 2017; Laugesaar et al. 2018; Gschaidmeier et al. 2021).

Higher incidence rates of epilepsy following ischemic perinatal stroke have been reported for AIS, but often these apply to patients with AIS and patients with PVI combined, particularly without distinguishing between the various vascular syndromes of AIS (Kirton et al. 2008; Billinghurst et al. 2017; Laugesaar et al. 2018; Sundelin et al. 2021).

Data about more detailed neuroimaging predictors of poststroke epilepsy are controversial. When some authors have found that involvement of the large branch of MCA is associated with development of poststroke epilepsy (M. R. Golomb et al. 2001; Wagenaar et al. 2018; Vojcek et al. 2021), then others have not (Meredith R. Golomb et al. 2007).

Based on radiological evaluation, it has been speculated that simultanous involvement of the deep brain structures and cortex may be associated with development of poststroke epilepsy (Kirton et al. 2008; Billinghurst et al. 2017;

Laugesaar et al. 2018; Ratika Srivastava et al. 2021). However, volumetric studies investigating the thalmus and basal ganglia have only been performed to describe the association between the deep brain structures and motor impairment (Craig, Carlson, and Kirton 2019; Hassett et al. 2022; Nigul Ilves, Lõo, et al. 2022). Therefore, we still do not know which children with perinatal stroke carry higher epilepsy risk and which neuroradiological features are predictive of post-stroke epilepsy.

Outcome studies on cognitive development in children with perinatal stroke have found rather unambiguously lower general cognitive skills compared to healthy children (Anderson et al. 2020; Elgendy et al. 2022). Earlier studies were often carried out by involving patients with both neonatal AIS and childhood AIS, without distinguishing between children with epilepsy and children without epilepsy (Kolk et al. 2011; Li et al. 2022; Jacomb et al. 2018; Anderson et al. 2020). Few studies have focused on finding differences between children with epilepsy and those without epilepsy following perinatal stroke and have found impairment of general cognitive performance and non-verbal functions in children with epilepsy (Fitzgerald et al. 2007; Gschaidmeier et al. 2021).

The current study was undertaken to fill the gap in our knowledge of epilepsy occurring after ischemic perinatal stroke. First, it is essential to determine which children with stroke have higher risk for developing epilepsy and how long the risk persists. Neuroradiological predictors could be the objective early features to rely on when predicting the risk for development of poststroke epilepsy. Second, early targeted intervention requires an understanding of whether long-term cognitive outcome is similar in children following stroke with epilepsy and in children without epilepsy.

4 LITERATURE REVIEW

4.1 Ischemic perinatal stroke: classifications, epidemiology, outcome

Ischemic perinatal stroke is defined as a group of different conditions in which a focal disruption of cerebral blood flow emerges (Raju et al. 2007). The interruption of blood supply is secondary to arterial or venous thrombosis or embolism and should be confirmed by neuroimaging or neuropathologic investigations (Raju et al. 2007).

4.1.1 Classification according to the time of diagnosis

Because the exact time of the vascular incident is almost always unknown, the classification of ischemic perinatal stroke is based on gestational or postnatal age at diagnosis (Raju et al. 2007). Fetal ischemic stroke is diagnosed before birth by using fetal imaging or, in stillbirth, by neuropathologic examination; neonatal ischemic stroke is diagnosed after birth before or on the 28th day of life and presumed perinatal ischemic stroke is diagnosed in infants or children older than 28 days. In presumed perinatal ischemic stroke it is presumed that the ischemic event occurred between the 20th week of fetal life and the 28th postnatal day (Raju et al. 2007).

4.1.2 Classification according to clinical and imaging criteria

Based on clinical and radiological imaging criteria, six specific disease states are recognized: acute presentation of perinatal stroke includes neonatal AIS, neonatal hemorrhagic stroke and neonatal cerebral sinovenous thrombosis; delayed presentation comprises presumed perinatal AIS, presumed perinatal PVI, and presumed perinatal hemorrhagic stroke (Dunbar and Kirton 2018; Fluss, Dinomais, and Chabrier 2019; Ferriero et al. 2019; Ratika Srivastava et al. 2021; R. Srivastava, Mailo, and Dunbar 2022).

4.1.3 Classification according to the vascular syndrome

By consensus definiton, ischemic perinatal stroke can be arterial or venous (Raju et al. 2007). AIS and PVI are the most prevalent vascular types of perinatal stroke (Dunbar et al. 2020). Among AIS up to 90% involves the MCA territory, 9% involves the posterior cerebral artery and only 1% involves the anterior cerebral artery (Wagenaar et al. 2018). Besides this, occlusion of specific arteries and branches of arteries produces characteristic infarcts on neuroimaging and should therefore be differentiated (Govaert et al. 2000; 2009; Kirton et al. 2008). Thus, an anatomic scoring tool for classification of ischemic perinatal stroke was developed and the following arterial and venous vascular syndromes were distinguished: 1) proximal M1 MCA infarction (PMI); 2) distal M1 MCA infarction (DMI); 3) anterior trunk (AT) of MCA infarction; 4) posterior trunk (PT) of MCA

infarction; 5) stroke of the lateral lenticulostriate arteries (LLS); 6) PVI (M. R. Golomb et al. 2001; Kirton et al. 2008; P. Ilves et al. 2016).

4.1.4 Epidemiology of perinatal stroke

A population-based study in 2020 in Canada found an overall birth prevalence of 1:1,100 for term-born perinatal stroke, but it varied widely for different stroke disease entities (Dunbar et al. 2020). For neonatal AIS, the prevalence was 1:3,000, for presumed perinatal AIS, 1:7,900, for presumed perinatal PVI, 1:6,000, but for presumed perinatal hemorrhagic stroke it was only 1:65,000 (Dunbar et al. 2020). A more recent US study has confirmed the prevalence of neonatal AIS to be 1:2,974 (Fraser et al. 2023). In Estonia the overall incidence rate of perinatal stroke was 63.4:100,000 live births in 2007, with 20:100,000 for neonatal stroke and 43.4:100,000 for presumed perinatal stroke (Laugesaar et al. 2007). For children aged 30 days to 18 years, the incidence rate of stroke in Estonia was 2.73:100,000 person-years and for people 45–54 years of age 120.9:100,000 which ranks the perinatal age group second in the risk of stroke (Laugesaar et al. 2010; Kõrv et al. 2021).

4.1.5 Outcome of ischemic perinatal stroke

According to a prospective national population-based study, neurological deficit after neonatal AIS develops in 60% of children and in 39% deficit arises only during later follow-up (deVeber et al. 2017). Another multimodal outcome study revealed some kind of deficit in 59% of children after neonatal AIS at the age of seven years: impaired language occured in 49%, cerebral palsy in 32%, low academic skills in 28%, active epilepsy in 11%, and global intellectual deficiency in 8% of the children (Chabrier et al. 2016). A prospective consecutive cohort study on outcome in term born children after ischemic perinatal stroke found combined deficits of motor, language and cognitive or behavioral functions in 90% of the children with neonatal and presumed perinatal AIS and in 53% of the children with presumed perinatal PVI at the age of seven years (Lõo et al. 2018). Another study of the group of children with presumed perinatal AIS persistent hemiparesis was found in all children, with almost 23% had persistent seizures and 55% had speech, behavior or learning problems (M. R. Golomb et al. 2001). Overall adverse outcome was reported also in all children with perinatal main branch of MCA stroke, while in other AIS subtypes adverse outcome was noted in 29–57% of children (Wagenaar et al. 2018).

4.2 Epilepsy after perinatal stroke

4.2.1 Epidemiology and timing

Epidemiological data about the development of epilepsy after perinatal stroke vary between studies. Depending mainly on the studied perinatal stroke syndromes and the length of follow-up, epilepsy develops in 6–71% of children with perinatal stroke (Laugesaar et al. 2018; Billinghurst et al. 2017; deVeber et al. 2017). A retrospective study of prenatal and neonatal AIS with different cerebral vascular territories, including 40/64 with unilateral MCA infarction and the rest with strokes in other cerebral artery territories or bilateral strokes, found that epilepsy developed in 46% of the patients by the median age of 43 months (Meredith R. Golomb et al. 2007). A more recent work on perinatal AIS with about the same follow-up time (i. e. median 41.7 months), comprising 90% of the patients with MCA territories infarction, discovered epilepsy in only 12% (Wagenaar et al. 2018). In a single-center prospective study the estimated cumulative incidence of poststroke epilepsy at two years was 11% in neonatal AIS and 19% in presumed perinatal AIS (Billinghurst et al. 2017). A nationwide population-based Swedish study on pediatric ischemic stroke found an overall epilepsy incidence rate of 27.0 per 100,000 person-years in ischemic perinatal stroke (Sundelin et al. 2021). A preliminary study addressing poststroke epilepsy in perinatal stroke in Estonia found that epilepsy developed most often after neonatal AIS (71%), following presumed perinatal AIS (50%), neonatal hemorrhagic stroke (20%), and presumed perinatal PVI (6%) with a median follow-up time 8.6 years (Laugesaar et al. 2018). A summary epilepsy incidence of 27.2% over a mean follow-up time of 10.4 years in perinatal AIS was established in a meta-analysis which included ten studies (Rattani et al. 2019).

Studies evaluating the timing of poststroke epilepsy have shown that at three years the Kaplan-Meier probability of remaining seizure-free was 73% in patients with neonatal AIS; and in patients with perinatal AIS the estimated cumulative incidence of epilepsy was 55% by 10 years of age, increasing only slightly over the following 10 years (Wanigasinghe et al. 2010; Wusthoff et al. 2011). A larger population-based study with a median follow-up time of 8.7 years after stroke found that risk of epilepsy after ischemic stroke was the highest within the first six months, but was still elevated in young adults; however that study involved patients with perinatal ischemic stroke and childhood ischemic stroke and did not differentiate between the vascular syndromes of ischemic stroke (Sundelin et al. 2021). Thus, although several studies have addressed the timing of epilepsy after stroke, the median follow-up time has been no longer than 10 years and these studies have addressed the different types of stroke in combination.

4.2.2 Risk factors of poststroke epilepsy

A meta-analysis of ten studies of perinatal AIS identified seven possible risk factors for poststroke epilepsy: smaller hippocampal volume, infarct detected on

prenatal ultrasound, a modified Alberta Stroke Program Early Computed Tomography score of ≥ 9, family history of seizures, development of cerebral palsy, and initial presentation with cognitive impairment or seizures (Rattani et al. 2019). There are also data indicating that more severe motor impairment, term delivery, neonatal seizures, and clinical evidence of neonatal infection or inflammation may be associated with development epilepsy (Wanigasinghe et al. 2010; Fox et al. 2016; Vojcek et al. 2021).

4.2.3 Course and outcome of epilepsy after ischemic perinatal stroke

There are only a few studies describing the course of epilepsy after ischemic perinatal stroke. These data show general favorable outcome of epilepsy after perinatal AIS where at 10 years from seizure onset only 15% of patients had active epilepsy, or after neonatal AIS where at seven years of age the prevalence of active epilepsy was 11% (Wanigasinghe et al. 2010; Chabrier et al. 2016). Poor control of epilepsy in the group of perinatal AIS was found in only 17% of children with poststroke epilepsy also in another study (Wanigasinghe et al. 2010). The parents of children with perinatal or childhood stroke have reported worse scores of physical, social, and school scales but also fatigue dimensions in children with epilepsy compared to children without epilepsy (S. E. Smith et al. 2015). More reports about the course of epilepsy after ischemic perinatal stroke are needed to plan the treatment and follow-up of patients with epilepsy.

4.3 Neuroimaging predictors of poststroke epilepsy

4.3.1 Vascular syndrome

Different neuroimaging predictors of poststroke epilepsy have been described without persistent consensus. An earlier study with limited participants showed that among children with a delayed diagnosis of perinatal AIS, four of the five patients with epilepsy had large branch territory infarctions (M. R. Golomb et al. 2001). Still, research into neonatal AIS with different vascular territories (incl. MCA, anterior cerebral artery and posterior cerebral artery) found that bilateral infarction or involvement of the large branch of MCA was not significantly associated with development of seizures after neonatal age (Meredith R. Golomb et al. 2007). In another study on neonatal AIS postneonatal epilepsy was most often presented in the group of main MCA infarction and, additionally, involvement of the cerebral pedunculi and bilateral lesions was independently associated with postneonatal epilepsy (Wagenaar et al. 2018). In children with neonatal AIS with neonatal seizures the location of stroke in the right MCA and multiple territories were significant risk factors for poststroke epilepsy (Suppiej et al. 2016). A recent study of neonatal AIS revealed significant association between the main branch of MCA infarction and epilepsy, as well as between epilepsy and

multiple strokes, defined as involvement more than one branch of the MCA (Vojcek et al. 2021).

4.3.2 Subcortical gray matter structures

A consecutive cohort study of presumed perinatal ischemic stroke, comprising different vascular syndromes of AIS and PVI, established that development of epilepsy was associated with cortical involvement, and involvement of the basal ganglia was associated with adverse motor outcome (Kirton et al. 2008). In a preliminary study of the different vascular subtypes conducted by our research team, cortical lesions, involvement of the thalamus and temporal lobe were independently associated with poststroke epilepsy in children with neonatal and presumed perinatal stroke (Laugesaar et al. 2018). A study on pediatric AIS, comprising both perinatal and childhood AIS, found that after neonatal AIS and presumed perinatal AIS remote symptomatic seizures and epilepsy occurred more often than after childhood AIS (Billinghurst et al. 2017). As in neonatal AIS infarcts were more likely to be multifocal or bilateral and in presumed perinatal AIS infarcts involved more often the basal ganglia, the authors speculated that simultanous involvement of the cortex and basal ganglia is more likely to lead to epilepsy (Billinghurst et al. 2017). The above these studies indicate that in the case of damage to different brain structures after perinatal stroke, outcome may be different; also these studies highlight the need for more detailed investigations of the neuroimaging predictors of poststroke epilepsy.

4.4 Volume studies of subcortical gray matter structures in epilepsy

4.4.1 Volume studies of subcortical gray matter structures in childhood epilepsy syndromes

Magnetic resonance fingerprinting has revealed tissue-property changes in the visually normalappearing thalamus and basal ganglia, with ipsilateral predominance and thalamic preference in pediatric and adult patients with focal epilepsies, which suggest the involvement of subcortical structures in patients with focal epilepsies (Tang et al. 2022). A volumetric study of different childhood epilepsies, excluding secondary epilepsies, revealed atrophy of the brain, particularly of the deep brain structures (putamen, thalamus, hippocampus and nucleus accumbens), while significant differences, compared to control, were found for the brain, lateral ventricle and putamen (Woźniak et al. 2022). In the case of mesial temporal epilepsy in young adults, volume quantitative analysis showed, besides bilateral hippocampal volume loss, also a bilateral reduced thalamic volume (Wu et al. 2020). A comprehensive review of voxel-based morphometry in patients with temporal lobe epilepsy (age not specified) analyzed 26 brain regions in relation to epilepsy and found changes most often in the hippocampus, but also in the

thalamus (Keller and Roberts 2008). The same study established that changes in the extratemporal structures, preferentially in the thalamus, were much more bilaterally distributed (Keller and Roberts 2008).

4.4.2 Volumetry of the thalamus, basal ganglia and hippocampus in epilepsy after perinatal stroke

Based on visual assessment, involvement of the thalamus and basal ganglia has been associated with development of poststroke epilepsy (Kirton et al. 2008; Billinghurst et al. 2017; Laugesaar et al. 2018; Ratika Srivastava et al. 2021). So far, volumetric studies have been aimed to describe the association of the size of thalamus and basal ganglia with motor impairment after perinatal stroke (Craig, Carlson, and Kirton 2019; Wiedemann et al. 2020; Hassett et al. 2022; Nigul Ilves, Lõo, et al. 2022). Only one study has described a reduction in the hippocampal volume of patients with epileptic seizures after perinatal AIS (Gold and Trauner 2014). Therefore, there is urgent need for volumetric studies addressing the relationship between the volume of the subcortical gray matter structures and epilepsy after ischemic perinatal stroke.

4.5 Cognitive outcome

4.5.1 General ability and specific cognitive functions in perinatal stroke

Studies on neonatal and childhood stroke have shown lower general cognitive skills already at 12 months post stroke, which remain relatively stable at the time of long-term follow-up at a mean age of 12.5 years, compared to typically developing children (Jacomb et al. 2018; Anderson et al. 2020). Although one study suggests that children with neonatal stroke perform better than children with early childhood stroke (i.e. 29 days to <6 years), the data of long-term outcome indicate that among children with neonatal stroke the deficit may appear in 39% only during longer follow-up (deVeber et al. 2017; Abgottspon et al. 2022). A mild or severe developmental delay was present in one fifth of children after neonatal stroke at two years, and in children with perinatal stroke cognitive performance was significantly lower compared to normative means at a mean age of 9.9 years (Elgendy et al. 2022; Li et al. 2022).

Among the specific cognitive functions, attention and executive functions seem to be negatively affected the most (Bosenbark et al. 2017; Li et al. 2022; Champigny et al. 2023). Another study on long-term outcome in different cognitive domains found that although attention was affected, children with neonatal stroke performed tasks on executive function at the same level as the children of the control group (Kolk et al. 2011). The most severely impaired cognitive area was the sensorimotor domain followed by the visuospatial and language domains (Kolk et al. 2011). Verbal learning and language deficit has been found in

different studies involving children with perinatal stroke or children with both neonatal stroke and childhood stroke (Ballantyne et al. 2008; Anderson et al. 2020; Abgottspon et al. 2022; Nigul Ilves, Männamaa, et al. 2022; Heimgärtner et al. 2024). Even when in most children with perinatal stroke language activation is reorganized to the unlesioned hemisphere, this can not ensure normal language outcome (Nigul Ilves, Männamaa, et al. 2022).

4.5.2 Cognitive outcome in childhood epilepsy syndromes

General cognitive deficit and impairment of specific cognitive functions are described in different studies with distinct childhood epilepsies. A large population-based study on childhood epilepsies found mild to profound mental impairment in 35% of the children; and additionally 20% of the children had a speech disorder or learning difficulties (Sokka et al. 2017). Patients with childhood epilepsy have worse results in most cognitive tasks already after the first seizure and cognitive impairment may be even more severe at long-term follow-up (Fastenau et al. 2009; Domańska et al. 2023). Adult patients with childhood onset epilepsy without remission exhibited worse performance in language and semantic functions, but also in visuomotor function, compared to those in remission and healthy controls (Karrasch et al. 2017). Deficit in executive function is the most frequently reported impairment in patients with focal and generalised childhood onset epilepsies (Cheng et al. 2017; Cainelli et al. 2021; Domańska et al. 2023). The other affected domains are attention, memory and visuomotor functions (Matricardi et al. 2016; Karrasch et al. 2017; Cainelli et al. 2021; Domańska et al. 2023). Usually, associated language problems are not infrequent, but some data indicate normal language processing (Karrasch et al. 2017; Savaş et al. 2020; Teixeira, Santos, and Oom 2020). Over 40% of children with early-onset epilepsy display difficulties in two or more neurobehavioral domains (Hunter et al. 2019).

4.5.3 General ability and specific cognitive functions in children with ischemic perinatal stroke and epilepsy

Available data about targeted research focusing on cognitive outcome in children with epilepsy after ischemic perinatal stroke is scanty. Some authors have found the adverse effect of epilepsy on the performance of attention and executive functions in children with perinatal stroke with epilepsy compared to children with perinatal stroke without epilepsy, or have speculated that these results may have been affected by the presence of epilepsy (Kolk et al. 2011; Bosenbark et al. 2017; Li et al. 2022; Champigny et al. 2023). In the group of children with presumed perinatal stroke cognitive impairment at a last follow-up of 58 months was associated with epilepsy (Fitzgerald et al. 2007). A study of patients with perinatal AIS or PVI, but from which the patients with a previous diagnosis of intellectual disability or with active seizures were excluded, found that epilepsy was the only sigificant risk factor for impaired non-verbal intelligence (Gschaidmeier et al. 2021). Worse scores in receptive language and externalizing behviors have also

been recorted for children with perinatal stroke with abnormal electroencephalography (EEG) (Mineyko et al. 2017). It is clear that more studies are needed in different cognitive domains, involving children who have developed epilepsy after ischemic perinatal stroke and comparing them with children who have not developed epilepsy after stroke.

4.6 Summary of the literature review

The perinatal period is the second most frequent age group at the risk of stroke before the age of 54 years. Ischemic perinatal stroke comprises different conditions of the focal disruption of cerebral blood flow and is divided into distinct syndromes depending on the time of diagnosis, imaging criteria and vascular territories affected. After perinatal stroke children experience difficulties in motor, language and cognitive or behavioral functions and about one third of them develop epilepsy. The parents of children with perinatal stroke bear a higher social and psychological burden, particularly in families where the child has additionally poststroke epilepsy.

The incidence rate of epilepsy after perinatal stroke varies widely between studies. Epilepsy develops more often after AIS than after PVI, but as AIS involves different vascular syndromes which cause distinct patterns of brain injury, it may determine outcome. Previous data suggest that large branch of MCA infarction may be associated with epilepsy, but targeted research on the vascular syndrome of perinatal stroke and epilepsy is scarce. Therefore, it is still unclear which vascular syndrome of ischemic perinatal stroke carries higher risk of epilepsy and how long epilepsy risk persists.

Based on radiological evaluation, earlier studies have demonstrated association between the changes of basal ganglia and epilepsy following perinatal stroke. Former volumetric studies on subcortical structures have been performed in association with motor outcome. Nevertheless, there are no volumetric data about the size of the thalamus and basal ganglia in children with epilepsy after ischemic perinatal stroke compared to children without epilepsy, as well as compared to typically developed children.

Several studies have shown deficit in general cognitive ability or in special cognitive domains in children after stroke compared to typically developed children. The issue of how children with epilepsy after ischemic perinatal stroke perform compared to children with stroke but without epilepsy still requires more research.

All these areas of research, i.e. the vascular syndrome of stroke and the volume of subcortical gray matter structures in relation to poststroke epilepsy, the course of epilepsy, as well as the features of the cognitive profile of children with poststroke epilepsy, are equally crucial in identifying children who are at the greatest risk of epilepsy, and in order to plan the follow-up and timely treatment of epilepsy, and early rehabilitation of children with ischemic perinatal stroke.

5 AIMS OF THE STUDY

The general aim of the study was to investigate development of epilepsy after ischemic perinatal stroke, in order to find out the neuroradiological predictors of epilepsy and the course of epilepsy, and to describe the cognitive profile of children with poststroke epilepsy.

We hypotesized that in different vascular syndroms of ischemic perinatal stroke and with different patterns of change in the subcortical gray matter structures the probability of having epilepsy as well as the cognitive outcome in children with epilepsy compared to children without epilepsy are different.

The specific aims were:

1. To evaluate which vascular syndrome of ischemic perinatal stroke has higher probability for developing poststroke epilepsy and affects the course of epilepsy (Paper I).

   Hypothesis: Epilepsy develops more often in children with PMI or DMI, compared to children with AT or PT infarction, or compared to children with PVI.

2. To evaluate the volume of the thalamus, basal ganglia and hippocampus in children after ischemic perinatal stroke in relation to poststroke epilepsy (Paper II).

   Hypothesis: The size of the ipsilesional thalamus, basal ganglia, and hippocampus is smaller in children with perinatal stroke who develop epilepsy compared to children who do not develop epilepsy and compared to healthy controls.

3. To evaluate general and specific cognitive functions in children with epilepsy and in children without epilepsy after ischemic perinatal stroke (Paper III).

   Hypothesis: Children with poststroke epilepsy have lower general cognitive ability compared to children without epilepsy, while the profile of their specific cognitive functions may be variable.

6 Subjects and Methods

6.1 Study population

The study population comprised children with ischemic perinatal stroke from the Estonian Pediatric Stroke Database (EPSD).

This study is part of a larger research on outcome in children with ischemic perinatal stroke identified from the EPSD (Laugesaar et al. 2007; P. Ilves et al. 2016; Laugesaar et al. 2018; Lõo et al. 2018; Nigul Ilves, Lõo, et al. 2022; Norman Ilves, Laugesaar, et al. 2022). The last date for the recruitment from the EPSD was June 15, 2022.

6.1.1 Estonian Pediatric Stroke Database

Data in the EPSD was collected retrospectively within an epidemiological study from 1994 to 2003 and prospectively from 2004 (Laugesaar et al. 2007; P. Ilves et al. 2016; Lõo et al. 2018; Nigul Ilves, Männamaa, et al. 2022; Norman Ilves, Laugesaar, et al. 2022). All children with pediatric stroke admitted to the Children's Clinic of Tartu University Hospital are included in the EPSD.

The EPSD involves radiological data and clinical data about pregnancy and birth history and symptoms during the neonatal period of the patients with perinatal stroke.

All radiological images (cerebral ultrasonography, computed tomography (CT) and MRI) are stored in the population-based Estonian Picture Archive from 2006. The images for the patients in the EPSD were independently reviewed by three neuroradiologists, who were blinded to clinical outcome. They confirmed the diagnosis of perinatal stroke and classified it according to the vascular type based on previous classifications of ischemic perinatal stroke (Raju et al. 2007; P. Ilves et al. 2016; Kirton et al. 2008).

The exclusion criteria for the EPSD are: absence of conformative cranial imaging (MRI or CT); structural disease other than stroke affecting the central nervous system (hypoxic-ischemic encephalopathy, central nervous system's infectious disease, tumor, cortical malformation, congenital anomaly), suggested on the basis of neuroimaging and clinical presentation.

6.1.2 General inclusion criteria

The general inclusion criteria for each substudy were: 1) MRI or CT confirmed diagnosis of unilateral ischemic perinatal stroke: neonatal AIS, presumed perinatal AIS or presumed perinatal PVI; 2) birth at gestational age ≥36 weeks.

The exclusion criteria were: 1) structural disease other than stroke affecting the central nervous system (hypoxic-ischemic encephalopathy, central nervous system's infectious disease, tumor, cortical malformation, congenital anomaly); 2) specific disease-causing gene variant or copy number variant suggested to be pathogenic for epilepsy, or developmental delay. Specific inclusion and exclusion criteria were established for each substudy.

6.1.3 Inclusion criteria for Paper I

The study participants identified from the EPSD fulfilled all of the general inclusion criteria and additionally the specific inclusion criteria of a clinical follow-up of at least 18 months.

The initial study group consisted of 87 term born children with ischemic perinatal stroke. Four patients were lost to outcome investigations after the diagnosis of stroke. The final study group involved 83 patients (83/87, 95%) with ischemic perinatal stroke: 39/83 (47%) patients with AIS (22 patients with neonatal AIS and 17 patients with presumed perinatal AIS) and 44/83 (53%) patients with presumed perinatal PVI (*Figure 1)*.

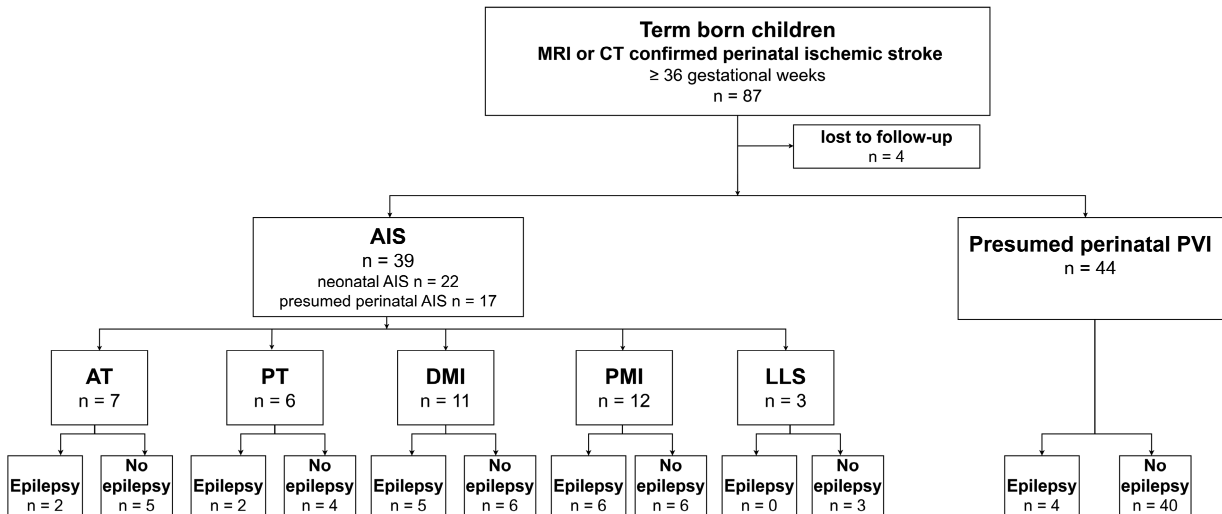

Figure 1. Patient selection (Paper I) (Vaher, Ilves, et al. 2024) (published with permission from John Wiley & Sons).
AIS–arterial ischemic stroke, PVI–periventricular venous infarction, AT–anterior trunk of distal middle cerebral artery (MCA) infarction, PT–posterior trunk of distal MCA infarction, DMI–distal M1 MCA infarction, PMI–proximal M1 MCA infarction, LLS– stroke of the lateral lenticulostriate arteries

6.1.4 Inclusion criteria for Paper II

The study participants identified from the EPSD fulfilled all of the general inclusion criteria and all specific inclusion criteria as follows: 1) follow-up 3T MRI scan including 3D T1 weighted imaging at the age of 6–18 years; 2) clinical follow-up of at least 4 years.

The initial study group involved 86 term born children with ischemic perinatal stroke. Four patients were lost to follow-up investigations after the diagnosis of stroke. Fourteen patients were excluded due to the age criteria and six patients refused to participate in the outcome study. The final study group consisted of 62 children with ischemic perinatal stroke (62/86, 72%): 15/62 (24.2%) patients with neonatal AIS, 14/62 (22.6%) patients with presumed perinatal AIS and 33/62 (53.2%) patients with presumed perinatal PVI (*Figure 2)*. The control group consisted of 46 healthy volunteers of age and sex matched children recruited from among the coworkers' relatives.

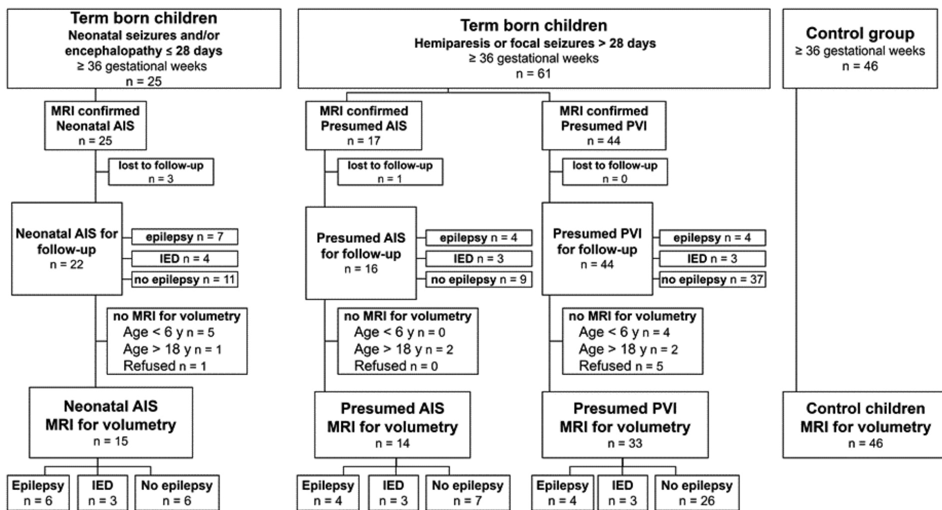

Figure 2. Patient selection (Paper II) (Vaher et al. 2023) (published with permission from Frontiers). AIS–arterial ischemic stroke, PVI–periventricular venous infarction, IED–interictal epileptiform discharges

6.1.5 Inclusion criteria for Paper III

The study participants identified from the EPSD fulfilled all of the general inclusion criteria and all specific inclusion criteria as follows: 1) follow-up 3T MRI scan beyond neonatal age; 2) assessment of cognitive outcome at the age of ≥7 years; 3) EEG investigation beyond neonatal age.

The initial study group involved 87 term born children with ischemic perinatal stroke. Four children were lost to follow-up investigations after the diagnosis of stroke. Six patients were excluded due to the age criteria; for 16 patients, cognitive assessment was missing and for nine patients, EEG was missing. One patient with PVI from the group of epilepsy was not able to perform cognitive assessment due to very poor cognitive abilities and was excluded from the final study group. The final study group consisted of 51/87 (58.6%) children: 37/51 (72.5%) patients without epilepsy, including 11/37 (29.7%) with interictal epileptiform discharges (IED) and without seizures, and 14/51 (27.4) patients with epilepsy *(Figure 3).*

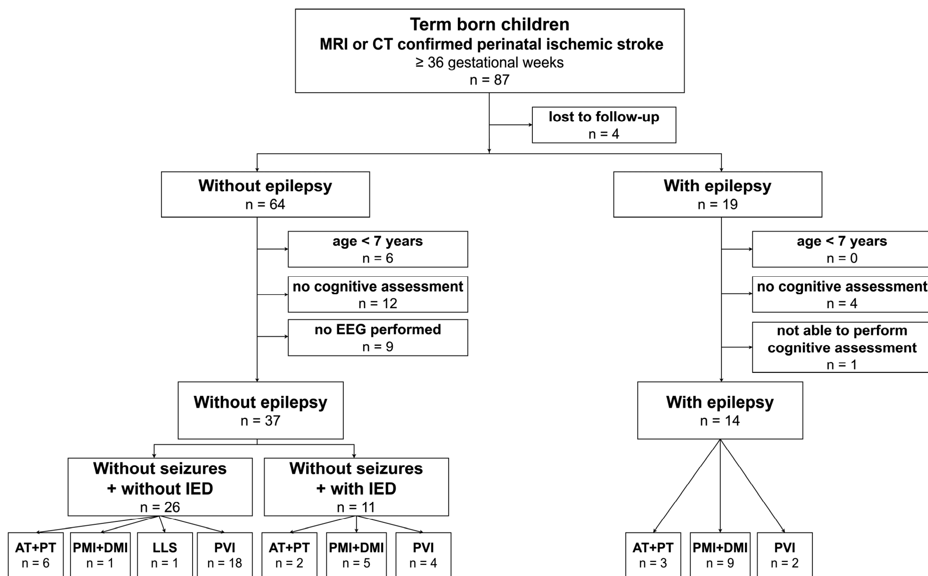

Figure 3. Patient selection (Paper III) (Vaher, Männamaa, et al. 2024) (published with permission from Frontiers). EEG–electroencephalography, IED–interictal epileptiform discharges, AT–anterior trunk of distal middle cerebral artery (MCA) infarction, PT–posterior trunk of distal MCA infarction, PMI–proximal M1 MCA infarction, DMI–distal M1 MCA infarction, LLS–stroke of the lateral lenticulostriate arteries, PVI–periventricular venous infarction

6.2 Methods

6.2.1 Clinical data

All children who fulfilled all general inclusion criteria and all specific inclusion criteria for the each substudy were invited to participate in the study by phone call.

Clinical information of the study patients was collected from medical records and patient interviews. Data about pregnancy and birth history, symptoms during the neonatal period, including neonatal seizures, age at the first epileptic seizure and age at the epilepsy diagnosis, EEG features, seizure semiology, antiseizure medication, seizure control, and presence of the status epilepticus and spike-wave activation in sleep were recorded for this study. According to definition, neonatal seizures were diagnosed on the basis of epileptiform activity on EEG as sudden, stereotype, and developing episode of abnormal electrographic activity with an amplitude of at least 2 μV and a minimum duration of 10 seconds, which might or might not be accompanied with clinical manifestation (Abend and Wusthoff 2012). In one patient from the AIS group neonatal seizures were diagnosed based on clinical features alone.

For Kaplan-Meier estimation, presence of epilepsy was ascertained also from the national digital Health Portal which provides patients' health and prescriptions' data in case the on-site visit was not possible. The last date for the diagnosis and outcome of epilepsy was June 14, 2023.

6.2.2 Radiological evaluation

Follow-up MRI after neonatal age for the study group (n=83) was performed with a 3T Philips Achieva MRI scanner with the 8-channel SENSE head coil (Philips Medical Systems, Best, The Netherlands). In 66/83 (79.5%) children MRI was performed without anesthesia at the age of 6–18 years, in 14/83 (16.9%) children postneonatal MRI with anesthesia, done earlier for clinical purposes, was resorted to, and in one child with AIS neonatal MRI at the age of six days was used for vascular classification. In 2/83 (2.4%) cases only CT was available for diagnosis and follow-up evaluation.

6.2.2.1 Anatomical and vascular classification

Three neuroradiologists, who were blinded to the clinical outcome of the patients, independently reviewed all MRI and CT images performed at the time of the diagnosis of perinatal stroke and during follow-up. The diagnosis of vascular syndrome was based on consensus agreement and a previous classification (Raju et al. 2007; Kirton et al. 2008; P. Ilves et al. 2016).

Based on age at the time of diagnosis, the subcategories of ischemic perinatal stroke in our study were: 1) neonatal ischemic stroke, diagnosed after birth before or on the 28th postnatal day; 2) presumed perinatal ischemic stroke, diagnosed in

infants older than 28 days, presuming that the ischemic event occurred from the 20th week of gestational age through the 28th postnatal day (Raju et al. 2007).

The study comprised three main perinatal stroke specific subtypes: neonatal AIS, presumed perinatal AIS and presumed perinatal PVI (Dunbar and Kirton 2018; Fluss, Dinomais, and Chabrier 2019).

Based on anatomical and vascular classifications, the following arterial and venous vascular syndromes were recognized: 1) PMI including the proximal MCA territory with lenticulostriate arteries, resulting in basal ganglia and distal MCA infarction, 2) DMI resulting in distal MCA territory infarction, but sparing the basal ganglia; 3) AT of distal MCA infarction as superior MCA division infarction comprising the frontal lobe anterior-to-central sulcus and the anterior temporal lobe; 4) PT of distal MCA infarction as inferior MCA division infarction comprising the parietal and posterior temporal lobes; 5) LLS affecting the basal ganglia and the posterior limb of the internal capsule, and 6) PVI as periventricular white matter medullary venous territory infarction affecting the basal ganglia to some degree and sparing the cortex (Kirton et al. 2008).

6.2.2.2 Volumetric analysis by segmentation (Paper II)

Volumetric analysis by segmentation was performed as described in an earlier study (Nigul Ilves, Lõo, et al. 2022). First, structural T1-weighted images with isotropic 1x1x1 mm voxels were obtained using a fast field echo sequence with TR=8.2ms, TE=3.8ms and a field of view of 256x256mm. The images were anonymized and right-side lesions were flipped along the x-axis after which all lesions were analyzed as left-side lesions.

The investigated subcortical gray matter structures were: thalamus, caudate nucleus, putamen, globus pallidus, hippocampus, amygdala and nucleus accumbens in both hemispheres. Analysis was performed using the FMRIB Software Library (FSL) (https://www.fmrib.ox.ac.uk/fsl/) version 6.0.5. For initial segmentation of the subcortical gray matter structures, the automatic segmentation tool FSL FIRST was used (Patenaude et al. 2011). After automatic segmentation, manual segmentation and quality control were done to correct the faults produced by stroke related morphologic changes. Manual segmentation was performed, using the FSL's tool FSLeyes version 1.4.5 in randomized subject order, by a single investigator who was blinded to the study group and the clinical outcome. The volume of the segmented structures was measured using the FSL's tool fslstats. Further, the measured volumes were normalized based on the individual's head size using an individual volumetric scaling factor generated by the FSL's SIENAX tool which allowed to convert the subject's brain volume to MNI152 standard space volume (S. M. Smith et al. 2002; Nigul Ilves, Lõo, et al. 2022).

For consistency of the measurement of the subcortical stuctures, a subset of children was formed for inter- and intrarater evaluation by selecting 50% of the children from each study group (AIS, PVI and control), using simple random sampling and taking account of the proportion of children with epilepsy. The

manual segmentation of the subset was repeated after four months by two investigators who were blinded to the previous segmentations and to each other.

6.2.3 Epilepsy and electroencephalography

6.2.3.1 Epilepsy diagnosis and outcome

Epilepsy was diagnosed using the criteria proposed by the International League Against Epilepsy (Fisher et al. 2014). In this study epilepsy was diagnosed if one of the following conditions was met: at least two unprovoked seizures occurring >24 hours apart or one unprovoked seizure with high recurrence risk (Fisher et al. 2014). The current study defined high recurrence risk if a single seizure occurred at least one month after stroke and was accompanied with epileptiform changes on EEG and structural changes on MRI. All epilepsy diagnoses and also EEG investigations from 2005 onwards were reviewed by the applicant.

A modified version of the Engel classification was used to describe the course and outcome of epilepsy: Class 0–seizure free and without antiseizure medications for at least six months; Class 1–seizure free, but on medication, or seizure free without antiseizure medications for less than six months; Class 2–less than one seizure a month; Class 3–one to four seizures a month; Class 4–5–30 seizures a month; Class 5–over 30 seizures a month (Meredith R. Golomb et al. 2007; Laugesaar et al. 2018).

Status epilepticus was defined as a condition leading to prolonged seizures and diagnosed using a time point of five minutes for bilateral tonic-clonic status epilepticus and 10 minutes for focal status epilepticus with impaired consciousness (Trinka et al. 2015).

Drug resistant epilepsy was diagnosed if two tolerated and appropriately chosen and used antiepileptic drug schedules failed to achieve sustained seizure freedom (Kwan et al. 2010).

Complicated epilepsy was defined as a modified Engel class of ≥3 or a history of status epilepticus or a history of spike-wave activation in sleep ≥85% or drug resistant epilepsy (Laugesaar et al. 2018).

6.2.3.2 Electroencephalography

EEG was performed as part of follow-up evaluation in case it had not been done after the period of infancy for clinical indications. EEG investigations from 2005 to 2011 are stored on digital video discs and from 2011 onwards in the digital neurophysiology database of Tartu University Hospital.

A standard protocol for postneonatal EEG included awake and sleep (daytime nap) periods. An international full 10–20 electrode placement system was used for investigation (Kuratani et al. 2016).

Focal IED were defined as transient epileptiform activity manifesting itself in up to two electrodes consistent with the same anatomical location. Regional IED were defined in case IED appeared in more than two electrodes, but in the same hemisphere, and in case of bilateral IED epileptiform activity was present in both

hemispheres. For localization of changes in background activity, the same classification was used as for IED.

Spike-wave activation in sleep or former electrical status epilepticus in sleep was defined as an EEG pattern which consists of continuous spike-and-slow-waves during sleep, affecting ≥85% of it (Kane et al. 2017; Specchio et al. 2022). For this, spike wave index was calculated (Tassinari et al. 2000). To calculate spike-wave index, EEG investigation was first empirically evaluated, and if estimated spike-wave index in sleep was over 50%, then the recording was browsed manually, defining the spike-wave percentage as at least one spike-wave complex per second during non-rapid eye movement sleep stage II evaluated for 10 minutes.

Based on epilepsy diagnosis and EEG findings, patients with perinatal stroke for Paper II and Paper III, were divided into three groups: a) group with epilepsy–patients with confirmed epilepsy diagnosis; b) group with IED–patients with epileptiform activity on EEG but without clinical seizures; c) group without epilepsy–patients without epilepsy or interictal EEG activity. A pooled group was formed on the basis of the epilepsy and IED groups for Paper II.

6.2.5 Outcome assessment

6.2.5.1 Global outcome assessment

Global outcome evaluation was made by a child neurologist at the time of an on-site visit using Pediatric Stroke Outcome Measure (PSOM) (Kitchen et al. 2012). It contains five subscales for measurement of neurological deficit and function: right sensorimotor, left sensorimotor, language production, language comprehension, and cognitive/behavior performance. Each subscale yields a deficit severity score: 0–no deficit, 0.5–mild deficit or normal function, 1–moderate deficit or impaired function, and 2–severe deficit or missing function.

6.2.5.2 Cognitive evaluation (Paper III)

Cognitive assessment was made by a trained clinical psychologist during a single visit by using the Kaufman Assessment Battery for Children, Second Edition (KABC-II) (Kaufman et al. 2005).

Three global scores of general cognitive ability were calculated. Fluid Crystallized Index (FCI) is the global score measuring general mental processing ability including acquired knowledge. Mental Processing Index (MPI) measures general mental processing ability, but excludes measures of acquired knowledge. Nonverbal Index (NVI) comprises a mixture of subtests that can be administered without verbal instructions and is responded motorically.

Additionally, five subscales were used to evaluate specific cognitive functions and to calculate specific index scores for describing the distinctive cognitive profile. The sequential processing subscale subtests are based on serial orders; they are temporally related to the preceding ones and measure sequential infor-

mation processing and short-term memory. The simultaneous processing subscale consists of subtests that require simultaneous processing with perceiving, manipulating, and thinking via visual patterns. The learning subscale covers cognitive abilities involved in the storing and retrieving newly or previously learned information, placing a premium on the attention-concentration process. The planning subscale contains subtests that measure high level cognitive abilities, such as decision-making, executive functions, problem solving and reasoning. The knowledge subscale relates to verbal abilities and acquired knowledge from one's own culture.

Age-appropriate standard scores (M=100, SD=±15) were used for measurement of general cognitive ability and specific index scores.

6.3 Statistical analysis

The statistical package SAS version 9.4 (SAS Institute, Cary, NC) and the R Statistical Software (version 4.0.2) were used for statistical analysis.

Normality of data was evaluated using the Shapiro-Wilk test. Continuous data were summarized as means with the 95% confidence interval (CI) or medians with the interquartile range (IQR), and categorical data, as absolute counts and percentages. The groups were compared employing one-way analysis of variance (ANOVA) F test for continuous variables and using Kruskal-Wallis or Welch's test (ANOVA) when data were not normally distributed, or when variances were not equal between the groups. If significant, post-hoc pairwise comparisons were examined using ANOVA Student's t method or the Mann-Whitney U test for continuous variables (as appropriate). For qualitative variables, the Chi-square test and Fisher's Exact test (when expected values were <5) were employed. All p-values were two-sided. The odds ratio (OR) and the 95% CI were used to estimate the measure of association.

6.3.1 Kaplan-Meier estimation (Paper I)

The Kaplan-Meier estimation of the proportion of subjects at any point during follow-up was employed. For calculation of cumulative incidence, age at the first epileptic seizure was used. Median follow-up time, whose calculation was based on the reverse Kaplan-Meier estimator, was the indicator of the length of follow-up (Schemper and Smith 1996). The Cox proportional hazards regression and the log-rank statistics were used to assess differences between the survival curves.

6.3.2 False discovery rate procedure (Papers II and III)

Multiple testing in each family of tests (Paper II: 12 demographic and clinical characteristics, 14 volume outcomes; Paper III: 8 cognitive function scores) was corrected using the false discovery rate linear step-up procedure (Benjamini and Hochberg 1995). The Benjamini-Hochberg critical values were calculated as $(i/m)Q$, where i is the rank in an ascending list of p values, m is the total number

of tests, and Q is a false discovery rate of 0.05. After significant global tests, post-hoc tests were performed using the Benjamini-Hochberg method.

6.3.3 Inter- and intra-observer variation (Paper II)

A subset of children was formed for inter- and intrarater evaluation by selecting 50% of the children from each study group (AIS, PVI and control), using simple random sampling and taking account of the proportion of children with epilepsy. For each child, inter- and intra-observer variation was calculated as the absolute value of the difference between two measurements of the thalamus, basal ganglia and hippocampus, divided by the value of the first measurement multiplied by 100 (Bunting et al. 2019). Inter- and intra-observer reliabilities were estimated as the mean of the percentage of the relative difference with a volume range for the segmented structures. The mean (range) inter-observer variation was 3.3% (2.2%–5.4%) and the mean (range) intra-observer variation was 4.4% (1.8%–6.4%) for all segmented structures. For the size of the thalamus, the mean (range) inter-observer variation was 1.8% (0.4%–3.3%) and the mean (range) of intra-observer variation was 3.0% (1.5%–4.4%).

6.4 Ethical approval and declarations

The research was conducted in accordance with the ethical standards of the University of Tartu on human experimentation and with the Helsinki Declaration of 1964 and its later revisions.

The Research Ethics Committee of the University of Tartu approved the research: protocol no 170/T-17 (from April 28, 2008); no 254/M-25 (from December 21, 2015), no 267/M-17 (from February 20, 2017); no 294/M-18 (from June 17, 2019); no 373/T-10 (from January 16, 2023).

Written informed consent was provided by all parents and individual participants older than seven years who were able to read.

7 RESULTS

7.1 Vascular syndrome and course of poststroke epilepsy (Paper I)

7.1.1 Demographics

The final study group consisted of 83 patients with ischemic perinatal stroke: 39 (47%) patients with neonatal and presumed perinatal AIS and 44 (53%) patients with presumed perinatal PVI. According to the vascular syndrome, the study group comprised 13/83 (15.7%) patients with AT or PT occlusion, 23/83 (27.7%) patients with PMI or DMI, 3/83 (3.6%) patients with LLS and 44/83 (53%) patients with presumed perinatal PVI. Epilepsy developed in 19/83 (22.9%) patients during a median follow-up of 15.1 years (95% CI: 12.4–16.5 years): in 15/39 (38%) patients with AIS and in 4/44 (9%) patients with PVI. Median age at follow-up for patients with epilepsy was higher compared to patients without epilepsy, 19.8 years (IQR: 14.0, 23.1) and 14.9 years (IQR: 9.2, 17.3), p=0.004, respectively *(Table 1)*.

In the group of children with epilepsy PSOM score was higher compared to patients without epilepsy, 2.5 (IQR: 2.0, 4.0) and 2.0 (IQR: 1.0, 2.8), p=0.018, respectively. There were no significant differences in gender, gestational age, Apgar score, need for emergency cesarean section, percentage of neonates small for gestational age, presence of neonatal seizures, or side of stroke between patients who developed epilepsy and those without epilepsy.

Table 1. Demographics and clinical characteristics (Vaher, Ilves, et al. 2024) (published with permission from John Wiley & Sons).

		Epilepsy (n=19)	Without epilepsy (n=64)	P value	OR (95% CI)
Male gender, n (%)		6 (31.6)	32 (50.0)	0.16	2.2 (0.7–6.4)
Gestational weeks at birth, median (IQR)		40 [39, 40]	40 [38, 40]	0.22	
Apgar score at 1 min, median (IQR)		8 [7, 8] NA=1	8 [7, 9] NA=3	0.37	
Apgar score at 5 min, median (IQR)		8 [8, 9] NA=1	9 [8, 9] NA=3	0.26	
Emergency cesarean section, n (%)		4 (21.1)	19/63 (30.2) NA=1	0.44	1.6 (0.5–5.5)
Neonatal seizures, n (%)		5 (26.3)	11 (17.2)	0.51	1.7 (0.5–5.8)
Side of stroke left, n (%)		15 (79.0)	37 (57.8)	0.095	2.7 (0.8–9.2)
Small for gestational age < 3 percentiles, n (%)		1 (5.3)	5/63 (7.9) NA=1	>0.99	1.6 (0.16–77)
AIS, n (%)		15 (79.0)	24 (37.5)	0.0015	6.3 (1.9–21)
	Neonatal AIS	8 (42.1)	14 (21.9)	0.079	2.6 (0.9–7.7)
	Presumed perinatal AIS	7 (36.8)	10 (15.6)	0.057	3.2 (0.8–11)
PVI		4 (21.1)	40 (62.5)		
Vascular syndromes of AIS, n (%)				0.23	
	AT+PT	4 (26.7)	9 (37.5)		
	PMI+DMI	11 (73.3)	12 (50.0)		
	LLS	0 (0)	3 (12.5)		
Age (median) at follow-up for epilepsy, years, (IQR)		19.8 [14.0, 23.1]	14.9 [9.2, 17.3]	0.004	
PSOM score, median (IQR)		2.5 [2.0, 4.0]	2.0 [1.0, 2.8]	0.018	

IQR–interquartile range; NA–not available; OR–odds ratio; CI–confidence interval; AIS–arterial ischemic stroke; PVI–periventricular venous infarction; AT–anterior trunk of distal middle cerebral artery (MCA) infarction; PT–posterior trunk of distal MCA infarction; LLS–stroke of the lateral lenticulostriate arteries; PMI–proximal M1 MCA infarction; DMI–distal M1 MCA infarction; PSOM–Pediatric Stroke Outcome Measure

7.1.2 Development of epilepsy in different vascular syndromes

The probability of having epilepsy was higher in the group of patients with AIS compared to patients with PVI, hazard ratio (HR)=5.3 (95% CI: 1.9–18.6), p=0.0009 *(Figure 4)*.

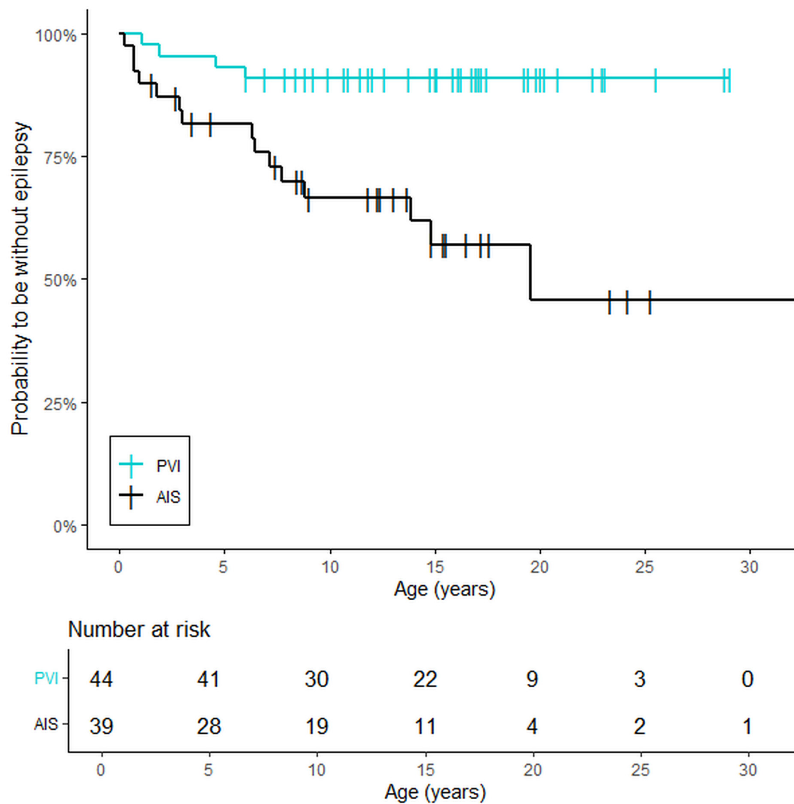

Figure 4. Kaplan-Meier survival probability curve of epilepsy for patients with AIS and PVI (Vaher, Ilves, et al. 2024) (published with permission from John Wiley & Sons). + - index cases without epilepsy, AIS–arterial ischemic stroke, PVI–periventricular venous infarction

Pairwise comparison showed that the probability of having epilepsy was significantly higher for patients with PMI or DMI compared to patients with PVI, HR=7.2 (95% CI: 2.5–26), p=0.0007 *(Figure 5).* Although the Kaplan-Meier curves were different, there was no statistical difference in the probability of having epilepsy between the group of AT infarction plus PT infarction compared to the group of PVI, HR=3.6 (95% CI: 0.89–15), p=0.069, or between the group of PMI plus DMI compared to the group of AT plus PT infarction, HR=2.0 (95% CI: 0.68–7.2), p=0.24. Among the patients with LLS none developed epilepsy during the follow-up period.

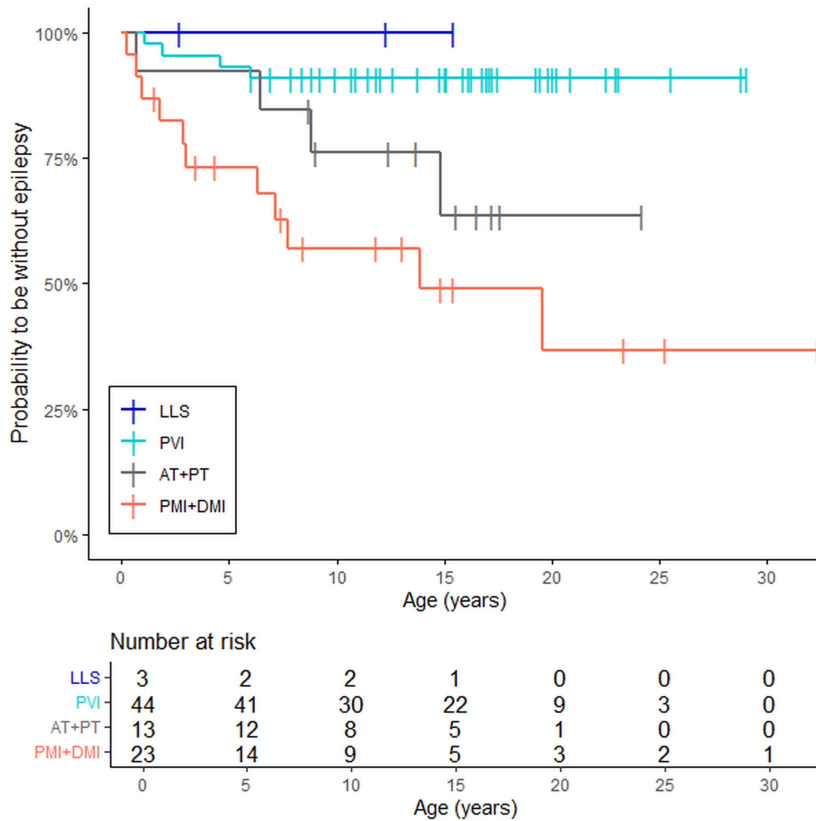

Figure 5. Kaplan-Meier survival probability curve of epilepsy in different vascular syndromes (Vaher, Ilves, et al. 2024) (published with permission from John Wiley & Sons). + – index cases without epilepsy, AT–anterior trunk of distal middle cerebral artery (MCA) infarction, PT–posterior trunk of distal MCA infarction, DMI–distal M1 MCA infarction, PMI–proximal M1 MCA infarction, LLS–stroke of the lateral lenticulostriate arteries, PVI–periventricular venous infarction

7.1.3 Cumulative survival function for epilepsy at different ages

The cumulative probability of being without epilepsy for the study group was 87.8% at five years (95% CI: 81.0–95.2), and 75.4% at a median age of 15.1 years (95% CI: 65.8–86.4) (*Figure 6, Table 2).*

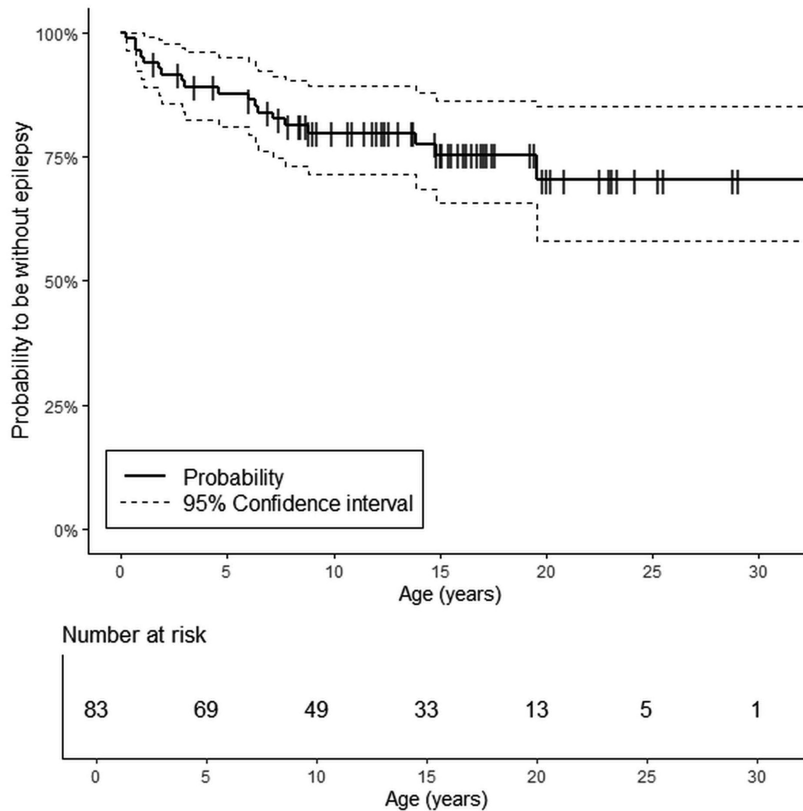

Figure 6. Kaplan-Meier survival probability curve of epilepsy for patients with ischemic perinatal stroke (Vaher, Ilves, et al. 2024) (published with permission from John Wiley & Sons). + – index cases without epilepsy

Table 2. Kaplan-Meier analysis of the probability of remaining without epilepsy (Vaher, Ilves, et al. 2024) (published with permission from John Wiley & Sons).

Year	Whole study group (n=83)	AIS (n=39)	PVI (n=44)	AT+PT (n=13)	PMI+DMI (n=23)
	Cumulative survival % (95% CI)				
0	100	100	100	100	100
1	95.2 (90.7–99.9)	89.7 (80.7–99.8)	100	92.3 (78.9–100)	82.4 (68.1–99.7)
2	91.5 (85.7–97.7)	87.1 (77.2–98.3)	95.5 (89.5–100)	92.3 (78.9–100)	82.4 (68.1–99.7)
3	89.1 (82.6–96.1)	81.7 (70.2–94.9)	95.5 (89.5–100)	92.3 (78.9–100)	73.2 (57.0–94.1)
4	89.1 (82.6–96.1)	81.7 (70.2–94.9)	95.5 (89.5–100)	92.3 (78.9–100)	73.2 (57.0–94.1)
5	87.8 (81.0–95.2)	81.7 (70.2–94.9)	93.2 (86.0–100)	92.3 (78.9–100)	73.2 (57.0–94.1)
6	86.5 (79.4–94.3)	81.7 (70.2–94.9)	90.9 (82.8–99.8)	92.3 (78.9–100)	73.2 (57.0–94.1)
7	83.9 (76.3–92.3)	75.8 (63.2–91.0)	90.9 (82.8–99.8)	84.6 (67.1–100)	68.0 (50.9–90.9)
8	81.2 (73.1–90.3)	69.9 (56.4–86.6)	90.9 (82.8–99.8)	84.6 (67.1–100)	57.1 (39.1–83.4)
9	79.8 (71.4–89.2)	66.6 (52.6–84.2)	90.9 (82.8–99.8)	76.2 (55.8–100)	57.1 (39.1–83.4)
10	79.8 (71.4–89.2)	66.6 (52.6–84.2)	90.9 (82.8–99.8)	76.2 (55.8–100)	57.1 (39.1–83.4)
11	79.8 (71.4–89.2)	66.6 (52.6–84.2)	90.9 (82.8–99.8)	76.2 (55.8–100)	57.1 (39.1–83.4)
12	79.8 (71.4–89.2)	66.6 (52.6–84.2)	90.9 (82.8–99.8)	76.2 (55.8–100)	57.1 (39.1–83.4)
13	79.8 (71.4–89.2)	66.6 (52.6–84.2)	90.9 (82.8–99.8)	76.2 (55.8–100)	57.1 (39.1–83.4)
14	77.6 (68.6–87.9)	61.8 (46.9–81.5)	90.9 (82.8–99.8)	76.2 (55.8–100)	48.9 (30.1–79.4)
15	75.4 (65.8–86.4)	57.0 (41.5–78.4)	90.9 (82.8–99.8)	63.5 (39.5–100)	48.9 (30.1–79.4)
16	75.4 (65.8–86.4)	57.0 (41.5–78.4)	90.9 (82.8–99.8)	63.5 (39.5–100)	48.9 (30.1–79.4)
17	75.4 (65.8–86.4)	57.0 (41.5–78.4)	90.9 (82.8–99.8)	63.5 (39.5–100)	48.9 (30.1–79.4)
18	75.4 (65.8–86.4)	57.0 (41.5–78.4)	90.9 (82.8–99.8)	63.5 (39.5–100)	48.9 (30.1–79.4)
19	70.4 (58.1–85.3)	57.0 (41.5–78.4)	90.9 (82.8–99.8)	63.5 (39.5–100)	48.9 (30.1–79.4)
20	70.4 (58.1–85.3)	45.6 (26.6–78.4)	90.9 (82.8–99.8)	63.5 (39.5–100)	36.7 (17.4–77.3)

CI–confidence interval; AIS–arterial ischemic stroke; PVI–periventricular venous infarction; AT–anterior trunk of distal middle cerebral artery (MCA) infarction; PT–posterior trunk of distal MCA infarction; PMI–proximal M1 MCA infarction; DMI–distal M1 MCA infarction

The risk to develop epilepsy persisted throughout childhood and young adulthood until the age of 20 years in the group of PMI plus DMI when the probability of being without epilepsy was 36.7% (95% CI: 17.4–77.3). In the group of AT plus PT infarction the survival function reached the lowest level at the age of 15 years when 63.5% (95% CI: 39.5–100) of the patients were without epilepsy. For patients with PVI, the risk of having epilepsy persisted until the age of six years, when the survival function was 90.9% (95% CI: 82.8–99.8) and remained at this level during the whole follow-up period (*Table 2).*

7.1.4 Features of poststroke epilepsy and electroencephalography

The median age at the time of the first epileptic seizure was 4.6 years (IQR: 1.1, 7.8) for all patients with ischemic perinatal stroke who developed epilepsy (*Table 3).* There were no significant differences in the median age of the first seizure between the groups with different vascular syndromes. In 11/19 (58%) patients epilepsy was diagnosed after the first known seizure. Four patients (21%) presented with status epilepticus at the time of epilepsy diagnosis, however for two of them, detailed history revealed previous focal seizures that had not been recognized earlier.

At least one complication occurred in 14/19 (73.7%) patients with epilepsy. Frequent seizures (Engel class ≥3) occurred in 11/19 (57.9%) patients, five (26.3%) patients had status epilepticus, two (10.5%) patients had spike-wave activation in sleep, and nine (47.4%) patients needed polytherapy. In complicated epilepsy, the first seizure occurred at the age of seven years or earlier in 12/14 (85.7%) cases versus 1/5 (20%) uncomplicated cases, OR=24 (95% CI: 1.2–1276), p=0.017.

Status epilepticus or spike-wave activation in sleep occurred significantly more often in patients with PVI compared to the whole AIS group: 4/4 (100%) and 3/15, (20%), OR=32 (95% CI: 1.2–870), p=0.009, respectively, and compared particularly to the AT plus PT infarction group, 0/4 (0%), OR=81 (95% CI: 1.3–5046), p=0.029, respectively. Patients with PMI or DMI had status epilepticus or spike-wave activation in sleep in 3/11 (27.3%) cases and frequent seizures in 7/11 (63.6%) cases. Two patients (18.2%) with PMI or DMI started with hypsarrhythmia and epileptic spasms followed by focal seizures occurred in one case and seizure remission in one case.

There were no significant differences in the neurophysiological characteristics, i.e. background activity changes or IED, between the different vascular syndromes.

Table 3. Clinical and neurophysiological characteristics of children with epilepsy according to the vascular syndrome (Paper I) (Vaher, Ilves, et al. 2024) (published with permission from John Wiley & Sons).

	Epilepsy n=19	PVI with epilepsy n=4	AIS with epilepsy n=15	AT+PT with epilepsy n=4	PMI+DMI with epilepsy n=11	AIS vs PVI P value, OR (95%CI)	AT+PT vs PMI+DMI vs PVI Overall p
Age (median) of first seizure, years, (IQR)	4.6 (1.1–7.8)	3.3 (1.5–5.3)	6.4 (0.9–8.8)	7.6 (3.6–11.8)	3.1 (0.9–7.8)	0.52	0.57
Complicated epilepsy, n (%)	14 (73.7)	4 (100)	10 (66.7)	1 (25)	9 (81.8)	0.53	0.075*
Status epilepticus or SWAS, n (%)	7 (36.8)	4 (100)	3 (20.0)	0 (0)	3 (27.3)	0.009, 32 (1.2–870)	0.0093**
Polytherapy, n (%)	9 (47.4)	3 (75)	6 (40.0)	1 (25.0)	5 (45.5)	0.30	0.41
Modified Engel class ≥3, n (%)	11 (57.9)	3 (75)	8 (53.3)	1 (25)	7 (63.6)	0.60	0.45
EEG only focal slowing, n (%)	12 (63.2)	2 (50)	10 (66.7)	1 (25)	9 (81.8)	0.60	0.13
EEG bilateral slowing, n (%)	2 (10.5)	1 (25)	1 (6.7)	0 (0)	1 (9.1)	0.39	0.68
EEG only focal IED, n (%)	2 (10.5)	0 (0)	2 (13.3)	1 (25)	1 (9.1)	>0.99	0.68
EEG regional IED, n (%)	10 (52.6)	2 (50)	8 (53.3)	1 (25)	7 (63.6)	>0.99	0.58
EEG bilateral IED, n (%)	7 (36.8)	2 (50)	5 (33.3)	2 (50)	3 (27.3)	0.60	0.54
EEG hypsarrhythmia, n (%)	2 (10.5)	0 (0)	2 (13.3)	0 (0)	2 (18.2)	>0.99	>0.99

IQR–interquartile range; OR–odds ratio; CI–confidence interval; AIS–arterial ischemic stroke; PVI–periventricular venous infarction; AT–anterior trunk of distal middle cerebral artery (MCA) infarction; PT–posterior trunk of distal MCA infarction; PMI–proximal M1 MCA infarction; DMI–distal M1 MCA infarction; SWAS–spike-wave activation in sleep ≥85%; IED–interictal epileptiform discharges

* Pairwise comparison between the groups of AT+PT and PMI+DMI OR=14 (95% CI: 0.9–208), p=0.077, between the groups of AT+PT and PVI, p=0.14; between the groups of PMI+DMI and PVI, p>0.99

** Pairwise comparison between the groups of AT+PT and PVI OR=81 (95% CI: 1.3–5046), p=0.029; between the groups of AT+PT and PMI+DMI, p=0.52; between the groups of PMI+DMI and PVI OR=14 (95% CI: 0.9–208), p=0.077.

7.1.5 Outcome of poststroke epilepsy

At the last follow-up, at a median age of 19.8 years (IQR:14.0, 23.1), 10/19 (52.6%) patients with epilepsy had been seizure free and off medication for over six months (Engel class 0) *(Table 4)*. Their mean follow-up time after the last seizure had been 12.3 years (95% CI: 7.8–16.7). Additionally 5/19 (26%) patients had been seizure free over six months, but were still on antiseizure medication (Engel class 1). For patients with Engel class 0 at the last follow-up, the mean period of active seizures for those with more than one seizure had been 2.7 years (95% CI: 0.5–5.0), but three patients with epilepsy had had only a single seizure.

Table 4. History of epilepsy for patients in remission (Vaher, Ilves, et al. 2024) (published with permission from John Wiley & Sons).

Patient's number	Age at first seizure (years)	Age at last seizure (years)	Engel class (maximum)	Age at last follow-up (years)	Period of active seizures (years)	Period of follow-up after last seizure (years)	Vascular syndrome
1	0.8	0.8	1	25.5	0	24.8	AT+PT
2	2.0	11.6	3	26.8	9.6	15.3	PVI
3	4.6	5.3	1	22.0	0.7	16.8	PVI
4	6.4	10.9	2	24.0	4.5	13.1	PMI+DMI
5	6.4	12.2	3	18.2	5.8	6.0	AT+PT
6	7.2	9.9	3	23.1	2.8	13.2	PMI+DMI
7	7.8	7.8	1	22.9	0	15.2	PMI+DMI
8	8.8	12.0	1	19.8	3.2	7.8	AT+PT
9	13.8	13.8	1	18.7	0	4.8	PMI+DMI
10	14.8	15.7	2	21.5	0.8	5.8	AT+PT

PVI–periventricular venous infarction; AT–anterior trunk of distal middle cerebral artery (MCA) infarction; PT–posterior trunk of distal MCA infarction; PMI–proximal M1 MCA infarction; DMI–distal M1 MCA infarction

7.2 Volume of the subcortical gray matter structures in poststroke epilepsy (Paper II)

7.2.1 Demographics

The final study group consisted of 62 patients with perinatal stroke: 15 (24.2%) children had neonatal AIS, 14 (22.6%) children had presumed perinatal AIS and 33 (53.2%) children had presumed PVI. The control group comprised 46 age and sex matched term born typically developed children. Epilepsy developed in 10/29 (34.5%) patients with AIS and in 4/33 (12.1%) patients with PVI, OR=3.8 (95%CI: 1.04–14), p=0.036. IED without epileptic seizures occurred additionally in 6/29 (20.7%) patients with AIS and in 3/33 (9.1%) patients with PVI (p=0.28) (*Table 5, Figure 2)*. Epilepsy or IED occurred more often in patients with AIS than in patients with PVI, 16/29 (55.2%) and 7/33, (21.2%), OR=3.8 (95%CI: 1.04–14), p=0.0057, respectively. Median age at the time of the first epileptic seizure was not different between patients with AIS and patients with PVI, 4.8 years and 3.3 years, p=0.62, respectively, with a median follow-up time of 12.8 years and 12.5 years, p=0.32, respectively.

Patients with AIS were delivered more often by emergency cesarean section (p=0.016) and had lower Apgar score at the 1st and 5th minutes (p<0.001) compared to patients with PVI. Neonatal seizures appeared in 10/15 (66.7%) children with neonatal AIS, but in none of the patients with PVI or presumed perinatal AIS.

There were no differences in gender, gestational age, median age at the time of follow-up MRI or median age at the last clinical follow-up, side of stroke, clinical features of epilepsy, and PSOM score between the patients of the AIS, PVI and control groups (*Table 5.)*.

Table 5. Demographics and clinical characteristics (Paper II) (Vaher et al. 2023) (published with permission from Frontiers)

	AIS (n=29)	PVI (n=33)	Control (n=46)	Overall p
Male gender, n (%)	15 (52)	14 (42)	27 (59)	0.36
Gestational weeks at birth, median (IQR)	40 (38, 40)	40 (39, 40)	NA	0.44
Apgar score at 1 min, median (IQR)	8 (5, 8)	8 (8, 9)	NA	<0.0001*
Apgar score at 5 min, median (IQR)	8 (7, 9)	9 (9, 9)	NA	<0.001*
Emergency cesarean section n (%)	12/28** (43)	5 (15)	NA	0.016*
Neonatal seizures in neonatal AIS, n (%)	10/15 (67)	NA	NA	NA
Side of stroke left, n (%)	21 (72)	16 (49)	NA	0.055
Age at follow-up MRI for volumetry, years, median (IQR)	10.7 (8.5, 14.1)	10.1 (7.7, 12.8)	10.7 (9.6, 13.1)	0.49
Age at last follow-up, years, median (IQR)	12.8 (10.8, 17.3)	12.5 (9.3, 14.8)	NA	0.32
Epilepsy, n (%)	10 (34.5)	4 (12.1)		0.036
Focal onset seizures, n (%)	9/10 (90)	4/4 (100)		>0.99
Epileptic spasms, n (%)	2/10 (20)	0/4 (0)		>0.99
Spike-wave activation in sleep ≥85%, n (%)	1/10 (10)	1/4 (25)		0.51
Status epilepticus, n (%)	1/10 (10)	2/4 (50)		0.18
Polytherapy, n (%)	5/10 (50)	3/4 (75)		0.58
IED on postneonatal EEG without epilepsy, n (%)	6 (20.7)	3 (9.1)		0.28
Epilepsy or IED in post-neonatal EEG, n (%)	16 (55.2)	7 (21.2)		0.0057*
PSOM score, median (IQR)	2.5 (1.5, 4.0)	2.0 (1.5, 2.5)		0.12

AIS–arterial ischemic stroke; PVI–periventricular venous infarction; IED–interictal epileptiform discharges; PSOM–Pediatric Stroke Outcome Measure; n–number of observations; IQR–interquartile range; N/A–not applicable; **–delivery mode not known for a single adopted child. Only the p values below the significance threshold of the adjusted false discovery rate (0.0167) are significant and marked with an asterisk (*).

7.2.2 Size of the subcortical gray matter structures in the AIS, PVI and control groups

The volume of the subcortical structures (both ipsilesional and contralesional) did not differ between patients with neonatal AIS and presumed perinatal AIS *(Table 6)*. Therefore, in further analysis, the groups of neonatal AIS and presumed perinatal AIS were considered jointly under the AIS group.

Table 6. Volume of the normalized subcortical gray matter structures in the groups of neonatal AIS and presumed perinatal AIS (Vaher et al. 2023) (published with permission from Frontiers)

	Neonatal AIS (n=15)	Presumed perinatal AIS (n=14)	P value
Ipsilesional			
Thalamus	8019 (6143–9895)	8435 (7003–9868)	0.71
Nucleus caudatus	5388 [2916, 6138]	5654 [4753, 6129]	0.65
Putamen	6109 [2001, 7786]	6736 [5449, 7786]	0.53
Globus pallidus	2032 [1370, 2373]	2266 [2093, 2453]	0.28
Hippocampus	4340 (3764–4916)	4621 (4177–5066)	0.42
Amygdala	1332 (1114–1551)	1451 (1266–1637)	0.38
Nucleus accumbens	456 [360, 685]	607 [480, 769]	0.33
Contralesional			
Thalamus	10637 (10046–11227)	10565 (9781–11350)	0.88
Nucleus caudatus	6109 (5665–6553)	6021 (5599–6442)	0.76
Putamen	7956 (7567–8345)	7822 (7217–8427)	0.69
Globus pallidus	2525 (2394–2656)	2443 (2242–2645)	0.47
Hippocampus	5286 (4923–5649)	5498 (5096–5901)	0.40
Amygdala	1410 (1214–1606)	1523 (1286–1760)	0.43
Nucleus accumbens	678 (554–802)	637 (547–727)	0.58

The data are presented in mm^3: mean with the 95% confidence interval [e.g. X (Y–Z)] or median with the 25th and 75th percentiles (e.g. X [Y, Z]) as statistically appropriate, AIS–arterial ischemic stroke

The ipsilesional thalamus, putamen, globus pallidus, and nucleus accumbens were smaller in children with AIS and in children with PVI compared to controls *(Table 7)*. In addition, children with AIS had a smaller ipsilesional hippocampus and a larger contralesional putamen compared to controls. Children with PVI had also a smaller ipsilesional caudate nucleus compared to controls *(Table 7*).

The size of the subcortical structures did not differ between children with AIS and PVI, except for the contralesional putamen which was larger in children with AIS compared to children with PVI (*Table 7).*

Table 7. Volume of the normalized subcortical gary matter structures in the AIS, PVI and control groups (Vaher et al. 2023) (published with permission from Frontiers)

	AIS (n=29)	PVI (n=33)	Control (n=46)	Overall p
Scaling factor	1.55 (1.46–1.64)	1.49 (1.43–1.55)	1.38 (1.35–1.42)	0.0007[bc]
Ipsilesional				
Thalamus	8220 (7102–9338)	9046 (8284–9808)	11456 (11232–11680)	<.0001[bc]
Caudate nucleus	5595 [4264, 6129]	5052 [4550, 5598]	5818 [5457, 6115]	0.0001[c]
Putamen	6323 [3480, 7786]	6908 [5931, 7612]	7289 [6976, 7791]	0.010[bc]
Globus pallidus	2137 [1489, 2373]	2219 [2005, 2381]	2451 [2321, 2535]	<.0001[bc]
Hippocampus	4600 [4052, 5124]	5026 [4436, 5394]	5230 [4993, 5425]	0.0017[b]
Amygdala	1390 (1253–1527)	1537 (1411–1663)	1592 (1493–1690)	0.051
Nucleus accumbens	575 (482–667)	624 (545–702)	747 (703–792)	0.0009[bc]
Contralesional				
Thalamus	10602 (10148–11057)	10760 (10349–11172)	11060 (10847–11274)	0.14
Caudate nucleus	5924 [5446, 6601]	5795 [5389, 6387]	6029 [5472, 6228]	0.64
Putamen	7891 (7559–8223)	7150 (6820–7480)	7277 (7089–7465)	0.0008[ab]
Globus pallidus	2486 (2374–2597)	2369 (2250–2489)	2496 (2442–2549)	0.094
Hippocampus	5388 (5133–5644)	5171 (4928–5415)	5296 (5148–5444)	0.37
Amygdala	1465 (1320–1609)	1672 (1540–1804)	1538 (1457–1619)	0.049
Nucleus accumbens	658 (586–731)	600 (552–649)	608 (573–643)	0.24

The data are presented in mm^3: mean with the 95% confidence interval [e.g. X (Y–Z)] or median with the 25th and 75th percentiles (e.g. X [Y, Z]) as statistically appropriate; only the overall p values below the significance threshold of the adjusted false discovery rate (0.027) are significant. Pairwise comparisons were made using the Benjamini-Hochberg method and only the p values below the significance threshold of the adjusted false discovery rate are therefore significant and marked with a superscript: [a] AIS versus PVI, [b] AIS versus control, [c] PVI versus control. AIS–arterial ischemic stroke, PVI–periventricular venous infarction

7.2.3 Size of the subcortical gray matter structures in the AIS and PVI groups with and without epilepsy compared to control group

All ipsilesional subcortical structures, except for the amygdala in children with epilepsy and except for the caudate nucleus in the pooled group of epilepsy plus IED, were smaller in the AIS group compared to control (*Figures 7–11, Table 8)*. At the same time, in children without epilepsy of the AIS group, only the ipsilesional thalamus was smaller compared to control. Among the contralesional structures, the thalamus was smaller in children with epilepsy of the AIS group and in children of the pooled group of epilepsy plus IED, and the putamen was larger in the pooled group, compared to control.

The ipsilesional caudate nucleus, globus pallidus, and nucleus accumbens were smaller in children with epilepsy of the group of PVI and in children of the pooled group of epilepsy plus IED, compared to control *(Table 9, Figures 8, 10, 11)*. In the pooled group of children with PVI also the ipsilesional thalamus and putamen were smaller compared to control *(Figures 7, 9)*. In children with PVI without epilepsy the ipsilesional thalamus, caudate nucleus, and globus pallidus were smaller compared to control.

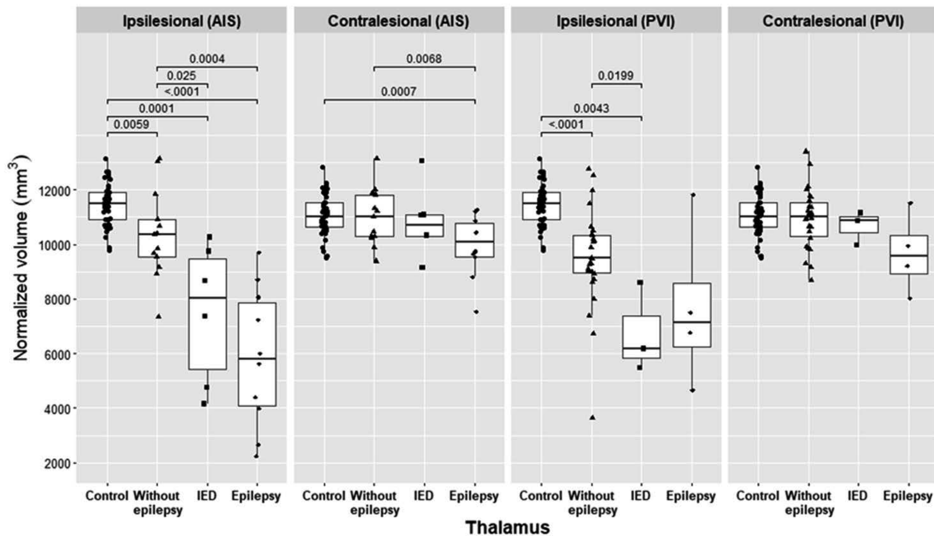

Figure 7. Volume of the normalized thalamus in the AIS, PVI and control groups (Vaher et al. 2023) (published with permission from Frontiers). AIS–arterial ischemic stroke; PVI–periventricular venous infarction; IED–interictal epileptiform discharges

Pairwise comparisons were made using the Benjamini-Hochberg method and only the p values below the significance threshold of the adjusted false discovery rate are significant and presented in the figure.

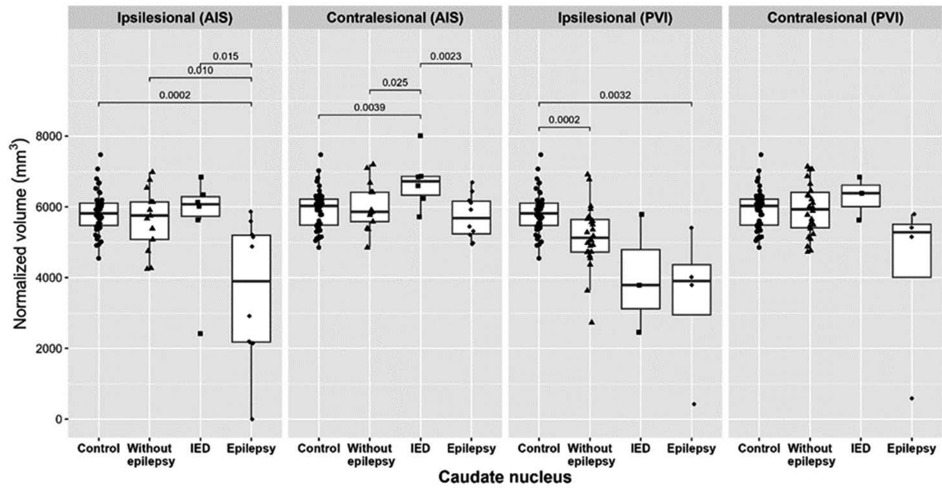

Figure 8. Volume of the normalized caudate nucleus in the AIS, PVI and control groups (Vaher et al. 2023) (published with permission from Frontiers). AIS–arterial ischemic stroke; PVI–periventricular venous infarction; IED–interictal epileptiform discharges

Pairwise comparisons were made using the Benjamini-Hochberg method and only the p values below the significance threshold of the adjusted false discovery rate are significant and presented in the figure.

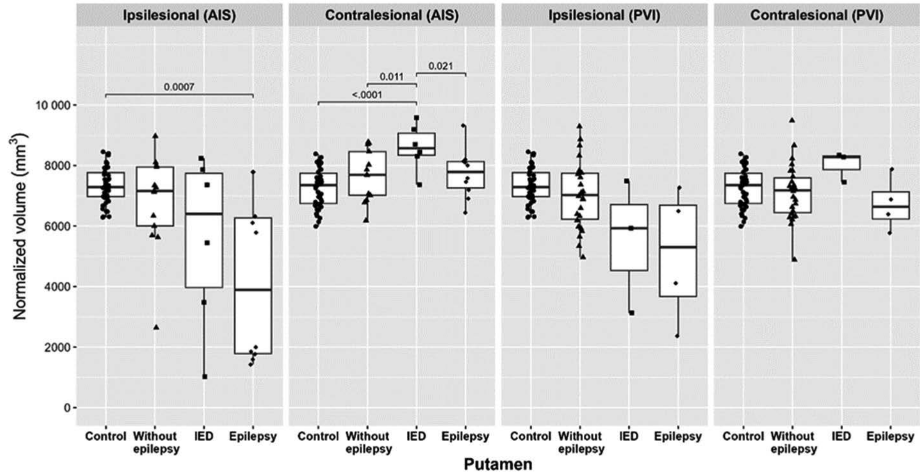

Figure 9. Volume of the normalized putamen in the AIS, PVI and control groups (Vaher et al. 2023) (published with permission from Frontiers). AIS–arterial ischemic stroke; PVI–periventricular venous infarction; IED–interictal epileptiform discharges

Pairwise comparisons were made using the Benjamini-Hochberg method and only the p values below the significance threshold of the adjusted false discovery rate are significant and presented in the figure.

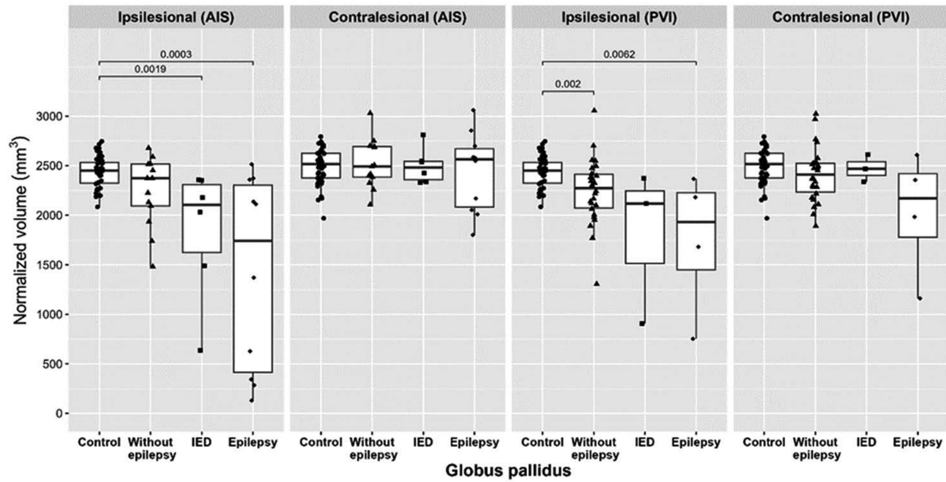

Figure 10. Volume of the normalized globus pallidus in the AIS, PVI and control groups (Vaher et al. 2023) (published with permission from Frontiers). AIS–arterial ischemic stroke; PVI–periventricular venous infarction; IED–interictal epileptiform discharges

Pairwise comparisons were made using the Benjamini-Hochberg method and only the p values below the significance threshold of the adjusted false discovery rate are significant and presented in the figure.

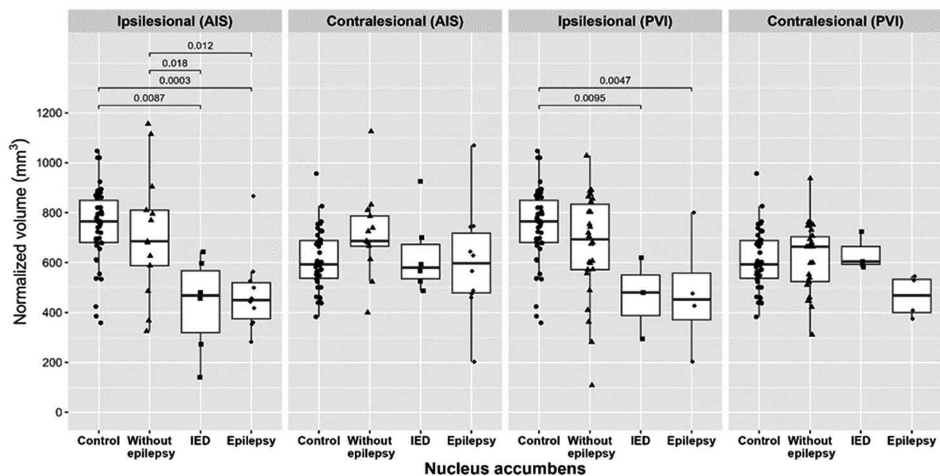

Figure 11. Volume of the normalized nucleus accumbens in the AIS, PVI and control groups (Vaher et al. 2023) (published with permission from Frontiers). AIS–arterial ischemic stroke; PVI–periventricular venous infarction; IED–interictal epileptiform discharges

Pairwise comparisons were made using the Benjamini-Hochberg method and only the p values below the significance threshold of the adjusted false discovery rate are significant and presented in the figure.

Table 8. Volume of the normalized subcortical gray matter structures in the AIS and control groups (Vaher et al. 2023) (published with permission from Frontiers)

	Control	AIS				AIS	
	(n=46)	Without epilepsy (n=13)	IED (n=6)	Epilepsy (n=10)	Overall p[1]	Epilepsy+ IED (n=16)	Overall p[2]
Scaling factor	1.41 [1.32,1.44]	1.36 [1.29,1.59]	1.59 [1.46,1.68]	1.57 [1.43,1.70]	0.0009[bc]	1.59 [1.46,1.69]	0.0046[xy]
Ipsilesional							
Thalamus	11508 [10905,11906]	10362 [9532,10897]	8016 [4766,9746]	5805 [3996,8065]	<.0001[abcde]	6614 [4278,8693]	<.0001[xyz]
Caudate nucleus	5818 [5457,6115]	5755 [5079,6138]	6074 [5637,6340]	3898 [2179,5214]	0.0021[cef]	5181 [2308,5943]	0.045
Putamen	7289 [6976,7791]	7161 [6005,7953]	6407 [3480,7871]	3892 [1770,6323]	0.0086[c]	5616 [1811,7576]	0.0071[y]
Globus pallidus	2451 [2321,2535]	2373 [2093,2517]	2105 [1489,2353]	1741 [343,2359]	0.0001[bc]	2072 [632,2355]	<.0001[yz]
Hippocampus	5230 [4993,5425]	4994 [4401,5306]	4326 [3217,5178]	4131 [3439,4817]	0.0007[c]	4131 [3348,4851]	0.0003[yz]
Amygdala	1621 [1350,1817]	1571 [1354,1699]	1079 [835,1480]	1316 [1190,1645]	0.0038[bd]	1271 [935,1518]	0.0046[yz]
Nucleus accumbens	765 [680,859]	685 [588,810]	468 [273,597]	450 [360,526]	0.0001[bcde]	456 [357,545]	<.0001[yz]
Contralesional							
Thalamus	11024 [10610,11527]	11000 [10290,11823]	10711 [10301,11084]	10083 [9526,10871]	0.0075[ce]	10380 [9590,11082]	0.028[y]
Caudate nucleus	6029 [5472,6228]	5861 [5586,6416]	6725 [6239,6868]	5685 [5214,6180]	0.016[bdf]	6150 [5380,6648]	0.65

	Control	AIS				AIS	
	(n=46)	Without epilepsy (n=13)	IED (n=6)	Epilepsy (n=10)	Overall p^1	Epilepsy+ IED (n=16)	Overall p^2
Putamen	7353 [6730,7779]	7692 [7020,8460]	8572 [8312,9196]	7793 [7195,8139]	0.0003[bdf]	8123 [7416,8572]	0.0013[y]
Globus pallidus	2516 [2375,2626]	2492 [2385,2693]	2481 [2336,2546]	2564 [2053,2698]	0.95	2542 [2248,2642]	0.86
Hippocampus	5251 [4989,5610]	5358 [4772,5844]	5550 [4867,6081]	5369 [5234,5806]	0.59	5369 [5087,6004]	0.64
Amygdala	1515 [1382,1697]	1603 [1404,1936]	1222 [1129,1397]	1445 [1275,1627]	0.31	1350 [1164,1567]	0.14
Nucleus accumbens	592 [534,691]	686 [666,786]	580 [525,700]	597 [475,743]	0.16	580 [487,721]	0.08

AIS–arterial ischemic stroke, IED–interictal epileptiform discharges

The data are presented as median [IQR] in mm3.

Overall p^1–comparison of children with epilepsy, without epilepsy, with IED, and controls. Only the overall p values below the significance threshold of the adjusted false discovery rate (0.037) are significant. Pairwise comparisons were made using the Benjamini-Hochberg method and only the p values below the significance threshold of the adjusted false discovery rate are significant and marked with a superscript: [a]–control versus without epilepsy; [b]–control versus IED; [c]–control versus epilepsy; [d]–without epilepsy versus IED; [e]–without epilepsy versus epilepsy; [f]–epilepsy versus IED.

Overall p^2–comparison of children without epilepsy, with epilepsy+IED, and controls. Only the p values below the significance threshold of the adjusted false discovery rate (0.030) are significant. Pairwise comparisons were made using the Benjamini-Hochberg method and only the p values below the significance threshold of the adjusted false discovery rate are significant and marked with a superscript: [x]–control versus without epilepsy; [y]–control versus epilepsy+IED; [z]–without epilepsy versus epilepsy+IED

Table 9. Volume of the normalized subcortical gray matter structures in the PVI and control groups (Vaher et al. 2023) (published with permission from Frontiers)

	Control	PVI				PVI	
	(n=46)	Without epilepsy (n=26)	IED (n=3)	Epilepsy (n=4)	Overall p^1	Epilepsy+ IED (n=7)	Overall p^2
Scaling factor	1.41 [1.32, 1.44]	1.47 [1.38, 1.56]	1.50 [1.46, 1.87]	1.58 [1.46, 1.87]	0.092	1.50 [1.42, 1.67]	0.017^{x}
Ipsilesional							
Thalamus	11508 [10905,11906]	9494 [8937,10350]	6177 [5474,8589]	7140 [5716,9669]	$<.0001^{abd}$	6771 [5474,8589]	$<.0001^{xyz}$
Caudate nucleus	5818 [5457,6115]	5128 [4725,5664]	3788 [2460,5792]	3905 [2109,4713]	$<.0001^{ac}$	3793 [2460,5410]	$<.0001^{xyz}$
Putamen	7289 [6976,7791]	7028 [6188,7758]	5931 [3132,7490]	5304 [3240,6884]	0.032	5931 [3132,7271]	0.013^{y}
Globus pallidus	2451 [2321,2535]	2273 [2064,2418]	2118 [907,2374]	1931 [1217,2274]	0.0005^{ac}	2118 [907,2367]	0.0001^{xy}
Hippocampus	5230 [4993,5425]	5046 [4436,5416]	4459 [4056,4711]	4230 [2798,5398]	0.076	4459 [3435,5026]	0.042
Amygdala	1621 [1350,1817]	1538 [1348,1889]	1080 [997,1344]	1640 [1231,1964]	0.17	1344 [997,1759]	0.39
Nucleus accumbens	765 [680,859]	693 [572,844]	480 [295,620]	452 [315,639]	0.0024^{bc}	476 [295,620]	0.0007^{yz}
Contralesional							
Thalamus	11024 [10610,11527]	11004 [10227, 11587]	10875 [9969,11153]	9573 [8612,10727]	0.25	9969 [9206,11153]	0.17
Caudate nucleus	6029 [5472,6228]	5931 [5389,6441]	6387 [5627,6841]	5284 [2871,5605]	0.13	5627 [5154,6387]	0.73

	Control	PVI				PVI	
	(n=46)	**Without epilepsy (n=26)**	**IED (n=3)**	**Epilepsy (n=4)**	**Overall p^1**	**Epilepsy+ IED (n=7)**	**Overall p^2**
Putamen	7353 [6730,7779]	7181 [6423,7639]	8280 [7454,8344]	6637 [6082,7383]	0.08	7454 [6392,8280]	0.49
Globus pallidus	2516 [2375,2626]	2411 [2218,2525]	2468 [2337,2612]	2170 [1572,2482]	0.10	2356 [1984,2608]	0.075
Hippocampus	5251 [4989,5610]	5210 [4907,5678]	4907 [4879,5258]	5172 [4368,5744]	0.63	4907 [4716,5628]	0.53
Amygdala	1515 [1382,1697]	1620 [1460,1925]	1426 [1032,1762]	2088 [1828,2176]	0.019	1762 [1426,2154]	0.15
Nucleus accumbens	592 [534,691]	664 [523,707]	604 [582,724]	469 [392,537]	0.14	545 [408,604]	0.33

PVI–periventricular venous infarction, IED–interictal epileptiform discharges

The data are presented as median [IQR] in mm^3.

Overall p^1–comparison of children with epilepsy, without epilepsy, with IED, and controls. Only the overall p values below the significance threshold of the adjusted false discovery rate (0.013) are significant. Pairwise comparisons were made using the Benjamini-Hochberg method and only the p values below the significance threshold of the adjusted false discovery rate are significant and marked with a superscript: [a]–control versus without epilepsy; [b]–control versus IED; [c]–control versus epilepsy; [d]–without epilepsy versus IED; [e]–without epilepsy versus epilepsy; [f]–epilepsy versus IED.

Overall p^2–comparison of children without epilepsy, with epilepsy+IED, and controls. Only the p values below the significance threshold of the adjusted false discovery rate (0.020) are significant. Pairwise comparisons were made using the Benjamini-Hochberg method and only the p values below the significance threshold of the adjusted false discovery rate are significant and marked with a superscript: [x]–control versus without epilepsy; [y]–control versus epilepsy+IED; [z]–without epilepsy versus epilepsy+IED.

7.2.4 Size of the subcortical gray matter structures in the groups of AIS and PVI with epilepsy

The ipsilesional thalamus was smaller in children of the AIS group with epilepsy and in children of the pooled group of epilepsy plus IED, either with AIS or PVI, compared to children without epilepsy *(Tables 8, 9, Figure 7)*.

In addition in children with AIS with epilepsy the ipsilesional caudate nucleus and nucleus accumbens were smaller compared to children with AIS without epilepsy *(Figures 8, 11)*.

Both children with AIS or PVI of the pooled group of epilepsy plus IED had, in addition to a smaller thalamus, also a smaller nucleus accumbens, compared to children without epilepsy. Patients with AIS in the pooled group of epilepsy plus IED had also a smaller ipsilesional globus pallidus, hippocampus and amygdala, and patients in the group of PVI with epilepsy plus IED had a smaller caudate nucleus, compared to children without epilepsy.

The contralesional thalamus was only smaller in children of the AIS group with epilepsy, compared to children without epilepsy, but not in children of the PVI group.

7.2.5 Size of the subcortical gray matter structures in the groups of AIS and PVI with interictal epileptiform discharges

In children with IED, with either AIS or PVI, the ipsilesional thalamus and nucleus accumbens were smaller compared to controls *(Tables 8, 9, Figure 7, 11)*. In children of the AIS group with IED, also the ipsilesional globus pallidus and amygdala were smaller, and the contralesional caudate nucleus and putamen were larger compared to children of the control group *(Figure 10, 11)*.

In children with AIS with IED, the ipsilesional thalamus, amygdala and nucleus accumbens were smaller and the contralesional caudate nucleus and putamen were larger compared to children without epilepsy *(Figures 7–9)*. Both the ipsi- and contralesional caudate nucleus and the contralesional putamen were larger in children with AIS with IED, compared to children with epilepsy.

In children with PVI with IED, the subcortical structures were not different from those of children with epilepsy *(Table 9, Figures 7–11)*.

7.3 General cognitive outcome and specific cognitive functions in children with poststroke epilepsy (Paper III)

7.3.1 Demographics

The final study group consisted of 51 patients: 14/51 (27.5%) patients had epilepsy, 11/51 (21.5%) had IED, but without epileptic seizures, and 26/51 (51%) were without epilepsy and without IED *(Table 10, Figure 3).*

There were no differences in gender, gestational age, Apgar scores, emergency cesarean section, neonatal seizures, side of stroke, general PSOM score, or median age at KABC-II testing between the group of epilepsy, the group with IED only and the group without epilepsy (*Table 10)*. PSOM motor score was higher in the group with epilepsy (p=0.049) and in the group with IED (p=0.038) compared to the group without epilepsy.

The study group consisted of 27 (53%) patients with AIS and 24 (47%) patients with PVI. The representation of distinct vascular syndromes in the group with epilepsy, in the group with IED only and in the group without epilepsy was different. Children with PMI or DMI were more represented in the group with epilepsy and in the group with IED compared to children with the other vascular syndromes, OR=45 (95% CI: 4.1–2047), p=0.0001 and OR=21 (95% CI: 1.7–1023), p=0.0054, respectively. In contrast, in the group without epilepsy there were more children with PVI compared to the other vascular syndromes, OR=14 (95% CI: 2.4–75) p=0.0009, respectively.

Table 10. Demographics and clinical characteristics (Paper III) (Vaher, Männamaa, et al. 2024) (published with permission from Frontiers)

	Without epilepsy (n=26)	**With IED (n=11)**	**Epilepsy (n=14)**	**P value**	**OR (95% CI)**
Male gender, n (%)	13 (50.0)	5 (45.5)	5 (35.7)	0.69	
Gestational weeks at birth, median (IQR)	40 (38, 40)	40 (38, 40)	40 (39, 40)	0.80	
Apgar score at 1 min, median (IQR)	8 (6, 9) NA=2	8 (7, 9)	8 (8, 8) NA=1	0.93	
Apgar score at 5 min, median (IQR)	9 (8, 9) NA=2	9 (8, 9)	8 (8, 9) NA=1	0.87	
Emergency cesarean section, n (%)	6/25 (24.0) NA=1	2 (18.2)	4 (28.6)	0.91	
Neonatal seizures, n (%)	3 (11.5)	3 (27.3)	4 (28.6)	0.30	
Side of stroke left, n (%)	16 (61.5)	3 (27.3)	10 (71.4)	0.068	

	Without epilepsy (n=26)	With IED (n=11)	Epilepsy (n=14)	P value	OR (95% CI)
Small for gestational age < 3 percentiles, n (%)	3/25 (12.0) NA=1	0 (0)	1 (7.1)	0.80	
Vascular syndromes, n (%)					
Anterior or posterior trunk of MCA infarction	6 (23.1)	2 (18.2)	3 (21.4)	>0.99	
Lenticulostriate arteries' infarction	1 (3.8)	0 (0)	0 (0)	>0.99	
Proximal or distal MCA infarction	1 (3.8)	5 (45.5)	9 (64.3)	<.0001	<.0001[a], 45 (4.1–2047) 0.43[b] 0.0054[c], 21 (1.7–1023)
Periventricular venous infarction	18 (69.2)	4 (36.4)	2 (14.3)	0.0029	0.0009[a], 14 (2.4–75) 0.35[b] 0.080[c]
PSOM general score, median (IQR)	1.5 (1.0, 2.5)	3.0 (1.0, 4.0)	2.5 (2.5, 3.5)	0.083	
PSOM motor score, median (IQR)	1.0 (0.5, 1.0)	1.0 (1.0, 2.0)	2.0 (0.5, 2.0)	0.047	0.049[a] 0.91[b] 0.038[c]
Age at KABC-II testing, median (IQR)	9.1 (7.8, 10.9)	8.9 (7.2, 9.8)	11.1 (7.8, 13.2)	0.19	

IED–interictal epileptiform discharges; IQR–interquartile range; NA–not available; OR–odds ratio; CI–confidence interval; MCA–middle cerebral artery; PSOM–Pediatric Stroke Outcome Measure. KABC-II–Kaufman Assessment Battery for Children, II edition
Pairwise comparisons were made and are marked with a superscript:
[a] Epilepsy versus without epilepsy
[b] Epilepsy versus IED
[c] Without epilepsy versus IED

7.3.1.1 Clinical features of epilepsy

Median age at the time of the first seizure in the group of epilepsy was 6.2 years (IQR: 2.8, 7.8) *(Table 11)*. Status epilepticus or spike-wave activation in sleep occurred in 4/14 (28.%) patients and 8/14 (57.1%) patients had frequent seizures and needed polytherapy. Cognitive assessment was performed after the first epileptic seizure in 11/14 (78.6%) patients. Median time from the first seizure in these patients was 8.2 years (IQR: 5.0, 9.7). In three patients cognitive assessment

was performed before the onset of epilepsy, at 1.1, 6.7, and 11.8 years before the first seizure, respectively.

Table 11. Clinical features of epilepsy (Vaher, Männamaa, et al. 2024) (published with permission from Frontiers)

	Epilepsy (n=14)
Age at first seizure, years, median (IQR)	6.2 (2.8, 7.8), min 0.3, max 19.6
Age at follow-up for epilepsy, years, median (IQR)	19.3 (14.0, 22)
Status epilepticus or spike-wave activation in sleep ≥85%, n (%)	4 (28.6%)
Polytherapy, n (%)	8 (57.1)
Frequent seizures (Engel class ≥3), n (%)	8 (57.1)
Duration of epilepsy at the time of KABC-II testing, years, median (IQR)*	8.2 (5.0, 9.7)

*in 11/14 patients whose testing was performed after the first seizure; IQR–interquartile range; KABC-II–Kaufman Assessment Battery for Children, II edition

7.3.2 General cognitive outcome

Children with epilepsy had significantly lower all general ability scores (FCI, MPI, NVI) compared to children without epilepsy. General ability did not differ between children with epilepsy and children with IED only (*Table 12, Figure 12).* Although there were no statistically significant differences in the scores of general cognitive ability between children with IED and children without epilepsy, mean FCI was 9.6% lower for children with IED compared to children without epilepsy, 82.1 (95% CI: 74.5–90.2) and 90.8 (95% CI: 85.2–96.4), p=0.077, respectively and mean NVI was 11.4% lower for children with IED compared to children without epilepsy, 85.8 (95% CI: 76.4–95.2) and 96.8 (95% CI: 89.6–103.9), p=0.077, respectively.

Table 12. Scores of general ability and specific cognitive functions for children with epilepsy and for children without epilepsy (Vaher, Männamaa, et al. 2024) (published with permission from Frontiers)

	Without epilepsy n=26	With IED n=11	Epilepsy n=14	Epilepsy versus without epilepsy P value	Epilepsy versus IED P value	Without epilepsy Versus IED P value
FCI	90.8 (85.2–96.4)	82.1 (74–90.2)	78.6 (69.3–88)	0.017*	0.56	0.077
MPI	89.7 (84.1–95.4)	81.8 (73.2–90.5)	78.1 (68.9–87.2)	0.021*	0.53	0.12
NVI	96.8 (89.6–103.9)	85.8 (76.4–95.2)	81.2 (72.7–89.8)	0.008*	0.44	0.077
SEQ	92.5 (85.4–99.6)	86.8 (79.2–94.4)	82.7 (74.3–91.2)	0.084	0.45	0.33
SIM	96.9 (90–103.9)	86.2 (73.2–99.2)	78.5 (69.8–87.2)	0.0018*	0.27	0.10
LEARN	86 [81, 97]	92 [78, 94]	79.5 [75, 92]	0.18	0.30	0.92
PLAN	96.2 (88.7–103.6)	85.2 (75.2–95.1)	82.5 (73-92)	0.026*	0.68	0.090
KNOW	92 [84, 108]	89 [87, 92]	80.5 [75, 87]	0.023*	0.024	0.24

The data are presented as score points: mean with the 95% confidence interval [e.g. X (Y–Z)] or median with the 25th and 75th percentiles (e.g. X [Y, Z]) as statistically appropriate. *Only the p values below the significance threshold of the adjusted false discovery rate of 0.038 for epilepsy versus without epilepsy, 0.0063 for epilepsy versus IED, and 0.0063 for without epilepsy versus IED are significant.

FCI–Fluid Crystallized Index, MPI–Mental Processing Index, NVI–Nonverbal Index, SEQ–Sequential Processing, SIM–Simultaneous processing, LEARN–Learning, PLAN–Planning, KNOW–Knowledge, IED–interictal epileptiform discharges

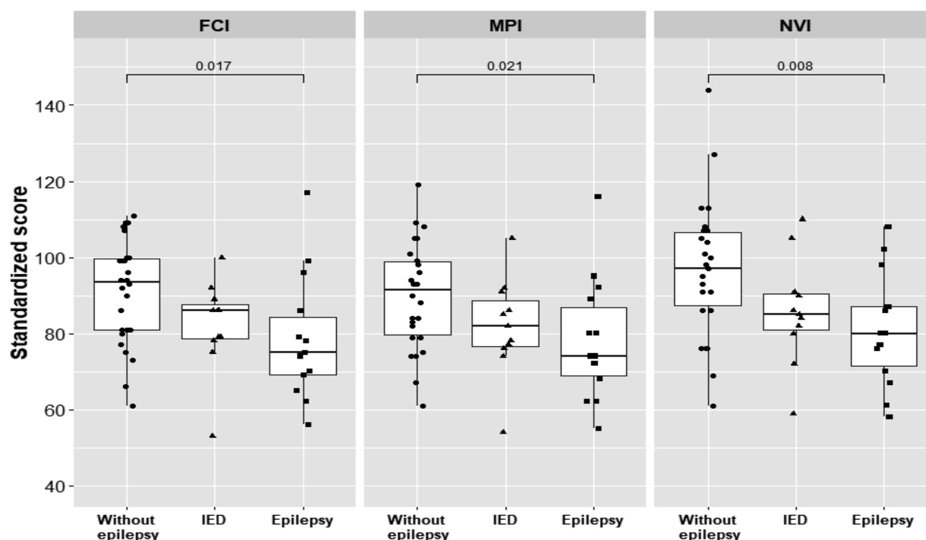

Figure 12. General ability scores for children with epilepsy and for children without epilepsy (Vaher, Männamaa, et al. 2024) (published with permission from Frontiers)

Only the p values below the significance threshold of the adjusted false discovery rate are significant and presented in the figure. FCI–Fluid Crystallized Index, MPI–Mental Processing Index, NVI–Nonverbal Index, IED–interictal epileptiform discharges

7.3.3 Specific cognitive functions

The cognitive profile was different in children with epilepsy and in children without epilepsy: simultaneous processing, planning, and verbal knowledge were significantly lower in children with epilepsy compared to children without epilepsy (*Table 12, Figure 13).* However, sequential processing score and learning score did not differ between children with epilepsy and those without epilepsy.

There were no significant differences in the scores of specific cognitive functions between children with epilepsy and those with IED, or between children without epilepsy and those with IED.

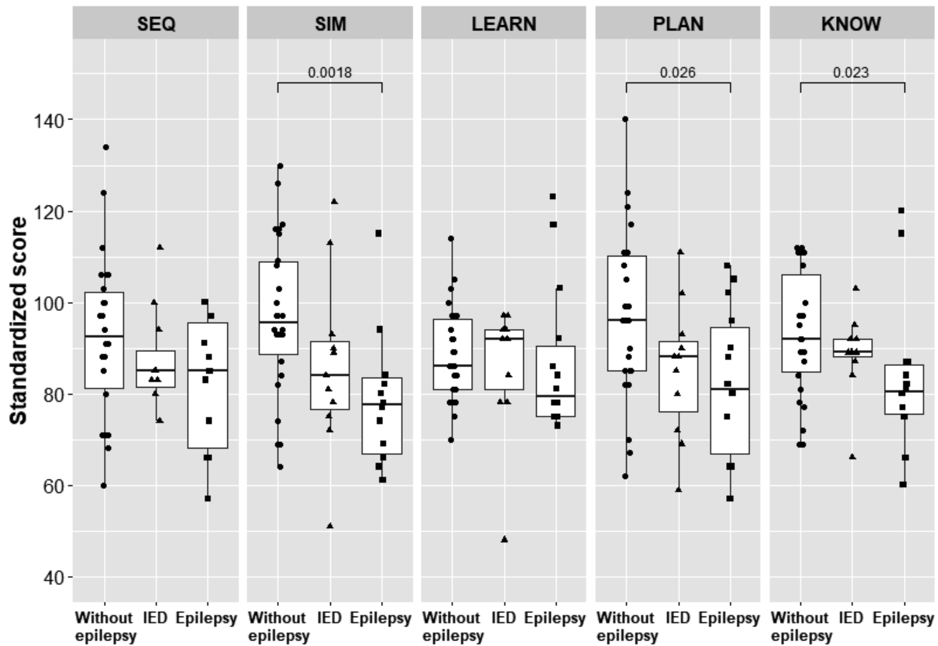

Figure 13. Scores of specific cognitive functions for children with epilepsy and for children without epilepsy (Vaher, Männamaa, et al. 2024) (published with permission from Frontiers)

Only the p values below the significance threshold of the adjusted false discovery rate are significant and presented in the figure. SEQ–Sequential Processing, SIM–Simultaneous processing, LEARN–Learning, PLAN–Planning, KNOW–Knowledge, IED–interictal epileptiform discharges

7.3.4 General ability and specific cognitive functions for children with epilepsy in relation to vascular injury and clinical features of epilepsy

Among the three general ability scores (FCI, MPI, NVI), NVI was lower for children with PMI or DMI compared to children with AT or PT infarction ($p=0.041$), as well as for children with frequent seizures (Engel class ≥3) compared to children with rarer seizures ($p=0.0199$). The score of specific cognitive function of planning was also lower for children with PMI or DMI compared to children with AT or PT infarction ($p=0.016$), as well as for children with frequent seizures (Engel class ≥3) compared to children with rarer seizures ($p=0.016$) *(Table 13)*. Nethertheless, after correction for multiple testing, the raw p values were above the new cut-off (0.0063) for the significance of a single comparison for the set of the variables. There were no differences in the scores of general ability or specific cognitive functions for children with AT or PT infarction, compared to children with PVI, and for children with PMI or DMI, compared to children with PVI.

There were no differences in the scores of general ability and specific cognitive functions between children with epilepsy with left side stroke and children with epilepsy with right side stroke. General ability scores and specific cognitive functions did not differ either between children with status epilepticus or spike-wave activation in sleep and children without these manifestations, or between children receiving polytherapy and children receiving monotherapy *(Table 13)*.

Table 13. Differences in the scores of general ability and specific cognitive functions for children with epilepsy in relation to vascular injury and clinical features of epilepsy (Vaher, Männamaa, et al. 2024) (published with permission from Frontiers)

	AT or PT infarction (n=3) vs PMI or DMI (n=9) p-value	AT or PT infarction (n=3) vs PVI (n=2) p-value	PMI or DMI (n=9) vs PVI (n=2) p-value	Left side stroke (n=10) vs right side stroke (n=4) p-value	With SE or SWAS (n=4) vs wihout (n=10) p-value	Polytherapy (n=6) vs monotherapy (n=8) p-value	Engel class ≥3 (n=8) vs Engel class <3 (n=6) p-value
FCI	0.16	>0.99	0.72	0.62	0.72	0.37	0.093
MPI	0.14	>0.99	0.81	0.57	0.72	0.40	0.091
NVI	0.041	>0.99	0.41	0.26	>0.99	0.30	0.0199
SEQ	0.31	>0.99	0.81	0.28	>0.99	0.24	0.33
SIM	0.23	0.77	0.12	0.065	>0.99	0.70	0.14
LEARN	>0.99	>0.99	0.72	0.28	0.77	0.74	0.43
PLAN	0.016	>0.99	0.72	0.48	0.72	0.44	0.016
KNOW	0.23	>0.99	0.91	0.89	0.36	0.20	0.36

Pairwise comparison was evaluated using the Wilcoxon-Mann-Whitney test. After correction for multiple testing, the cut-off P value for the significance of a single comparison for the set of the variables was 0.0063.

FCI–Fluid Crystallized Index, MPI–Mental Processing Index, NVI–Nonverbal Index, SEQ–Sequential Processing, SIM–Simultaneous processing, LEARN–Learning, PLAN–Planning, KNOW–Knowledge, AT–anterior trunk of distal middle cerebral artery (MCA) infarction, PT–posterior trunk of distal MCA infarction, PMI–proximal M1 MCA infarction, DMI–distal M1 MCA infarction, SE–status epilepticus, SWAS–spike-wave activation in sleep ≥85%

8 DISCUSSION

The current research provides a comprehensive approach to the neuroimaging, clinical, and neurophysiological features and cognitive outcome in children with epilepsy after ischemic perinatal stroke. The most significant finding of the study was that complex assessment of neuroimages that describes the exact type of stroke and the territory of the occluded vessel defining thus the vascular syndrome, can predict development and course of epilepsy after ischemic perinatal stroke. Another major finding of this study demonstrated that smaller size of the thalamus and basal ganglia can predict the risk of poststroke epilepsy. The current study also found lower general cognitive ability in children with epilepsy and identified a different pattern of deficit in specific cognitive functions in children with poststroke epilepsy compared to those without epilepsy. This study adds new knowledge to the issue which children with ischemic perinatal stroke are at higher risk of epilepsy and contributes to our understanding of cognitive outcome in children with poststroke epilepsy, both of which have implications for the future clinical practice through providing possibilities for targeted monitoring of epilepsy and aimed rehabilitation, as well as for early treatment for these children and expert advice for the parents.

8.1 Neuroimaging predictors and timing of epilepsy after ischemic perinatal stroke (Paper I)

8.1.1 Vascular type and poststroke epilepsy

This study found that during a median follow-up of 15.1 years for all children epilepsy developed in 22.9% of the patients with ischemic perinatal stroke. The probability of having epilepsy was significantly higher in patients with perinatal AIS compared to patients with presumed perinatal PVI.

Among patients with AIS, epilepsy developed in 15/39 (38%). In previous studies, the reported incidence varied even among patients with AIS, being 11%–71% for neonatal AIS and 19–50% for presumed perinatal AIS, with a summary epilepsy incidence of 27.2% for perinatal AIS (Billinghurst et al. 2017; Laugesaar et al. 2018; Rattani et al. 2019). However, this study, comprising both neonatal AIS and presumed perinatal AIS, found higher incidence of epilepsy among patients with perinatal AIS. A major reason for this difference in incidence in previous studies is the very wide time range of the follow-up of patients; 1.5–17 years in the abovementioned meta-analysis (Rattani et al. 2019).

Among patients with PVI in the present study, epilepsy developed in 4/44 (9%). Earlier data about epilepsy incidence after presumed perinatal PVI is very limited, but it appears to be 6% or less, particularly at the presentation of presumed perinatal PVI (Kirton et al. 2010; Laugesaar et al. 2018). The results of the present study provide valuable information about development of epilepsy

after presumed perinatal PVI and further confirm the significantly lower incidence of poststroke epilepsy after PVI compared to perinatal AIS.

8.1.2 Vascular syndrome in relation to poststroke epilepsy

The probability of developing epilepsy was different in the distinct vascular syndromes of ischemic stroke. Pairwise comparison of the different vascular syndromes showed that for patients with PMI or DMI the probability of having epilepsy was significantly higher compared to patients with PVI. At the same time, the results of this study did not show significant differences between the vascular syndromes of AIS, or betweeen PVI and children with AT or PT infarction, although the Kaplan-Meier survival curves did not overlap. This demonstrates that for detecting all possible statistical differences between large strokes like PMI or DMI and smaller strokes like AT or PT infarctions and LLS, larger study groups are needed. Some previous studies have found that epilepsy occurs more often in main or complete MCA infarction than in strokes in other vascular territories (M. R. Golomb et al. 2001; Wagenaar et al. 2018; Vojcek et al. 2021). However, in non-main MCA branch infarction only the involvement of the cerebral peduncle and bilateral lesions were associated with postneonatal epilepsy (Wagenaar et al. 2018). The findings of the present study suggest that not all children are at an equal risk of epilepsy after ischemic perinatal stroke and hence targeted follow-up is indicated. Vascular classification is feasible already in early postneonatal radiological evaluation. Therefore, the exact vascular syndrome should be integrated in the radiological diagnosis of ischemic perinatal stroke in order to predict the risk of poststroke epilepsy.

8.1.3 Time of development of poststroke epilepsy

Median age at the first epileptic seizure for all children who developed epilepsy was 4.6 years.

Analysis of Kaplan-Meier survival probability revealed that in the group of AIS cumulative survival without epilepsy decreased throughout childhood and young adulthood, while in the group of PVI the survival function declined until the age of six years when it was 90.9% and remained at this level during the whole follow-up period. The estimated probability of being without epilepsy decreased particularly in the group of PMI or DMI until young adulthood, but in the group of AT or PT infarction until the age of 15 years. Previously it has been described that after pediatric ischemic stroke the risk of epilepsy remaines elevated for 20 years in all children, however, that study comprises both perinatal and childhood stroke and does not differentiate between vascular syndromes (Sundelin et al. 2021). Investigations of only patients with perinatal stroke have found the estimated cumulative incidence of epilepsy to be 55% in perinatal AIS by 10 years of age in one study and 40.8% in all perinatal stroke syndromes by 18 years of age in another study (Wanigasinghe et al. 2010; Laugesaar et al. 2018). Both studies established only a slight increase in the risk of epilepsy after the first 10 years of follow-up (Wanigasinghe et al. 2010; Laugesaar et al. 2018). In contrast

to these earlier findings, the risk of epilepsy until young adulthood did not persist in all children with ischemic perinatal stroke in the present study, but only in patients with AIS, particularly patients with PMI or DMI; thus in patients with PVI all epilepsy cases occurred before the school age. The results of present study suggest that detailed distinction of the vascular syndrome helps predict the risk and time of epilepsy development after ischemic perinatal stroke; and children with PVI should be closely monitored for epilepsy until school age and patients with AIS, especially PMI or DMI should monitored until young adulthood.

8.1.4 Clinical features and outcome of poststroke epilepsy

The study found that altogether 73.7% of patients with epilepsy had at least one complicated manifestation of it. Among the patients with complicated epilepsy, 26% had had status epilepticus and 10% had had spike-wave activation in sleep. It is noteworthy that in 4/19 (21%) patients epilepsy presented with status epilepticus at the time of epilepsy diagnosis. However, for two of them, detailed history revealed previous focal seizures that had not been recognized earlier. Although the study showed that in children with PVI the probability of having epilepsy is lower compared to the other vascular syndromes, all children with PVI with epilepsy had status epilepticus or spike-wave activation in sleep, which makes odds of these manifestations 81 times higher than in children with AT or PT infarction. Why children with PVI and epilepsy have a higher risk of status epilepticus is unclear and needs further research. An earlier study on epilepsy in patients with perinatal AIS found poorly controlled epilepsy in 17% and these authors admit that despite the relatively good outcome, some of these children required initial aggressive management (Wanigasinghe et al. 2010). The findings of the present study indicate that children with ischemic perinatal stroke, both those with AIS and those with PVI, should be closely monitored for complications of epilepsy, especially in pre-school age. For patients with ischemic perinatal stroke, antiseizure medication should be considered after the first seizure.

Two children (10%) with epilepsy in the study group presented with epileptic spasms and hypsarrhythmia followed by focal seizures in one and remission in the other. Both of these children had had neonatal PMI. All other children presented with focal onset seizures. In a study of perinatal AIS, the authors reported that 26% of the children with epilepsy presented with epileptic spasms, which is more than in the cohort of the present study (Wanigasinghe et al. 2010). Another study on presumed perinatal AIS found epileptic spasms in 14% of the children (Bektaş et al. 2019). However, as the cohort of the present study comprises both patients with AIS and patients with PVI, this difference in the study population may explain the lower incidence of epileptic spasms in this study.

There were no significant differences between the vascular syndromes in seizure frequency, changes in the EEG background or spread of IED.

The long-term outcome of epilepsy in this study cohort was favorable. Although some epilepsy complication occurred in almost 74% of patients, 53% of the patients with epilepsy had been seizure free and off medication over six

months and another 26% had been seizure free over six months, but on medication at the last follow-up at a median age of 19.8 years. It is notable that patients who had been in remission more than 12 years of follow-up after the last seizure, had had no epilepsy recurrence. Favorable outcome of epilepsy has been described also in previous reports. Among patients with perinatal AIS 12% were without active epilepsy and 59% were with well controlled epilepsy at the last follow-up of 34 months, but only 15% had active epilepsy at 10 years from seizure onset (Wanigasinghe et al. 2010; Billinghurst et al. 2017). In a cohort of patients with only neonatal AIS the prevalence of active epilepsy was 11% at follow-up at seven years of age (Chabrier et al. 2016).

The present study supports the concept that despite various possible complications during the course of epilepsy, the overall outcome is favorable with long-lasting remission (Wanigasinghe et al. 2010). In patients with poststroke epilepsy, particularly those with PVI, more attention should be paid to possible complications. Thus, after the first seizure antiseizure medication should be considered while a certain number of patients require aggressive epilepsy treatment. Treating physicians, as well as parents need to be aware of the potential different manifestations of epilepsy.

8.2 Volume of the subcortical gray matter structures (Paper II)

This study provided the first comprehensive assessment of the volume of the thalamus, basal ganglia and hippocampus in children with ischemic perinatal stroke in relation to poststroke epilepsy.

The study revealed that the ipsilesional size of the thalamus and basal ganglia in children with poststroke epilepsy differs not only from that in the children of the control group, but there are also differences in this regard between children with epilepsy and those without epilepsy.

Children with AIS and poststroke epilepsy had a smaller ipsilesional thalamus, caudate nucleus and nucleus accumbens, but also a smaller contralesional thalamus compared to children with AIS but without epilepsy. Based on visual assessment of radiological images, the involvement of the basal ganglia and cortex, or the thalamus and basal ganglia, has been described earlier in development of epilepsy (Kirton et al. 2008; Billinghurst et al. 2017; Laugesaar et al. 2018; Wagenaar et al. 2018). However, the volumetry of the thalamus and basal ganglia has been perfomed in children with perinatal stroke only in association with motor outcome (Gold and Trauner 2014; Craig, Carlson, and Kirton 2019; Hassett et al. 2022; Nigul Ilves, Lõo, et al. 2022). The results of the present study on the thalamus and basal ganglia provided detailed insights into the pattern of changes in the size of the thalamus and specific basal ganglia, demonstrating the need for assessing the subcortical gray matter structures and supporting earlier findings of visual observations of the subcortical structures in children with poststroke epilepsy (Billinghurst et al. 2017; Laugesaar et al. 2018; Wagenaar et al. 2018).

The most intriguing findings of the present study were derived from the comparison of the subcortical gray matter structures between children with IED only and those with epilepsy or without epilepsy. In the AIS group, the ipsi- and contralesional caudate nucleus and the contralesional putamen were larger in children with IED compared to children with epilepsy. The larger contralesional caudate nucleus and putamen were also noted in children with IED compared to children without epilepsy or controls. This kind changes were not expressed in children with epilepsy compared to children without epilepsy. Previous functional studies of seizures have shown the involvement of the caudate nucleus and putamen in generating ictal activity during epileptic seizures (Aupy et al. 2018; Devergnas et al. 2012). This may suggest that, besides the smaller thalamus, also concomitant damage to the caudate nucleus and putamen is needed to generate epileptic seizures; and that the larger contralesional caudate nucleus and putamen in children with IED may indicate presence of compensatory or protective mechanisms, which should be explored in future research.

In children with PVI with epilepsy the subcortical gray matter structures differed from those of the children of the control group, but not from children with PVI, but without epilepsy. As there was no statistical difference in the size of the thalamus and basal ganglia between children with epilepsy and children with IED in the group of PVI, a pooled group was formed on the basis of the groups of epilepsy and IED. In children with PVI in the pooled group of only IED plus epilepsy, the ipsilesional thalamus, caudate nucleus and nucleus accumbens were smaller compared to children without epilepsy. In PVI, typically the cortex is spared and also the basal ganglia are relatively spared (Kirton et al. 2008). Thus, the present study demonstrated that in some children with PVI the thalamus and basal ganglia are also smaller, and in the pooled group of epilepsy plus IED, children with PVI showed changes that were similar to changes in children with AIS and poststroke epilepsy.

The results of this study indicate that it is important to perform follw-up MRI at the chronic stage of stroke and to measure the volume of the thalmus and basal ganglia for predicting the risk for devolopment of poststroke epilepsy, but also IED.

8.3. Cognitive outcome of poststroke epilepsy (Paper III)

8.3.1 General cognitive ability

This study found lower scores in all general ability indexes in children with neonatal or presumed perinatal ischemic stroke and poststroke epilepsy compared to children with stroke, but without epilepsy. Earlier studies of children with neonatal or perinatal stroke, both those with AIS and those with PVI, have shown lower general cognitive performance already at two years of age with persisting deficit at a mean age of 9.9 years regarding normative means (Elgendy et al. 2022; Li et al. 2022). A former study suggested that the lower cognitive results in this

group of children with perinatal stroke could be accounted for the presence of patients with epilepsy in this group, however these authors did not distinguished between children with epilepsy and children without epilepsy or compare them (Li et al. 2022). The present study is consistent with a study of children with presumed perinatal AIS where the authors showed that cognitive impairment at the last follow-up was associated with epilepsy (Fitzgerald et al. 2007).

Numeral other studies have also been dedicated to cognitive outcome after pediatric stroke, however the cognitive functions assessed and the methods used have large variability and the study groups often combine patients with both perinatal and childhood stroke, or the authors compare patients with stroke and typically developed children (Jacomb et al. 2018; Anderson et al. 2020; Champigny et al. 2023).

The findings of the current study suggest that children with ischemic perinatal stroke, who have increased likelihood of developing epilepsy, need attention not only in relation to development of epilepsy, but also in relation to cognitive development. Considering other factors, i.e. vascular syndrome of stroke, side of stroke, presence of status epilepticus or spike-wave activation in sleep, polytherapy, and frequent seizures, which may affect cognitive function in children with poststroke epilepsy, we failed to establish any statistically significant changes. Studies with large study groups focusing on these domains are needed in the future.

8.3.2 Specific cognitive functions

The study found lower scores in the subscales of simultaneous processing, planning, and verbal knowledge for children with epilepsy compared to children without epilepsy. These results indicate deficit in tasks of simultaneous processing of visual information, which measure executive functions, problem-solving, and reasoning abilities and are related to verbal abilities and acquired knowledge; at the same time, sequential information processing, short-term memory, and storing and retrieving newly learned information remain unaffected in children with poststroke epilepsy compared to children without epilepsy. This study confirms the findings of previous studies regarding the outcome of perinatal stroke where the presence of epilepsy is considered to have an adverse effect on attention and executive functions (Kolk et al. 2011; Bosenbark et al. 2017; Champigny et al. 2023). However, another study of patients with both perinatal AIS and presumed perinatal PVI found that epilepsy was a significant risk factor for only non-verbal intelligence (Gschaidmeier et al. 2021). Regarding the profile of specific cognitive functions, patients with poststroke epilepsy in this study have a similar profile as is observed in other childhood-onset epilepsy syndromes, where worse performances have been found across the measures of language and semantic functions and visuomotor functions (Karrasch et al. 2017). This finding could be explained by different damage to networks in children with poststroke epilepsy compared to children after perinatal stroke who have no epilepsy, and should be considered in targeted rehabilitation.

8.3.3 Interictal epileptiform discharges and cognitive functions

This study did not find differences in the scores of general cognitive ability or specific cognitive function between patients with epilepsy and patients with IED only.

Earlier studies have suggested that IED may affect the cognitive profile, e.g. central information processing speed, short-term verbal memory, visual-motor integration, receptive language, and externalizing behaviors (Ebus et al. 2012; Mineyko et al. 2017). Therefore, we analysed children without epilepsy in two separate groups: children without epileptic seizures and without IED and children without epileptic seizures but with IED. Although it was not statistically significant, the study found considerably lower scores of Fluid Crystallized Index, Non-verbal Index, and the planning subscale for children with IED only compared to children without epilepsy and without IED. The peak of spike-wave activation in sleep (former electrical status epilepticus during slow-wave sleep) is around the age of 4–5 years (Arican et al. 2021). Hence the results of this study suggest that these lower scores in general and specific cognitive domains may be important in clinical practice and follow-up post-neonatal EEG investigation in pre-school age is recommended also for children without epileptic seizures in order to identify children who are at a risk of cognitive deficit. Anyhow, further research is needed to ascertain the relevance of these data.

The results of this study complement the understanding of the cognitive performance of children with ischemic perinatal stroke in relation to epilepsy. Although the scores of general cognitive ability for children with poststroke epilepsy are worse compared to children without epilepsy, sequential information processing, short-term memory, and storing and retrieving newly learned information remain at the same level as in children without epilepsy. The patients with ischemic perinatal stroke and particularly for patients with poststroke epilepsy, but also for patients with IED only, besides general cognitive evaluation, also different specific domains of cognitive functions should be assessed and targeted rehabilitation established.

8.4 Limitations

8.4.1 Group size

Ischemic perinatal stroke with its overall prevalence of 1:1,100 is not a rare disease, but distinct vascular syndromes of perinatal stroke are very rare, particularly considering the Estonian population of 1,374,687 at the beginning of 2024 and a birth rate of 10,949 in 2023 ("Orphanet: Quality charter<strong>About Rare Diseases</Strong>," n.d.; Dunbar et al. 2020; "Rahvaarv | Statistikaamet," n.d.). Because of this, the study groups were relatively small for making statistical conclusions in all aspects. Nevertheless, almost all (95%) children with ischemic perinatal stroke with a median follow-up of 15.1 years from EPSD were included in this study. Although the subgroups of the study were small, the results of the study showed also some statistically non-significant differences which were considered important in clinical practice and which would provide future directions of research not only for our team, but for all scientists exploring perinatal stroke.

8.4.2 Data collection

As the data collection period was long, the data may be inconsistent due to changed clinical practice and definitions. Prospective collection of patients in EPSD was started in 2004, from 1994 to 2003 patient collection was retrospective. To make the study population homogenous, all neuroimages from 1994 were reviewed by neuroradiologists who confirmed the vascular syndrome of stroke.

To define patients with epilepsy in compliance with the currently valid definition, all cases were reviewed by the applicant. It was also possible to review all digital EEG investigations from 2005 onward.

The clinical data of the patients who were included into the database during the first years were mainly based on previous case histories on paper files. However, besides hospital-based digital case histories starting from 1997, the national digital Health Portal, which contains patient data starting from 2007 and provides information about all visits to family doctors and specialists, final diagnoses, and prescriptions from the national digital Prescriptions Center from 2010 onward, was used to ascertain the data.

8.4.3 Volumetry assessment

Large stroke lesions deform the thalamus and other brain structures and make it difficult to evaluate them by automatic segmentation. Therefore, manual segmentation was performed. To evaluate the hazard of bias, also inter- and intra-rater reliabilities were estimated with high agreement between measurements, especially in the case of measuring the size of the thalamus.

As epilepsy started at different patient ages, there was a gap between the first epileptic seizure and follow-up MRI, because of which we cannot exclude the impact of epileptic seizures itself on the volume of the subcortical gray matter structures.

8.4.4 Timing of EEG in patients without epileptic seizures

There was no standardized age at which EEG was performed in patients without epileptic seizures. Before our first study on epilepsy in patients with perinatal stroke in 2018, EEG was performed for clinical purposes in case of suspicion of epileptic seizures (Laugesaar et al. 2018). However, there is still no standardized protocol established to whom and at what age to perform EEG among patients with perinatal stroke who have no epileptic seizures. Therefore, for the present study, a previous post-neonatal EEG study done for clinical purposes or an EEG done at the time of the last follow-up at non-standardized age was used. Thus, possible IED may not have been detected in all children.

8.4.5 Timing of cognitive assessment

Assessment of cognitive functions based on KABC-II in children was performed at the age of ≥7 years. The timeframe of 7–18 years is wide, but it was opted for to evaluate not only general ability but also as many specific cognitive functions as possible. However, the results of the first testing were used, if testing was performed more than once after the age of seven years, and the median time of the duration of epilepsy was 8.2 years (IQR: 5.0, 9.7) at the time of cognitive testing, which was more uniform than the overall timeframe. Although in many cases epilepsy is manifested before school-age, comprehensive evaluation of cognitive functions at this age is limited. Longitudinal studies are needed to evaluate cognitive functions during childhood and teenage in children with poststroke epilepsy, as well as in children with IED.

8.4.6 Factors other than epilepsy affecting cognitive outcome

The findings of the study cannot rule out the possible effect of medication on cognitive performance in children with epilepsy. However, there was no difference in cognitive ability scores between children receiving monotherapy and children receiving polytherapy. The other factors analysed, i.e. vascular syndrome, the side of stroke, the presence of status epilepticus or spike-wave activation in sleep, and frequent seizures did not show statistical impact to the cognitive scores. One patient with PVI with complicated epilepsy had to be excluded because she was not able to perform the cognitive tests due to severe cognitive deficit. Still, these results should be treated with caution as the subgroups were small. More research is required to determine the interaction between variables other than epilepsy and the cognitive performance of children with perinatal stroke.

8.5 Contribution to the field

This systematic research of children with ischemic perinatal stroke established neuroimaging features predictive of development of poststroke epilepsy and demonstrated the actual profile of different cognitive domains in children with poststroke epilepsy.

The study comprises both most frequent types of ischemic perinatal stroke, i.e. AIS and PVI, and indicates that epilepsy developes more often in perinatal AIS than in presumed perinatal PVI. Moreover, the study demonstrated that the PMI or DMI vascular syndrome carries the highest risk for development of epilepsy, whereas in the case of PVI the risk is the lowest. The long follow-up time of the study with a median of 15 years revealed that in PMI or DMI epilepsy risk persists until young adulthood, but in PVI it only persists until the end of preschool age. According to the above results, the diagnosis of perinatal stroke should integrate also the exact vascular type and the vascular syndrome of stroke in order to develop a targeted monitoring plan of epilepsy for each vascular syndrome of stroke.

The results show that PVI carries higher risk for development of complications of epilepsy, although some complication manifests itself in almost three fourths of all epilepsy patients. However, despite possible complications, remission of epilepsy is achieved in a great majority of the patients. These data implicate that children with poststroke epilepsy should be monitored very closely for complications, especially at the beginning of epilepsy and aggressive treatment should be started promptly where needed.

The study is the first to demonstrate that smaller size of the ipsilesional thalamus, caudate nucleus and nucleus accumbens is related to poststroke epilepsy. Also, it confirms that volumetric segmentation is a reliable method of evaluating the thalamus and basal ganglia to predict the risk of epilepsy after ischemic perinatal stroke. The results suggest that evaluation of the thalamus and basal ganglia should be included in the radiological investigation of patients with perinatal stroke.

This study demonstrated that not all children with ischemic perinatal stroke have similar cognitive outcome. Evidence from the study suggests that, compared to children without epilepsy after perinatal stroke, children with poststroke epilepsy perform worse in general cognitive ability and in tasks that require simultaneous processing of visual information, which measures executive functions, problem-solving, and reasoning abilities and which are related to verbal abilities and acquired knowledge. Awareness of the cognitive profile provides an opportunity to use less affected cognitive domains in the rehabilitation of children with poststroke epilepsy.

Besides differences between children with epilepsy and children without epilepsy, the study also indicates that in children with IED only, the size of the subcortical gray matter structures and the cognitive profile are more similar to these features in children with epilepsy than in children without epilepsy. The scores of general cognitive ability and specific cognitive function did not differ between

children with epilepsy and children with IED only. Fluid Crystallized Index and Nonverbal Index, as well as the score of the planning subscale were lower for children with IED compared to children without epilepsy, but as the groups were small, the results were not statistically different. These data provide support that as both IED and epilepsy may affect the cognitive profile of children after perinatal stroke, then EEG investigation in pre-school age may be indicated for all children after perinatal stroke. Hopefully, the results of this study would also initiate further studies considering the effect of IED on cognition.

In conclusion, the findings of this research highlight the importance of classifying the vascular syndrome of perinatal stroke and follow-up radiological evaluation of the thalamus and basal ganglia in predicting the risk of epilepsy. Depending on the vascular syndrome, patients with PMI or DMI should be closely monitored for epilepsy until early adulthood, but patients with PVI should be monitored until school-age. Evaluating cognitive outcome, not only general ability but also special cognitive abilities should be assessed in patients with perinatal stroke with or without epilepsy. This would allow to provide targeted rehabilitation by making use of less impaired cognitive functions. As IED may contribute to cognitive deficit, EEG investigation should be performed to all patients with ischemic perinatal stroke in pre-school age.

Apart from clinical importance, the findings of this study will contribute to our understanding of development of poststroke epilepsy in perinatal stroke, as well as our understanding of the overall epilepsy network.

9 CONCLUSIONS

I. Children with neonatal or presumed perinatal PMI or DMI have higher probability for developing poststroke epilepsy than children with presumed perinatal PVI. In patients with PVI epilepsy develops before school age, while in patients with PMI or DMI the risk remains high until young adulthood. In patients with AT or PT infarction, there was less status epilepticus or spike-wave activation in sleep compared to patients with PVI.

It is important to integrate the precise vascular syndrome of stroke, i.e. AT or PT infarction, PMI, DMI, LLS or PVI in routinely used radiological diagnosis to predict the risk for development and course of epilepsy.

II. Children with ischemic perinatal stroke with combined damage to the thalamus and basal ganglia, particularly combined with a smaller ipsilesional caudate nucleus and nucleus accumbens, are at higher risk for development of poststroke epilepsy. More extensive volume loss of the subcortical gray matter structures in patients with epilepsy were observed in the group of perinatal AIS compared to patients with presumed perinatal PVI. The profile of the changes in the thalamus and basal ganglia in children with IED only was more similar to that in children with epilepsy. However, a larger ipsi- and contralesional caudate nucleus and a larger contralesional putamen were found in children with IED compared to children with epilepsy in the group of AIS.

The follow-up radiological evaluation of the thalamus and basal ganglia is important in predicting the risk of epilepsy and timely interventions and should be implemented in the general post-neonatal follow-up of children with ischemic perinatal stroke.

III. Children with ischemic perinatal stroke and poststroke epilepsy show lower scores of general cognitive ability compared to children with stroke, but without epilepsy. Among the specific cognitive subscales, the scores for simultaneous processing, planning, and knowledge were lower in children with epilepsy compared to those without epilepsy, which indicates deficiencies in verbal abilities and executive functions. No differences were establish in the scores of general cognitive ability and specific cognitive function between patients with epilepsy and patients with IED only.

For targeted rehabilitation, assessment of not only general ability, but also of special cognitive abilities is crucial for using less impaired cognitive functions in the rehabilitation of children with epilepsy and with IED. EEG investigation in pre-school age is recommended in order to identify children with IED which may affect cognitive functions as well epilepsy.

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11 SUMMARY IN ESTONIAN

Epilepsia ajaliselt sündinud perinataalse isheemilise insuldiga lastel: neuroradioloogilised tunnused, kliiniline kulg ja kognitiivsed kaugtulemused

11.1 Sissejuhatus

Perinataalne isheemiline insult hõlmab erinevaid kliinilis-radioloogilisi sündroome, mis tekivad kindla paikkonna verevarustuse häire korral ajus ja mis jaotatakse diagnoosimise aja järgi üsasiseseks, vastsündinu perioodi ja hilise diagnoosiga perinataalseks isheemiliseks insuldiks (Raju et al. 2007). Perinataalse isheemilise insuldi kaks peamist tüüpi on periventrikulaarne venoosne insult (PVI) ja arteriaalne isheemiline insult (AII), mis enamasti haarab keskmist ajuarterit (Raju et al. 2007; Kirton et al. 2008; Wagenaar et al. 2018). Kõige sagedasemad perinataalse isheemilise insuldi vaskulaarsed sündroomid on: 1) keskmise ajuarteri proksimaalse M1 osa infarkt; 2) keskmise ajuarteri distaalse M1 osa infarkt; 3) keskmise ajuarteri distaalse osa eesmise tüve infarkt; 4) keskmise ajuarteri distaalse osa tagumise tüve infarkt; 5) külgmiste läätstuuma-juttkeha arterite infarkt; 6) periventrikulaarne venoosne infarkt (Kirton et al. 2008). Viimaste rahvusvaheliste uuringute alusel on perinataalse insuldi haigestumus 1:1100 sünni kohta (Dunbar et al. 2020). Varasemate uuringute andmetel Eestis on kõigi perinataalse perioodi insuldivormide üldine esmashaigestumuskordaja 63,4:100 000 elussünni kohta (Laugesaar et al. 2007). Selline haigestumus on sageduselt teisel kohal laste ja noorte täiskasvanute (kuni 54 a.) erinevates eagruppides tekkivate insultide seas Eestis, kus see oli 120,9:100 000 isiku-aasta kohta 45–54 aastaste hulgas (Laugesaar et al. 2010; Kõrv et al. 2021).

Perinataalsest insuldist tingitud jääknähte esineb, kas eraldi või kombineerituna, enamikul insulti läbipõdenud lastest (Chabrier et al. 2016; Lõo et al. 2018). Kõige sagedamini põhjustab perinataalne insult motoorset defitsiiti, kõnehäireid, käitumisprobleeme, õpiraskusi ja epilepsiat (Chabrier et al. 2016; Laugesaar et al. 2018; Lõo et al. 2018; Wagenaar et al. 2018). Kuna tegemist on lapseeas tekkinud, kuid elukestvate häiretega, halvendab see ka perinataalset insulti põdenud laste, nende vanemate ja perede toimetulekut ning on majanduslikult koormav nii peredele kui ühiskonnale (Gardner et al. 2010; S. E. Smith et al. 2015).

Epilepsia perinataalse insuldi järgselt tekib erinevate autorite andmetel 6–71% lastest olenevalt insuldi tüübist (Billinghurst et al. 2017; deVeber et al. 2017; Laugesaar et al. 2018). Kõige sagedamini on kirjeldatud epilepsia esinemist AII järgselt, kuid ei ole teada, millise kindla vaskulaarse sündroomi korral on tõenäosus epilepsia tekkeks suurem (Kirton et al. 2008; Billinghurst et al. 2017; Laugesaar et al. 2018).

Uuringud on näidanud, et perinataalse insuldi järgselt võib epilepsia tekkida ka kuni kahekümnendate eluaastate alguseni (Laugesaar et al. 2018; Sundelin et al. 2021). Enamusel juhtudel perinataalse insuldi järgselt tekib aga epilepsia enne

kümnendat eluaastat (Wanigasinghe et al. 2010; Laugesaar et al. 2018). Varasemad uuringud ei ole eraldi välja toonud epilepsia kujunemise riski erinevate isheemilise insuldi vaskulaarsete sündroomide korral ega epilepsia tekke riski muutumist ajas.

Kuvamisuuringute, eelkõige magnetresonantstomograafia (MRT) kujutiste visuaalsel hindamisel on leitud, et epilepsia teket võib seostada keskmise ajuarteri suure haru insuldiga, aga ka samaaegse subkortikaalsete hallaine struktuuride ja ajukoore haaratusega (Kirton et al. 2008; Billinghurst et al. 2017; Laugesaar et al. 2018; Ratika Srivastava et al. 2021). Samas täpsemaid objektiivseid uuringuid talamuse ja basaaltuumade mahu hindamiseks on tehtud vaid motoorsete kahjustuste uurimiseks (Craig, Carlson, and Kirton 2019; Hassett et al. 2022; Nigul Ilves, Lõo, et al. 2022). Seetõttu ei ole teada, milliste subkortikaalsete hallaine struktuuride muutuste korral on risk epilepsia tekkeks kõrgem.

Kognitiivse arengu uuringud perinataalse insuldi kaugtulemuste korral viitavad üldistele madalamatele kognitiivsetele võimetele perinataalset insulti põdenud lastel võrreldes tervete lastega (Anderson et al. 2020; Elgendy et al. 2022). Samas on mitmetes kognitsiooni uuringutes kaasatud samaaegselt nii vastsündinu AII-ga kui lapseea AII-ga patsiendid ning ei ole eraldi uuritud epilepsiaga lapsi või võrreldud epilepsiaga lapsi nende lastega, kellel epilepsiat insuldi järgselt ei tekkinud (Kolk et al. 2011; Anderson et al. 2020; Jacomb et al. 2018; Li et al. 2022).

11.2 Uuringu eesmärgid ja hüpoteesid

Uuringu üldiseks eesmärgiks oli uurida epilepsia teket perinataalse isheemilise insuldi järgselt, tuvastada võimalikud neuroradioloogilised tunnused, mis on seotud epilepsia kujunemisega, ning uurida epilepsia kulgu ja kognitiivseid kaugtulemusi epilepsiaga lastel.

Spetsiiiflised eesmärgid ja hüpoteesid olid:
1. Uurida epilepsia tekkimist perinataalse isheemilise insuldi järgselt ja leida, millise vaskulaarse sündroomi korral on epilepsia teke tõenäosem ja kas vaskulaarne sündroom mõjutab epilepsia kulgu (I publikatsioon).
Hüpotees: keskmise ajuarteri proksimaalse või distaalse M1 osa insuldi korral on epilepsia tekke tõenäosus suurem. Erinevate vaskulaarsete sündroomide korral võib insuldijärgse epilepsia kulg olla erinev.

2. Uurida talamuse ja basaaltuumade mahtu perinataalset isheemilist insulti põdenud lastel ja kontrollgrupi lastel, et leida seosed epilepsia tekkega (II publikatsioon).
Hüpotees: perinataalse isheemilise insuldi tagajärjel kujunenud epilepsiaga lastel esinevad talamuse ja basaaltuumade muutused, mida ei ole neil lastel, kellel epilepsiat ei kujunenud.

3. Uurida üldist kognitiivset võimekust ja spetsiifilisi kognitiivseid funktsioone lastel, kellel on kujunenud perinataalse isheemilise insuldi järgselt epilepsia, ja võrrelda neid lastega, kellel epilepsiat ei ole tekkinud (III publikatsioon).
Hüpotees: perinataalse isheemilise insuldi järgselt tekkinud epilepsiaga laste kognitiivne profiil on erinev nende laste kognitiivsest profiilist, kellel epilepsiat ei tekkinud.

11.3 Uuritavad ja meetodid

Uuringusse kaasati perinataalset isheemilist insulti põdenud lapsed Eesti laste insuldi andmekogust, kes olid sündinud ≥36 rasedusnädalal ja kellel ei olnud diagnoositud teisi kesknärvisüsteemi haigusi. Kokku haarati uuringusse 83/87 (95%) last Eesti laste insuldi andmekogust, kes jaotusid järgnevalt: 39/83 (47%) last AII-ga (22 last vastsündinu AII-ga ja 17 last hilise diagnoosiga AII-ga) ja 44/83 (53%) last hilise diagnoosiga PVI-ga. Kontrollgrupi lasteks olid vabatahtlikud, soo ja vanuse poolest sobivad, tüüpilise arenguga ja ilma neuroloogiliste haigusteta 46 last. Uuringus osalenud nii insuldiga kui kontrollgrupi laste vanematelt, ja samuti lastelt, kes oskasid lugeda, saadi kirjalik nõusolek uuringus osalemiseks. Uuringukava on heaks kiitnud Tartu Ülikooli inimuuringute eetika komitee.

Kliinilised andmed ema raseduse ja sünnituse, lapse arengu ja epilepsia kujunemise osas koguti vanematelt ja haiguslugudest.

Insuldiga laste üldise arengu ja neuroloogilise leiu hindamiseks kasutati *Pediatric Stroke Outcome Measurement* mõõdikut, mis on rahvusvaheline tööriist hindamaks insulti põdenud laste kaugtulemusi (Kitchen et al. 2012).

MRT ajukahjustuse ulatuse hindamiseks teostati *3T Philips Achieva* skanneriga. Radioloogilised uuringud perinataalse insuldi diagnoosi ja tüübi kinnitamiseks vaadati üle kolme neuroradioloogi poolt. Eristati järgmisi perinataalse isheemilise insuldi vaskulaarseid sündroome: 1) keskmise ajuarteri proksimaalse M1 osa infarkt; 2) keskmise ajuarteri distaalse M1 osa infarkt; 3) keskmise ajuarteri distaalse osa eesmise tüve infarkt; 4) keskmise ajuarteri distaalse osa tagumise tüve infarkt; 5) külgmiste läätstuuma-juttkeha arterite infarkt; 6) periventrikulaarne venoosne infarkt (Kirton et al. 2008).

Volumeetriliseks hindamiseks (II publikatsioon) MRT uuringud anonümiseeriti ja analüüsiti *FMRIB Software Library (FSL)* (https://www.fmrib.ox.ac.uk/fsl/) version 6.0.5. tarkvara abil kahe erineva uurija poolt, kes ei teadnud teineteise hinnatud uuringu tulemusi. Esmalt teostati automaatne struktuuride hindamine, millele järgnes manuaalne korrigeerimine. Mõõdeti talamuse, sabatuuma, kooriku, kahkjaskeha, mandelkeha, naalduva tuuma ja hipokampuse mahtu.

Epilepsia diagoositi vastavalt Rahvusvahelise Epilepsiavastase Liiga väljatöötatud diagnoosi kriteeriumitele (Fisher et al. 2014). Epilepsia kaugtulemusi hinnati Engeli kohandatud klassifikatsiooni abil (Meredith R. Golomb et al. 2007).

Vaskulaarsete sündroomide, kognitiivsete võimete ja subkortikaalsete hall-aine struktuuride mahtude hindamisel võrreldi omavahel laste andmeid, kellel kujunes epilepsia, nende laste andmetega, kellel epilepsiat ei kujunenud. Uuritavate struktuuride mahtu võrreldi lisaks ka kontrollgrupi laste andmetega (II publikatsioon).

Insuldiga laste kognitiivset arengut hindas kliiniline psühholoog, kasutades *Kaufman Assessment Battery for Children II* testipatareid (III publikatsioon) (Kaufman et al. 2005). Omavahel võrreldi andmeid lastel, kellel kujunes epilepsia, nende laste andmetega, kellel epilepsiat ei kujunenud.

Tulemuste analüüsimiseks kasutati statistika programme SAS (versioon 9.4) ja R (versioon 4.0.2).

11.4 Tulemused

Perinataalse isheemilise insuldi vaskulaarsete sündroomide uuring (I publikatsioon) näitas, et mediaan jälgimisaja 15,1 aasta korral tekkis epilepsia 22,9% (19/83) lastel. Epilepsia tekkis sagedamini neil lastel, kellel oli AII (38%), kui neil lastel, kellel oli PVI (9%), (p=0,0009). Vaskulaarsete sündroomide paariviisilise võrdluse alusel tekkis epilepsia sagedamini neil lastel, kellel oli olnud keskmise ajuarteri proksimaalse M1 osa või distaalse M1 osa infarkt, kui lastel, kellel oli olnud PVI (p=0,0007). Kogu perinataalse isheemilise insuldi grupis oli kumulatiivne tõenäosus olla ilma epilepsiata mediaanvanuse 15,1 juures 75,4%. Erinevate vaskulaarsete sündroomide Kaplan-Meieri elulemusanalüüs näitas, et kuni 20-ndate eluaastate alguseni püsis tõenäosus haigestuda epilepsiasse neil uuritavatel, kellel oli olnud keskmise ajuarteri proksimaalse M1 osa või distaalse M1 osa infarkt. Neil lastel, kellel oli olnud PVI, püsis epilepsia risk kuni 7. eluaastani ning edaspidi uusi epilepsia juhte ei lisandunud.

Mediaanvanus esimese epileptilise hoo ajal oli 4,6 aastat. Vähemalt üks epilepsia kulgu raskendav faktor (sagedased epileptilised hood, epileptiline staatus, spaik-aeglase laine aktivatsioon une ajal ≥85%, polüfarmakoteraapia) esines 73,7% epilepsiaga lastest. Epileptilist staatust või spaik-aeglase laine aktivatsiooni ≥85% une ajast esines rohkem neil lastel, kellel oli olnud PVI, kui neil lastel, kellel oli olnud keskmise ajuarteri distaalse osa eesmise või tagumise tüve infarkt (p=0,029). Epileptilise staatuse tekkel diagnoositi epilepsia 21% (4/19) juhtudest, kuigi hilisem anamnees selgitas, et kahel juhul olid juba eelnevalt esinenud fokaalsed epileptilised hood. Epilepsiaga patsientide mediaanjälgimisaja lõpuks 19,8 a. vanuses olid 52,6% neist patsientidest hoovabad ja ilma ravita üle 6 kuu.

Talamuse ja basaaltuumade volumeetrilisel uuringul (II publikatsioon) kaasati uuringusse need lapsed, kellele oli teostatud kontroll-MRT uuring insuldi kroonilises faasis 6–18 a. vanuses. Lõpliku uuringugrupi selle analüüsi jaoks moodustasid 62 perinataalse isheemilise insuldiga last: 15 last neonataalse AII-ga, 14 last hilise diagnoosiga perinataalse AII-ga ja 33 last hilise diagnoosiga PVI-ga. Omavahel võrreldi lapsi, kellel epilepsia tekkis, nende lastega, kellel epilepsiat ei tekkinud, ja kontrollgrupi lastega. Uuringus selgus, et kahjustusepoolsed talamuse,

sabatuuma, kooriku, mandelkeha, naalduva tuuma ja hipokampuse mahud olid AII-ga lastel, kellel oli epilepsia, väiksemad võrreldes kontrollgrupi laste omadega. Nendel AII-ga lastel, kellel epilepsiat ei esinenud, oli kontrollgrupi lastega võrreldes ainult kahjustusepoolne talamus väiksem. Kahjustuse vastaspoolel asuvatest struktuuridest oli lastel, kellel esines epilepsia, väiksemamahulisem talamus võrreldes kontrollgrupi lastega. PVI järgselt tekkinud epilepsiaga lastel olid väiksemamahulised kahjustusepoolsed sabatuum, kahkjaskeha ja naalduv tuum võrreldes kontrollgrupi lastega. Ilma epilepsiata lastel olid PVI järgselt võrreldes kontrollgrupi lastega väiksemamahulised kahjustusepoolsed talamus, sabatuum ja kahkjaskeha.

Võrreldes epilepsiaga lapsi ilma epilepsiata lastega ilmnes, et lastel, kellel oli AII, olid kahjustusepoolne talamus, sabatuum ja naalduv tuum ning kahjustusele vastaspoolne talamus väiksemamahulised kui ilma epilepsiata lastel. Samasugused muutused, nagu olid AII grupi lastel kahjustusepoolselt, esinesid lastel, kellel oli olnud PVI, kui moodustasime ühise grupi lastest, kellel oli epilepsia või kellel ilmestusid EEG uuringul interiktaalsed epileptiformsed avaldused, ja võrdlesime neid ilma epilepsiata laste vastavate näitajatega.

Kognitiivsete kaugtulemuste lõplikku uuringugruppi (III publikatsioon) kaasati 51 last: 37 last ilma epilepsiata, sealhulgas 11/37 last interiktaalsete epileptiformsete avaldustega, kuid ilma epileptiliste hoogudeta, ja 14/51 epilepsiaga last. Väljaarvamise kriteeriumiteks olid: 1) kognitiivse uuringu puudumine ≥7 a. vanuses; 2) vastsündinu perioodi järgse EEG uuringu puudumine. See uuring tuvastas, et perinataalse isheemilise insuldi järgselt tekkinud epilepsiaga laste üldise kognitiivse võimekuse näitajad KABC-II järgi on madalamad, kui neil lastel, kellel epilepsiat ei tekkinud. Spetsiifiliste võimete profiil oli aga erinev: samaaegse töötluse, planeerimise ja verbaalsete teadmiste alaskoorid olid madalamad epilepsiaga lastel, kuid järjestikuse töötluse ja õppimise alaskoorid olid samad nagu lastel, kellel epilepsiat ei olnud.

Uuringu teostamisel esinesid ka teatud kitsaskohad. Kuigi haarasime uuringusse enamuse Eesti laste insuldi andmekogus perinataalse isheemilise insuldiga lastest, oli erinevates alarühmades patsientide arv liiga väike, et tuua välja statistiliselt olulisi tulemusi. Andmed kuni 2003. a. olid kogutud tagasiulatuvalt ja alates 2004. a. jooksvalt, mis võis mõjutada andmete kvaliteeti. Talamuse ja basaaltuumade mahtude mõõtmine oli keeruline insuldi laialdaste kahjustuste korral. Kognitiivsete funktsioonide hindamisel ei olnud rühmade väiksuse tõttu võimalik statistiliselt välja tuua teisi kognitiivseid valdkondi mõjutavaid faktoreid peale epilepsia.

11.5 Järeldused

I. Neil perinataalse isheemilise insuldiga lastel, kellel oli olnud keskmise ajuarteri proksimaalse M1 osa või distaalse M1 osa infarkt, on suurem tõenäosus epilepsia kujunemiseks kui neil lastel, kellel oli olnud PVI. Epilepsia tekke risk püsib keskmise ajuarteri proksimaalse M1 või distaalse M1 osa infarkti korral kuni 20-ndate eluaastate alguseni, PVI korral püsib epilepsia tekke risk kuni eelkoolieani.

Epilepsia kulg oli raskem neil lastel, kellel oli olnud PVI, võrreldes lastega, kellel oli olnud keskmise ajuarteri distaalse osa eesmise või tagumise tüve infarkt. Perinataalse isheemilise insuldi diagnoosimisel on oluline määrata vaskulaarne sündroom, et täpsemalt prognoosida epilepsia kujunemist.

II. Need perinataalse isheemilise insuldiga lapsed, kellel esineb kombineeritud talamuse ning naalduva ja sabatuuma kahjustus, evivad suuremat riski epilepsia kujunemiseks kui need lapsed, kellel sellist kahjustust ei kujune. Aju subkortikaalsete hallaine struktuuride kahjustus on suurem lastel, kellel oli AII, võrreldes lastega, kellel oli PVI. Insuldi ägeda perioodi möödudes on vajalik teha kontroll-MRT uuring hindamaks talamuse ja basaaltuumade suurust, mis annab võimaluse täpsemalt prognoosida epilepsia kujunemist.

III. Perinataalse isheemilise insuldi järgselt kujunenud epilepsiaga laste üldine kognitiivne võimekus on madalam kui ilma epilepsiata lastel, kuid spetsiifiliste kognitiivsete funktsioonide profiil näitas madalamaid tulemusi ainult samaaegse töötluse, planeerimise ja verbaalsete teadmiste alaskoorides. Insuldi järgselt tekkinud epilepsiaga lastel on oluline hinnata ka spetsiifilisi kognitiivseid funktsioone, et rehabilitatsioonis ja arendustegevuses arvestada lapse tugevamaid ja nõrgemaid võimeid.

Käesolev uuring näitab, et perinataalse isheemilise insuldi täpse vaskulaarse sündroomi määramine ning talamuse ja basaaltuumade suuruse hindamine on oluline insuldijärgse epilepsia tekke tõenäosuse hindamisel. Uuring tõi välja ka selle, et epilepsiaga lastel esineb perinataalse insuldi järgselt rohkem kognitiivset defitsiiti kui neil insuldiga lastel, kellel epilepsiat ei kujunenud.

Andmed selle kohta, kellel võib tekkida insuldi järgselt epilepsia ja milline on nende laste edasine kognitiivne profiil, aitab nende lastega tegelevatel arstidel ja tugispetsialistidel paremini ja sihipäraselt jälgida neid, kes on epilepsiast rohkem ohustatud, ning õigeaegselt sekkuda. Teadmised lapse arengu eripäradest on abiks vanemate nõustamisel, et vähendada teadmatusest tulenevaid hirme tuleviku ees ja kasutada taastusravis ära lapse tugevamaid külgi.

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13 PUBLICATIONS

14 CURRICULUM VITAE

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Education:

1974–1985 Türi Secondary School
1985–1991 University of Tartu, Faculty of Medicine, pediatrician
1991–1992 University of Tartu, internship, pediatrician
1992–1997 University of Tartu, residency, pediatrician
2018 University of Tartu, Faculty of Medicine, pediatric neurologist
2020–2024 University of Tartu, Faculty of Medicine, doctoral studies in medicine

Professional employment:

1997–2023 Tartu University Hospital, consultant, child neurologist
2005–.... Tartu University Hospital, EEG specialist
2016–.... Ida-Viru Central Hospital, child neurologist, part time
2021–.... Põlva Hospital, child neurologist, part time
2023–.... Tartu University Hospital, senior-consultant, child neurologist
2023–2024 University of Tartu, Faculty of Medicine, Institute of Clinical Medicine, junior Research Fellow in Radiology

Membership and organizational activity:

1997–…. Estonian Association of Pediatricians, member
1997–…. Baltic Child Neurology Association, member
2005–…. Estonian Clinical Neurophysiology Association, member
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2021–…. COST Action CA20124, Maximising impact of multidisciplinary research in early diagnosis of neonatal brain injury (AI-4-NICU), member of WG1 (1. Data Protocols and Management)

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15 ELULOOKIRJELDUS

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Haridus:

1974–1985	Türi Keskkool
1985–1991	Tartu Ülikool, Arstiteaduskond, pediaatria eriala
1991–1992	Tartu Ülikool, internatuur, pediaatria
1992–1997	Tartu Ülikool, residentuur, lastearst
2018	Tartu Ülikool, meditsiiniteaduste valdkond, pediaatria eriala neuroloogia kõrvalerialaga
2020–2024	Tartu Ülikool, doktoriõpe, meditsiiniteaduste valdkond, arstiteadus

Töökogemus (teenistuskäik):

1997–2023	SA Tartu Ülikooli Kliinikum, arst-õppejõud, lasteneuroloog
2023–2024	Tartu Ülikool, kliinilise meditsiini instituut, radioloogia noorem-teadur
2005–....	SA Tartu Ülikooli Kliinikum, EEG spetsialist
2016–....	SA Ida-Viru Keskhaigla, lasteneuroloog, osakoormusega
2021–....	AS Põlva Haigla, lasteneuroloog, osakoormusega
2023–....	SA Tartu Ülikooli Kliinikum, vanemarst-õppejõud, lasteneuroloog

Erialaorganisatsiooniline tegevus:

1997–….	Eesti Lastearstide Selts, liige
1997–….	*Baltic Child Neurology Association*, liige
2005–….	Eesti Kliinilise Neurofüsioloogia Selts, liige
2013–2021	Eesti Peavalu Selts, juhatuse liige
2013–….	Eesti Peavalu Selts, liige
2013–….	Eesti Epilepsiavastane Liiga, liige
2015–2022	Eesti Epilepsiavastane Liiga, juhatuse esimees
2019–….	Euroopa referentsvõrgustiku *ERN-EpiCARE* (haruldased ja kompleksed epilepsiad) kaasliikme Tartu Ülikooli Kliinikum esindaja
2019–….	*European Paediatric Neurology Association*, liige
2020–….	Euroopa referentsvõrgustiku *ERN-EpiCARE* (haruldased ja kompleksed epilepsiad) vastsündinute epileptiliste hoogude ja epilepsiate töögrupi liige

2021–…. COST Action CA20124, *Maximising impact of multidisciplinary research in early diagnosis of neonatal brain injury (AI-4-NICU)*, korralduskomitee, Eesti esindaja

2021–…. COST Action CA20124, *Maximising impact of multidisciplinary research in early diagnosis of neonatal brain injury (AI-4-NICU)*, töörühma liige (*1. Data Protocols and Management)*

Publikatsioonid:

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3. **Vaher, Ulvi**; Ilves, Norman; Ilves, Nigul; Laugesaar, Männamaa, Mairi; Loorits, Dagmar; Kool, Pille; Ilves, Pilvi (2024). The thalamus and basal ganglia are smaller in children with epilepsy following perinatal stroke. IPSo 2024 Congress Abstract Proceedings: IPSO 2024. Toronto, Kanada: IPSO, 22
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