Official Journal of the European Paediatric Neurology Society

Review article

Perinatal stroke syndromes: Similarities and diversities in aetiology, outcome and management☆

Joel Fluss [a], *Mickaël Dinomais* [b,c], *Stéphane Chabrier* [d,e,*]

[a] *Pediatric Neurology Unit, Geneva Children's Hospital, 6 rue Willy-Donzé, 1211 Genève 4, Switzerland*
[b] *CHU Angers, Département de Médecine Physique et de Réadaptation, CHU Angers-Capucins, F-49933, Angers, France*
[c] *Université d'Angers, Laboratoire Angevin de Recherche en Ingénierie des Systèmes (LARIS) EA7315, F-49000, Angers, France*
[d] *CHU Saint-Étienne, French Centre for Paediatric Stroke, Paediatric Physical and Rehabilitation Medicine Department, INSERM, CIC 1408, F-42055, Saint-Étienne, France*
[e] *INSERM, U1059 Sainbiose, Univ Saint-Étienne, Univ Lyon, F-42023, Saint-Étienne, France*

ARTICLE INFO

Article history:
Received 27 September 2018
Received in revised form
4 February 2019
Accepted 24 February 2019

Keywords:
Paediatric stroke
Development
Brain recovery
Plasticity

ABSTRACT

With a birth-prevalence of 37–67/100,000 (mostly term-born), perinatal stroke encompasses distinct disease-states with diverse causality, mechanism, time of onset, mode of presentation and outcome.

Neonatal primary haemorrhagic stroke and ischemic events (also divided into neonatal arterial ischemic stroke and neonatal cerebral sinus venous thrombosis) that manifest soon after birth are distinguished from presumed perinatal – ischemic or haemorrhagic – stroke. Signs of the latter become apparent only beyond the neonatal period, most often with motor asymmetry or milestones delay, and occasionally with seizures. Acute or remote MRI defines the type of stroke and is useful for prognosis.

Acute care relies on homeostatic maintenance. Seizures are often self-limited and anticonvulsant agents might be discontinued before discharge. Prolonged anticoagulation for a few weeks is an option in some cases of sinovenous thrombosis. Although the risk of severe impairment is low, many children develop mild to moderate multimodal developmental issues that require a multidisciplinary approach.

Contents

1. Introduction 369
2. Neonatal arterial ischemic stroke (NAIS) 369

☆ All authors have read and approved the submitted manuscript. The manuscript has not been submitted elsewhere nor published elsewhere in whole or in part.

* *Corresponding author*. Fax: +41 33477127613.
E-mail address: stephane.chabrier@chu-st-etienne.fr (S. Chabrier).

https://doi.org/10.1016/j.ejpn.2019.02.013
1090-3798/

2.1. Epidemiology . . . 370
2.2. Pathogenesis . . . 370
2.3. Clinical manifestations . . . 372
2.4. Imaging . . . 372
2.5. Management . . . 373
2.6. Outcome . . . 373
3. Perinatal haemorrhagic stroke (PHS): neonatal haemorrhagic stroke (NHS), haemorrhagic transformation of a primary ischemic injury and presumed PHS . . . 374
3.1. Epidemiology . . . 374
3.2. Clinical manifestations and imaging . . . 374
3.3. Management and outcome . . . 375
4. Neonatal cerebral sinus venous thrombosis (CSVT) . . . 376
4.1. Epidemiology . . . 376
4.2. Clinical and imaging manifestations . . . 376
4.3. Management . . . 376
4.4. Outcome . . . 377
5. Presumed perinatal ischemic stroke: arterial presumed perinatal ischemic stroke (APPIS) and periventricular venous infarction (PVI) . . . 377
5.1. Epidemiology and pathogenesis . . . 377
5.2. Clinical manifestations . . . 377
5.3. Imaging . . . 377
5.4. Management and outcome . . . 378
6. Conclusion and therapeutic perspectives . . . 378
Sources of funding . . . 379
Conflicts of interest . . . 379
Disclosures . . . 379
Acknowledgments . . . 379
Supplementary data . . . 379
References . . . 379

1. Introduction

While being suspected for more than a century, the diversity of perinatal cerebrovascular disorders has long been ignored.[1] Neuroimaging has revolutionised this field and underlying pathophysiological mechanisms are starting to be elucidated, leaving open the prospect of preventive, neuroprotective and therapeutic strategies.

As in later periods in life, perinatal stroke is dichotomized in ischemia and haemorrhage. The generic term *perinatal ischemic stroke* encompasses "*heterogeneous conditions with a brain injury due focal cerebral arterial or venous occlusion, occurring between 20 weeks of foetal life through 28th postnatal day*".[2] This definition and its main subcategories, have been complemented by a more mechanistic classification, relying on imaging findings. They enable the recognition of diverse categories of cerebrovascular complications that can be identified in the setting of acute manifestations in term newborns (or either incidentally) or later in infancy in case of delayed presentation.[3,4] Ischemic stroke can also occur in preterm newborns, in whom it presents with some distinct features.[5]

The delineation of *perinatal haemorrhagic stroke* (PHS) is more challenging, due to numerous conditions in the perinatal period that present with intracranial bleeding, particularly in the preterm.[6] Perinatal haemorrhagic stroke is thus generally restricted to term and near-term newborns, who manifest "*with encephalopathy, seizures, altered mental status, and/or neurological deficit within the first 28 days of life with a focal collection of blood within the brain parenchyma confirmed by neuroimaging or autopsy*".[7] By analogy with its ischemic counterpart, is divided into *neonatal* haemorrhagic stroke (NHS) that manifests early, *haemorrhagic transformation* of a primary (arterial, venous or hypoxic) ischemic injury and *presumed* PHS in case of delayed presentation.[7]

In sum, six main perinatal stroke syndromes can be delineated, that differ regarding the timing of the insult and of the clinical presentation, whether it is primary haemorrhagic or ischemic, and in the latter, whether it is related to an arterial or a venous occlusion (Fig. 1 and Table 1). Two population-based studies have estimated the birth-prevalence of the whole spectrum of perinatal stroke between 37 and 67/100,000.[8] The aim of the present paper is to emphasize recent advances that have allow a better understanding of the pathophysiology, management and outcome of the various form of perinatal stroke conditions. This review will not cover foetal ischemic and haemorrhagic stroke identified on prenatal imaging.[9]

2. Neonatal arterial ischemic stroke (NAIS)

NAIS has been the most studied and will serve as a paradigm for other entities, notably concerning outcome. Although now well recognised, its complex pathogenesis has not been solved, hindering the implementation of preventive actions.

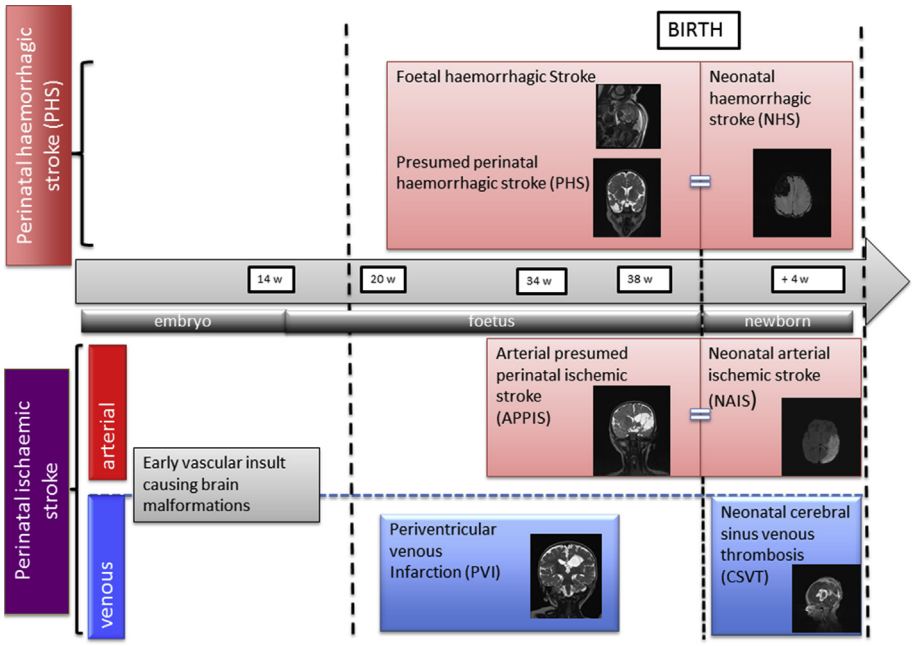

Fig. 1 – The various perinatal stroke syndromes according to timing and vascular mechanisms. Haemorrhagic transformation of primary ischaemic lesion is not showed. W: weeks.

2.1. *Epidemiology*

According to the five available population-based studies specifically dedicated to NAIS, its birth-prevalence in term and near-term newborns varies from 6 to 17/100,000.[10] In the Swiss Paediatric Stroke Registry that collects longitudinally all paediatric ischemic strokes since 2000, the observed figure for NAIS is 13/100,000 (95% confidence interval 11–16/100,000) or 1/8000 live births.[11] It must here highlighted that most studies on NAIS have excluded preterm newborns, in whom AIS is most often found incidentally by routine cranial ultrasound (CUS) screening in the absence of overt clinical manifestations. One single-centre study has estimated the birth-prevalence of perinatal AIS to be around 7/1000 in newborns with a gestational age (GA) of less than 34 weeks.[12,13]

NAIS cannot be reduced to a single determinant and numerous maternal, foetal and neonatal characteristics have been emphasized. Beyond this apparent diversity, case–control studies dedicated to NAIS (n = 7; 353 patients) have identified with high consistency four sets of risk factors: (1) male sex, (2) obstetrical determinants (first pregnancy, caesarean section), and two perinatal complications: (3) perpartum hypoxia, and (4) foetal/neonatal inflammatory state.[14] Perinatal asphyxia concomitant to NAIS, reflected by perpartum markers, is demonstrated in all case–control studies as well as in one meta-analysis.[15] Current evidence suggests that although both conditions share similar determinants, hypoxic-ischemic encephalopathy (HIE) *per se* is rarely associated with true infarction.[16] Most studies emphasize the role of materno-foetal infection/inflammation that might be responsible for placental inflammatory and thrombotic modifications.[14,17]

Much interest was focused initially on inherited or acquired prothrombotic states but their contribution to perinatal stroke is probably minor.[18] Furthermore, it does not seem to change the acute and long-term management or the outcome, notably the risk of recurrence.[19] As a consequence, a systematic screening of biological prothrombotic factors is no longer recommended in NAIS, except in specific circumstances such as multiple thrombosis, a thrombotic family history, or recurrent miscarriages suggestive of anti-phospholipid syndrome.[20]

In summary, most studies seeking to identify risk factors associated with NAIS are converging to a multifactorial origin. Furthermore, the risk is dramatically increased when these factors (essentially perpartum events) are cumulative.[16] The onset of stroke in this narrow time-window might be increased by the physiological hypercoagulable state of the peripartum period. The implication of instrumental delivery and birth trauma has been a matter of medico-legal debates. Due to the high number of assisted deliveries and the rare occurrence of NAIS, it is assumed that forceps or vacuum's use is not causative. Yet one cannot rule out that under specific circumstances such as macrosomia and shoulder dystocia, traumatic cervical arterial injury can lead to stroke. These cases are however exceptional and should be carefully investigated.[21,22]

In addition, specific neonatal conditions such as bacterial meningitis and congenital heart disease or invasive care after birth (central catheter, cardiac surgery/procedure, extra-corporeal membrane oxygenation) may predispose to NAIS. Hypoglycemia might predispose to posterior artery stroke.[23] Primary cerebral neonatal arteriopathy is exceptional and might be part of a diffuse genetic disorder.[24] In preterm AIS, twin-to-twin transfusion syndrome, foetal heart rate abnormality and hypoglycemia are independent risk factors.[12]

2.2. *Pathogenesis*

It is presumed that the main materno-foetal interface, namely the placenta, plays a key role, being furthermore the most

Table 1 – General overview of perinatal stroke syndromes.

Type of stroke	Birth-prevalence (37–67/100,000)	Main causes and risk factors (often plural)	Mechanism	Clinical findings	Outcome
Neonatal arterial ischemic stroke (NAIS)	- 6–17/100,000 in newborns ≥35 GA (670/100,000 ≤GA with specific findings: see text)	**Symptomatic cases** - Bacterial meningitides - Cardiac disease/ procedures - ECMO **Cryptogenic cases** - Chorioamnionitis - Perpartum asphyxia - Male sex and nulliparity	**Cryptogenic cases** - Placental cerebral embolism - Focal arteriopathy including cerebral vasculitis and (rarely) trauma	- Repeated focal seizures - In an otherwise healthy term/ near term newborn	- **CP**: 1/3 (depending on the extend and on the localization of the infarct site) - **Epilepsy**: 15% - **Learning/behavioural difficulties**: ++ - **Recurrence**: exceptional
Presumed perinatal ischemic stroke (APPIS + PVI)	- 20–29/100,000	**APPIS** - Similar to NAIS **PVI** - Preeclampsia, foetal hypotrophy	**APPIS** - Probably similar to NAIS **PVI** - In utero (≤34 GA) germinal matrix haemorrhage leading to compression of the medullary veins and focal venous infarction of the periventricular white matter	**Delayed presentation** (by definition) - Most often through motor deficiency - Rarely with seizures, learning difficulties or systematic imaging	- **CP**: quasi systematic due to the mode of presentation - **Epilepsy and learning/behavioural difficulties**: higher than NAIS for APPIS and lower for PVI - **Recurrence**: exceptional
Perinatal haemorrhagic stroke (PHS; restricted by definition to term/near term newborns)	- 16/100,000	**Symptomatic** (rare) **cases** - Bleeding diathesis (thrombocytopenia) - Vascular malformation - Cardiac disease/ procedures **Cryptogenic cases** - Perpartum asphyxia - Small for GA	- Primary bleeding in symptomatic cases - Haemorrhagic transformation of an ischemic injury (due to stroke or HIE) - In case of uni- or bilateral thalamic haemorrhage, suspect straight sinus thrombosis (see infra)	**Acute presentation** Similar to NAIS (seizures ++) and eventually more severe in case of intracranial hypertension **Delayed presentation** Similar to PPIS	- **Acute stage:** more severe than NAIS (mortality risk up to 25%) - **Long term:** depending on the extend and localization of the lesion and comorbid conditions (worse in symptomatic cases) - **Recurrence**: exceptional
Neonatal cerebral sinus venous thrombosis (CSVT)	- 1.4–12/100,000	**Symptomatic cases** - Severe neonatal condition: meningitis, dehydration, HIE … **Cryptogenic cases** - Gestational hypertension - Chorioamnionitis - Perpartum asphyxia	Virschow's triad	**Acute presentation** Similar to NAIS (seizures ++) **Discovered incidentally** in case of a severe disorder (e.g. meningitis) or as an incidental finding in case of systematic imaging survey (preterm, small for GA)	- **Long term:** depending on the association with parenchymal injury and comorbid conditions - **Epilepsy** with continuous spike and wave during sleep - **Recurrence**: exceptional

GA: gestational age; **ECMO**: extracorporeal membrane oxygenation; **HIE**: hypoxic ischemic encephalopathy; **CP**: cerebral palsy; APPIS: arterial presumed perinatal ischemic stroke; PVI: periventricular venous infarction; HIE: hypoxic ischemic encephalopathy.

plausible embolic source.[22,25] Due to foetal circulation characteristics, a clot migrating from the umbilical vein will indeed preferentially embolize to the left cerebral hemisphere through the foramen ovale, which is actually the main site of infarction observed *in vivo*. In addition, an elegant study has shown that multiple thrombi can be found on this direct route from placenta to brain and even in other systemic organs, thus endorsing the placenta-embolic hypothesis.[26] Some cases with carotid or middle cerebral artery (MCA) occlusion have been reported, but cerebral vessels are usually patent at the time of first imaging leading one to suspect that vessel recanalization has already occurred.[22] When available, a placental disorder is found in 80% of cases in the form of foetal placental thrombotic vasculopathy or chorioamnionitis with foetal endovasculitis.[17,27] Chorioamnionitis might lead to the release of cytokines, thus promoting diffuse foetal arteriopathy, thrombus formation and eventually in preclinical models, intracranial arteritis.[14,28] Other potential embolic (e.g. cardiac) sources might exist.[29] When a traumatic birth injury is presumed, cervical artery dissection is theoretically plausible but has rarely been proven.[30] A carotid artery occlusion might be a warning sign.[22]

The high propensity for seizures as leading manifestations of neonatal stroke rather than a neurological deficit is explained by specific characteristics and properties of the immature brain, including excitatory GABAergic neurons and bilateral corticospinal tracts projections.[31]

2.3. *Clinical manifestations*

The prototypic scenario is characterised by: 1) unilateral repetitive clonic seizures, at Day 1–3; 2) in a term baby who is otherwise well; and 3) whose imaging reveals an infarction with preferential involvement of the superficial left MCA territory. Seizures occurring <12 h after birth are uncommon in NAIS and point to HIE. Mixed patterns are however possible.[32]

Seizures can be the sole symptom in half of newborns.[11,21] Altered level of consciousness, tone abnormality, focal neurological deficits, unexplained apnoea and respiratory or feeding difficulties are found in less than one third.[33] Persisting encephalopathy, namely significant depressed level of alertness, tone, reflexes and respiratory drive, is unusual in NAIS and should lead to consider differential diagnoses. In the preterm, acute clinical manifestations are unusual and the diagnosis is often made incidentally upon systematic cerebral imaging screening.[5,12]

2.4. *Imaging*

CUS, a reliable bedside imaging tool in the neonatal intensive care unit, is often performed at first line. In cortical ischemic stroke, it may detect an area of triangular cortical-based hyperechogenicity within an arterial territory and coupled Doppler examination can eventually detect a luxury perfusion. A recent Spanish study reports that CUS sensitivity to detect an acute NAIS might be higher than previously reported, if performed in experienced hands.[34] A similar conclusion was reached in the setting of perforator ischemic strokes that are captured by serial CUS screening in ill-newborns, notably preterm.[35] Nevertheless the main limit of CUS remains its low sensitivity in non-experience hands, for small lesions and stroke outside of the MCA territory.[36,37] In addition, crucial data regarding the precise localisation and extent of the infarct might not be identified.[25,38] Computed tomography (CT) is not recommended due to radiation and low sensitivity in the acute phase.[20]

Magnetic Resonance Imaging (MRI) is thus the modality of choice in order to confirm the diagnosis and to provide additional prognostic information.[37,39] The parenchymal examination should be supplemented by MR angiography (MRA) of the cerebral and the neck arteries. Diffusion Weight Imaging (DWI) is the most useful sequence at onset showing restricted diffusion within a few hours: high B1000 signal and low restriction coefficient values that persist for 6–10 days.[40] High signal on T2-sequences with loss of grey-white matter differentiation and low signal on T1-sequences become obvious after a few days. This pattern will rapidly evolve to loss of tissue leading to cystic change visualized from Day 14.

The size and location of the infarct are better circumscribed if the MRI is postponed or repeated after a few days, and have important prognostic values. Most newborns show an acute infarct within the MCA territory, but different patterns of involvement are associated with diverse outcome.[41] Concomitant involvement of the cerebral cortex, the basal ganglia and the posterior limb of the internal capsule is strongly associated with the development of a unilateral cerebral palsy (UCP).[141,42] Restricted diffusion at the level of the cerebral peduncle or above, representing pre-Wallerian degeneration of the corticospinal tract (CST; visualized at best after Day 2–3), strongly predicts unfavourable motor outcome (Fig. 2a).[43,44] Cerebral peduncle atrophy, reflecting established degeneration of the motor tracts, can also be identified within a few weeks and is prognostic of UCP (Fig. 2b).[45] Other similar network injuries (also called diaschisis), remote from the infarct, are described in the thalamus, the corpus callosum (Fig. 2c) as well as in the cerebellum.[46–49] In addition, vessel occlusion at the level of the carotid artery or MCA is often associated with an extended stroke and unfavourable outcome.[22,50]

Posterior circulation stroke (isolated or in association with other arterial territories) represents only 10% of NAIS in large series and is associated with a better outcome, despite frequent visual field defects[23,41] Neonatal cerebellar stroke are even rarer, notably in term newborns.[51] Perforator stroke, that affects deep brain structures in relation with occlusion of perforator collaterals of the main cerebral arteries, is probably underdiagnosed due to lack of symptoms and frequent occurrence in the preterm period, during which it is most often detected on routine CUS. An associated concomitant cortical stroke is however not rare and is associated with a worse outcome.[52]

[1] Cerebral Palsy is currently defined as a group of permanent motor disorders due to a non-progressive damage occurring early in the developing brain. Unilateral cerebral palsy represents a common subtype where only one side of the body is affected.

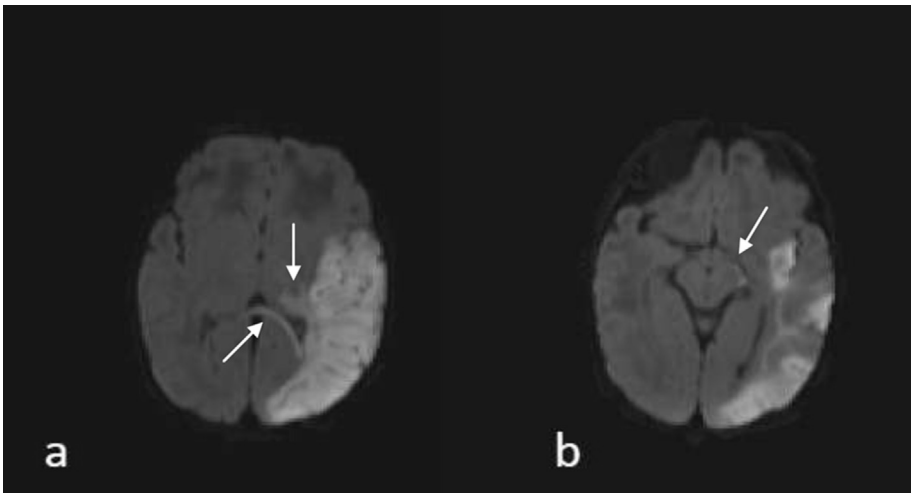

Fig. 2 – Diffusion Weight MRI of a 4-day-old neonate with hypotonia and right focal seizures. The images are consistent with a left superficial median cerebral artery infarct. a) Network injury is visible at level of the pulvinar and the splenium of the corpus callosum; b) Restricted diffusion on the left cerebral peduncle suggests early wallerian degeneration.

2.5. *Management*

The treatment is largely supportive unless there is a treatable medical condition or complication.

A baseline routine electroencephalogram (EEG) recording is often sufficient. Interictal focal sharp waves with preserved background activity in the healthy hemisphere are the typical finding. If available, early continuous EEG-video monitoring to detect subclinical seizures and to monitor responses treatment is advocated.[53,54] Seizures are often self-limited or controlled with phenobarbital but exceptions are described. As they rarely persist beyond the neonatal period, and given the potential neurotoxicity of antiepileptic drugs on the immature brain, the recommendation is now to shorten the duration of antiepileptic treatment. Most newborns can be discharged without medication, although practice varies widely across centres.[4,20] Some centres do even not start any antiepileptic drugs. If available, the placenta should be submitted for pathological evaluation.[17] The recurrence risk being very low, the use of antithrombotics is not recommended unless a persistent source of embolism or a severe thrombophilia is documented.

Similarly to adult stroke and other forms of perinatal brain injury (prematurity and HIE), neuroprotective approaches have been developed. Hypothermia has been found in a single-centre study to reduce the number of seizures in HIE newborns with coexisting NAIS, and is promising in preclinical models.[55,56] A pilot study with erythropoietin could not detect any beneficial effect in a small sample.[57] At this stage, the recommended neuroprotective measure is to maintain neonatal homeostasis (O_2, temperature, hydration, glycaemia …), as in similar situations with neonatal distress, including acute forms of other perinatal stroke syndromes: see infra.

2.6. *Outcome*

Beyond the neonatal period, regular surveillance all along the child development is needed to identify the occurrence of epilepsy and signs of motor and cognitive sequelae possibly amenable to intervention programs. Due to the multimodal form of impairments, a multidisciplinary approach is required and tailored to the patient's needs. Recent homogeneous cohorts have provided precious data regarding short- and medium-term outcome that are important to share carefully with affected parents in the neonatal ward, where stress and anxiety can lead to misconceptions and unrealistic projections about future.[4,11,41,58,59] These data also serve to guide neurodevelopment surveillance and counselling. As a general rule, the larger the stroke, the higher the risk of sequelae is.[41]

Neonatal mortality is around 2%, and not directly related to stroke.[11,33,41] Stroke *recurrence* after NAIS has also been shown to be around 1–2% and affects predominantly those newborns with known risk factors, such as congenital heart disease.[16,19,60] Clinical experience shows that NAIS does not recur in siblings.

Earlier studies reported a rate of *epilepsy* up to 30–50% after perinatal stroke, but these were not exclusively focusing on NAIS. Recent prospective studies of term/near term NAIS populations give now more consistent data, with four main findings. (i) The risk of epilepsy is homogeneous, and lower than initially presumed: 9% at 2 years in the Swiss Neuropaediatric Stroke Registry data (n = 74),[11] 13% at 2.5 years in a Philadelphian cohort (n = 46),[61] 12% at 3.5 years in a pooled population of children from UK and the Netherlands (n = 151),[41] 15% at 7 years in our experience (n = 80)[59] and 16.4% at 8.5 years in an Italian cohort (n = 55).[62] Epilepsy being not necessarily permanent, the prevalence of active epilepsy in any given period is lower than the cumulative incidence over time. (ii) Most children received monotherapy.[11,59,61–63] This signifies that post-NAIS epilepsy is rarely refractory. (iii) Large, bilateral and multiple strokes are predictive factors, while maintenance of antiepileptic drugs beyond the neonatal period seems not.[11,41,61](iv) Epilepsy tends to cluster with CP, poor academic performances and cognitive impairments[41,59]

Recent data show that the rate of CP is close to 30% with the majority of affected children being classified GMFCS[2] grade I or II.[41,59] In other words, all children walk independently. Upper limb is more affected. Poor hand function, seen in a minority of patients, often clusters with other forms of disabilities.[59,66] Motor outcome can be predicted above all by the involvement of the CST at any level[41,52,67] This reliable prediction is explained by the limited plasticity of the sensorimotor system, whose maturation is achieved early in life. Hence, NAIS may trigger structural changes in both grey matter and white matter regions involved and remote from the infarct site. The atrophy in the remote white matter regions, notably in perilesional white matter close to the body of corpus callosum and cerebral peduncle, is related to controlesional, but also ipsilesional hand function[67,68]

Whatever the side and the extent of the lesion, preserved *speech ability* is the rule, although the trajectory of early oral language milestones can be slightly delayed.[41,59,69] More subtle deficits might emerge in school years where sophisticated linguistic abilities need to be mastered.[70] Functional MRI studies have indeed shown that early injury of the language network in the dominant hemisphere can be partially compensated by a controlateral homotopic reorganization.[71] The right-hemispheric language reorganization after unilateral left hemispheric lesion appears particularly efficient in the neonatal period.[72] Data regarding written language are pending.

Three prospective studies have explored school-age *global cognitive* outcome after NAIS. Ricci et al. observed that children had global intelligence scores in the normal range.[73] Westmacott et al. found in addition that NAIS preschoolers did not differ from controls, but cognitive deficits, notably in the non-verbal reasoning domain, may emerge later.[58] In the French cohort, despite preserved intellectual abilities in most children, a significant subset of children manifests low academic performance, which is well-correlated with language skills.[59]

Outcome synthesis. All in all, the studies looking at NAIS outcome show that severe neurodevelopmental sequelae are rare, and that almost all children achieve independent mobility, adequate communication skills and subnormal to normal intellectual abilities. Taken altogether, approximately 60% of children exhibit mild forms of neurodevelopmental disabilities at school age, which can be easily overlooked by parents and by professionals. These various forms of disabilities (cognitive impairment, behavioural disturbances, CP, epilepsy …) tend to co-occur, indicating complex interconnected pathways in neurodevelopment after early brain injury. This combined with environmental and psychosocial determinants likely impact everyday aspects of the child's and family's real life.

[2] Motor function was classified according to the Gross Motor Function Classification System (GMFCS).[64,65] The GMFCS is a validated five-level classification system to stratify CP patients according to their level of independent gross motor function on the basis of self-initiated movements with particular emphasis on sitting, walking, and wheeled mobility. The levels could be summarised as: Level I: subject walks without limitations, II: walks with limitations, III: walks using a hand-held mobility device (crutches or canes …), IV: self-mobility with limitations, may use powered mobility, and V: transported in a manual wheelchair.

3. Perinatal haemorrhagic stroke (PHS): neonatal haemorrhagic stroke (NHS), haemorrhagic transformation of a primary ischemic injury and presumed PHS

3.1. *Epidemiology*

A recent population-based report found a term/near term birth-prevalence of primary NHS at 10.5/100,000. In the same study, the overall birth-prevalence of PHS (i.e. including haemorrhagic transformation of ischemic injury and presumed PHS) was 16/100,000.[7] This is in line with previous data (6.2/100,000).[74] It is important to stress that these figures do not include isolated subdural or subarachnoid haemorrhage, neither germinal-matrix related bleeding occurring in preterm newborns.[6] Therefore, the prevalence of PHS should be differentiated from previous data gathering all forms of neonatal intracranial haemorrhage, including asymptomatic ones.[75]

Occasionally, a defined medical condition explains the stroke: haemostasis disorders (especially neonatal thrombocytopenia, with platelets count <30,000/mm^3), cerebrovascular malformation, trauma, and congenital heart disease/procedure.[76] Those causes are usually readily identified but represent a minority.[7,74,75,77] Interestingly, in cryptogenic NHS, risk factors are close to those of NAIS, notably biomarkers of perpartum asphyxia, which suggest shared mechanisms between both entities. Whether the duration of labour, the mode of delivery or the use of assisting devices are additional independent factors, is controversial in PHS.[75,77] Many authors agree that pre-existing materno-foetal conditions are primarily associated with PHS rather than the mode of delivery.[7,75,78,79]

3.2. *Clinical manifestations and imaging*

Manifestations during the neonatal period are often acute, with both focal and systemic symptoms, including seizures, unexplained apnoea, encephalopathy, feeding difficulties, fever and irritability.[7,75,77] A bulging fontanel or an excessive growth of the cranial vault is occasionally reported.

Due to its easy availability, CUS is often performed first and can detect significant supratentorial parenchymal lesions. It carries however some limitations for small lesions and hemorrhage involving the posterior fossa or the convexities.[6,80] Despite its good sensitivity for acute hemorrhage, the use of CT in neonatal brain imaging is not anymore recommended due to ionizing radiation. Including in the emergency setting, the preferential imaging modality is MRI. It must be carried out with appropriate sequences sensitive to blood content to better delineates the site of bleeding and associated ischemic areas, and will help to understand the underlying pathology (Fig. 3).[6] Especially in the context of unexplained intraventricular haemorrhage or mixed ischemic-haemorrhagic lesions, MR venography (MRV) is indicated to search for sinus venous thrombosis that can mimic a primary NHS.[77]

Presumed PHS are less commonly identified that their ischemic equivalent (see section 5). Children might present with global developmental delay, seizures and early hand

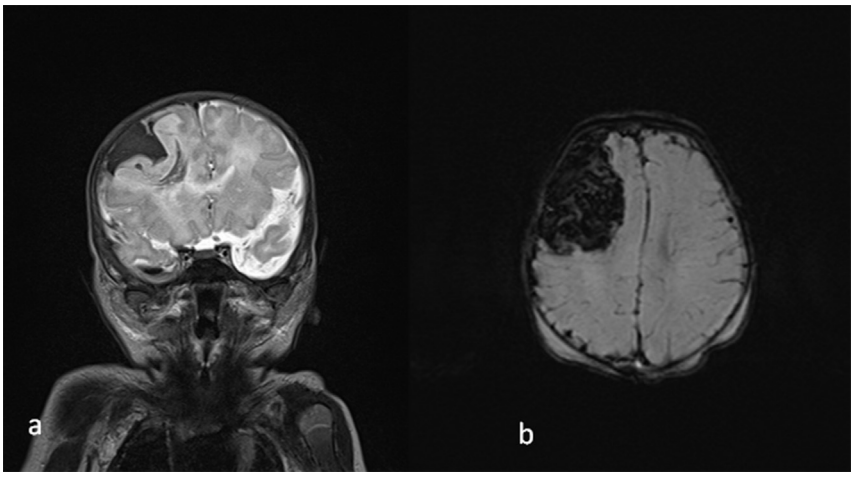

Fig. 3 – Term neonate with focal seizures and lethargy. a) On this coronal T2-weighted image, a large area of low signal intensity (dark) in the right frontal cortex is identified corresponding to a subpial hematoma. The underlying brain tissue is compressed and has mixed low and high signal intensity corresponding to a swollen brain parenchyma with haemorrhagic content. b) Susceptibility weighted imaging of the same neonate confirming large area of brain haemorrhage in the right frontal region. Despite extensive work-up, no underlying cause was found.

asymmetry. The detection on imaging of a circumscribed old brain lesion with haemosiderin deposits can lead to consider the diagnosis of presumed PHS (Fig. 4). Investigations should seek to identify a predisposing condition such as hereditary haemorrhagic telangiectasia or bleeding diathesis.[4] If associated features are present such as congenital cataracts, extensive white matter changes on imaging or in the presence of a suggestive family history, *COL4A1/2* mutations should be searched.[81,82]

3.3. *Management and outcome*

Most often, the management is supportive and often requires a multidisciplinary approach: neonatology, haematology, neurology, and neurosurgery. Haemoglobin level should be monitored and blood products transfusion might necessary. Prompt haematological work-up is mandatory to identify a bleeding diathesis (immune thrombocytopenia, coagulopathy, extracorporeal membrane oxygenation-related haemostatic disturbances) that will require specific forms of treatment.[6,79] It is of interest to observe that PHS related to foetal/neonatal thrombocytopenia is often multicompartimental involving in particular the subarachnoid space, which might raise the suspicion.[82,83] Other exceptional causes of PHS that require specialised management include ruptured neonatal intracranial aneurysms and arteriovenous malformations.[85,86]

Acute decompressive craniectomy and/or hematoma evacuation is rarely performed in PHS and is reserved for cases with massive or infratentorial haemorrhage inducing herniation, brain stem compression or acute obstructive hydrocephalus when an external ventricular drain placement might be required.[7,75,87] The indication for surgery should be particularly weighed if the haemorrhage is thought to be

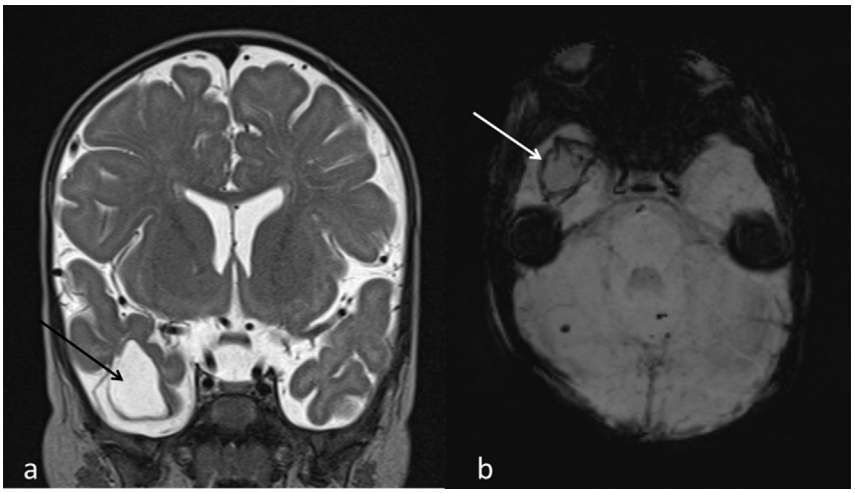

Fig. 4 – Mild gross motor delay with axial hypotonia in a 5-month-old infant. a) MRI shows a right temporal porencephaly (coronal T2-weighted image). b) On specific sequences (SWI; axial view) with susceptibility to blood content, blood products deposits on the wall of the cavity are well demonstrated.

secondary in order to avoid damage to an underlying preserved brain tissue.[88]

PHS is encumbered with significant mortality related to the extent of the initial haemorrhage. Long-term outcome for survivors is however often better than for its ischemic counterpart and more favourable than expected initially despite a dramatic presentation at onset.[75,79] This said, outcome is worst when PHS is associated with either NAIS, HIE or a chronic deleterious condition such as haemophilia.[7,79,89] The risk of *recurrence* is low and the occurrence of *epilepsy* varies from 10 to 15%.[7,90]

4. Neonatal cerebral sinus venous thrombosis (CSVT)

4.1. *Epidemiology*

Newborns represent the most affected age-group of children affected by CSVT, with a birth-prevalence of 1.4–12/100,000 and a male predominance.[91] This is however likely to be underestimated due to heterogeneous non-specific manifestations, lack of clinicians' awareness, and difficulties in confirming the diagnosis.[91] Common materno-foetal determinants are gestational hypertension, chorioamnionitis, foetal distress and perpartum asphyxia. Although prothrombotic disorders are frequently reported, their contribution is probably minor.[91,92] Mechanical compression of the superior sagittal sinus in supine position might represent an easily prevented cause through adequate positioning.[93] As for NAIS and PHS, pathogenesis cannot be usually reduced to a single cause, but involves many of the factors mentioned above.

4.2. *Clinical and imaging manifestations*

Most newborns with CSVT present at birth or within the first week with non-specific signs that explains the diagnostic delay. Seizures at onset (in approximately 60–70%) will prompt neuroimaging. CSVT as an incidental finding already occurs, either in severely ill-newborns (e.g. in case of bacterial meningitis) or in asymptomatic newborns, notably those with extremely low birthweight.[91,94] In rare cases, newborns have been discharged home and a dramatic delayed presentation with seizures and encephalopathy may reflect the abrupt onset of intraventricular haemorrhage. This delayed presentation can also be mild and unspecific.[94,95]

The goal of imaging is to detect a thrombus or an absent flow in the brain venous system and associated parenchymal injuries.[96] Conversely, the detection of an unexplained centrally located brain ischemic or haemorrhagic lesions raises the possibility of a CSVT and imaging modalities will confirm this suspicion.[92] Although CUS and CT venography may have a role, MRV is the gold standard.[91,94] Careful imaging interpretation is however mandatory in newborns where flow gaps in the venous system are frequent. Contrast-enhanced MRV might be required, particularly in the acute phase.[97] Multiple sinuses involvement is common and simultaneous involvement of both the superficial and the deep venous system is related to worse outcome. Parenchymal (often ischemic and haemorrhagic) injury is detectable in half of cases.[91,92,98] Intraventricular haemorrhage with a unilateral thalamic haemorrhage is a typical presentation of neonatal CSVT often caused by straight sinus thrombosis (Fig. 5a,b).[95]

4.3. *Management*

In regard to significant long-term morbidities, and the tendency to observe thrombus propagation with a higher risk of brain damage, a number of paediatric stroke centres have addressed the necessity to plan clinical trials on the utility of anticoagulation therapy (ACT) in neonatal CSVT.[99,100] It appears indeed that low molecular-weighted heparin is safe in newborns, even in the setting of significant haemorrhage.[100] There is however insufficient data to determine if ACT is efficient and it remains indicated on a case-by-case basis.[92,99,101] A pragmatic attitude is to initiate ACT if there is thrombus propagation in order to prevent additional brain insults. Due to

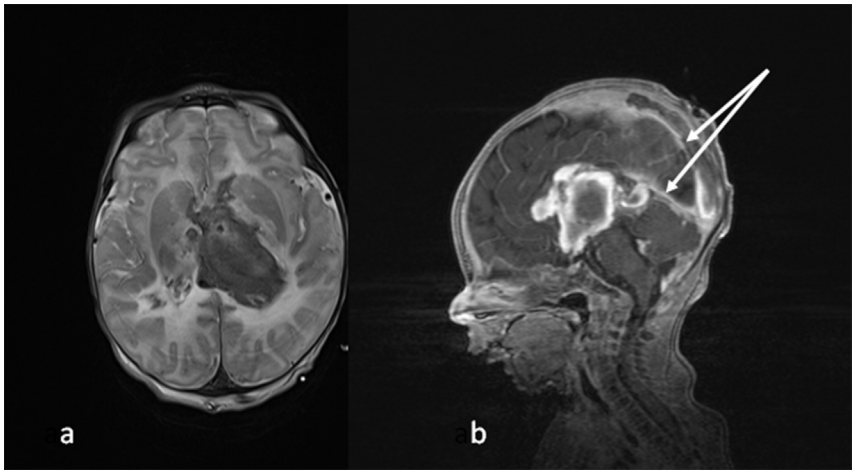

Fig. 5 – Five-day-old term neonate who presented abruptly with lethargy and opisthotonus. A large thalamic haemorrhagic stroke is seen on this axial T2-weighted image with contiguous intraventricular haemorrhage. On contrast-enhanced MR venography, large filling defects corresponding to extended thrombi are seen (double-arrow) along the superior sagittal sinus and the straight sinus.

rapid sinus recanalization in infants, the duration should be shorter that in older children and radiological reassessment can be done already at 6–12 weeks.[92,98,102]

4.4. Outcome

The high incidence of intracranial haemorrhage and of comorbid medical conditions might partly explain the *mortality* rate, which has been reported as 2–19%.[91,103] Most surviving children exhibit *neurodevelopmental impairment*, including *epilepsy*.[91,99,102,104] Adverse outcome is predicted by the presence of a parenchymal infarct, bilateral involvement and neurological comorbidities.[92,102] The subgroup of term newborns, with deep venous thrombosis and thalamic haemorrhage is at risk of developing late onset epilepsy with continuous spike and wave during sleep or related spectrum, that might lead to cognitive and behavioural sequelae.[95]

5. Presumed perinatal ischemic stroke: arterial presumed perinatal ischemic stroke (APPIS) and periventricular venous infarction (PVI)

Due to similar presentation despite distinct pathophysiology, both entities are discussed simultaneously while emphasizing relevant differences.

5.1. Epidemiology and pathogenesis

Prevalence of presumed perinatal ischemic stroke is probably underestimated due to the difficulty to register all children whose presentation is subtle and delayed. The Estonian Paediatric Stroke Database brought a figure of birth-prevalence to be around 40/100,000.[8] Two-thirds are due to PVI and one-third to APPIS. The same ratio was found in Japan.[105]

Most of the materno-foetal risk factors already discussed with NAIS, PHS and CSVT have been incriminated and similar conclusions have been reached regarding the multifactorial origin of these perinatal vascular events.[106] Antepartum conditions such as pre-eclampsia, infections and past history of miscarriage are found more frequently in PVI than in NAIS.[107,108] Interestingly, acute perpartum factors are found in the other way more often in APPIS vs. PVI, raising the question that some (most?) APPIS are occurring around birth, and are possibly missed paucisymptomatic NAIS.[108]

Otherwise, antepartum conditions are in line with the presumed pathogenesis of PVI, which correspond to the well-recognised germinal matrix haemorrhage of the preterm, yet occurring here in utero. This haemorrhage leads to compression of the medullar veins that drain the periventricular white matter causing a venous infarction. Timing of insult corresponds therefore from 24 to 34 weeks' GA.[106]

5.2. Clinical manifestations

Early hand preference and asymmetric reaching can be already detected in the first months of life.[109] This usually becomes obvious after 4–6 months and is the main reason for referral, but the diagnosis is commonly delayed for many months after the first parental concern.[68] Neurological examination reveals a varied spectrum of impairment, from subtle differences in hand dexterity or arm neglect to major spasticity with limited hand and finger movements. Although there are in general no sensory complaints, deficit in tactile perception can be demonstrated.[110] According to the topography of the lesion, predominant upper limb impairment is typical in APPIS, while PVI tends to cause predominant lower limb spasticity.[105]

A minority of infants with APPIS present with epileptic spasms or focal seizures rather than by motor features.[107,111] Finally, a small subset of children will present with non-specific signs such as developmental delay.

5.3. Imaging

MRI confirms the clinical suspicion, determines the mechanism and the extent of insults and provides important data regarding prognosis.

In APPIS, the porencephalic cyst involves cortical and subcortical grey matter in the MCA territory.[112,113] Some visible remnant fibres can be functional.[114] In case of PVI, there is periventricular tissue loss, gliosis and eventually haemosiderin deposition while cortex and basal ganglia are spared.[112] PVI can be either very subtle with little deformation of the lateral ventricle and corpus callosum tissue loss or much larger extending to the subcortical layer (Fig. 6a,b).

New MRI techniques coupled with diffusion tensor imaging, repetitive transcranial magnetic stimulation and functional MRI have enabled a better understanding of the reorganization of the motor and somatosensory cortex including related pathways, as well as the language areas after a focal perinatal brain injury.[115–117] These modalities, currently restricted for research purposes, might be important in the future to predict adverse outcome and to guide early intervention.[116,118] Numerous neuroimaging and neurophysiological data have highlighted the influence of timing, size, and location of early brain injury on the plasticity of the brain motor system and of the hand function.[119]

Briefly, unilateral injury to the developing brain can lead to different patterns of reorganization.[71,120] Many patients with pre- or perinatally acquired unilateral lesions to the motor cortex or the CST will develop ipsilateral cortico-spinal pathways that allow the unaffected hemisphere to partially control the paretic hand. This type of interhemispheric reorganization is often observed following unilateral periventricular lesions (as in PVI), which damage the CST in the periventricular white matter, but might also be seen following perinatal AIS.[121] Mirror movements are a clinical argument in favour of this interhemispheric reorganization of motor function.[122,123]

In contrast, in a group of patients with unilateral perinatal MCA stroke, primary motor cortex (M1) has been found to be represented in the ipsilesional precentral gyrus.[124] Functional MRI studies, which enable visualization of cortical motor activity, corroborate these findings and show that active movements of the paretic hand activate areas in both the ipsi- and controlesional hemispheres.[125] Abnormal maintenance of these ipsilateral CST, that could seem, at first glance, a favourable condition, represents clinically a form of

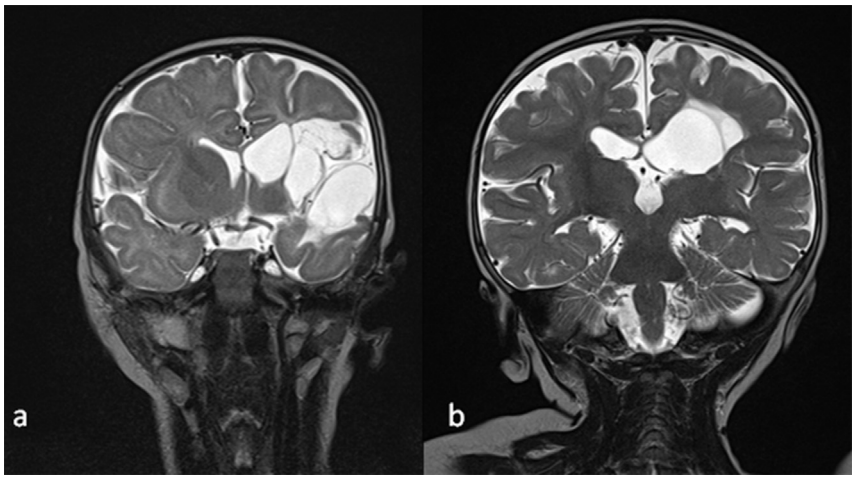

Fig. 6 – Coronal T2-weighted images of two children who presented with delayed onset. a) A large porencephalic cavity in the left sylvian territory is seen in this 5-month-old boy who was seen first in the emergency department with infantile spasms. Simultaneously, the parents were reported diminished reaching and grasping of the right hand. (b) This child was referred due to left hand preference at the age of 7 months. Left periventricular white matter loss is well visible.

maladaptive model of plasticity inducing excessive mirror movements hindering proper rehabilitation and might restrict the use of constraint-induced movement therapy.[126–129]

5.4. *Management and outcome*

Being the main clinical manifestation, *UCP* is present in almost all cases.[130] As evidence-based guidelines are lacking, there is much debate regarding the timing and the type of early intervention that can be implemented.[131–133]

The risk of associated *cognitive impairment* and *learning disabilities* should not be overlooked when the child enters school. Children with cortical involvement, i.e. with APPIS, have a higher risk.[105,112] Most of them have however normal-range intellectual abilities with perceptual non-verbal reasoning often lower than verbal abilities that tend to be better preserved whatever the side and the extent of the lesion.[134,135] Although there is no true cognitive decline, global impairment might appear more obvious as children are growing, due to insufficient intellectual resources to master more complex skills, including sophisticated linguistic knowledge.[136–138] Active epilepsy has been repeatedly reported to impact cognitive outcome, with a cumulative effect over time.[136,139]

Cognitive assessment should go beyond the simple assessment of intelligence by standardized tests. Many children with UCP will present with learning disabilities, visuo-spatial deficits, and weak executive and attention skills.[140–142] Mathematic learning disorder appears to be particularly prevalent among children with CP.[141] *Epilepsy*, more frequent in APPIS than in PVI, negatively impacts the degree of recovery and optimal plasticity.[105,112,143]

6. Conclusion and therapeutic perspectives

This overview of the various syndromes should enable the clinician to better appreciate the diversity of the lesions labelled perinatal stroke. Although useful in clinical practice, this term encompasses distinct early brain injuries, not only regarding their mechanisms but also their timing, their risk factors and, above all, their consequences for the developing brain.

Preclinical and epidemiological studies remain critical to better clarify the various predictive and prognostic determinants and their respective contributions in the distinct entities in order to plan meaningful management, as well as preventive and neuroprotective strategies. As shown in this review, most of the situations described cannot be reduced to a single causative link, but bring together numerous maternal, foetal and neonatal risk factors that culminate around the time of birth. Despite significant progresses, these preventive and acute neuroprotective strategies for reducing the incidence and the impact of early brain injuries (including the various perinatal stroke syndroms) in the developing brain remain at the preclinical stage.[144,145]

Irrespective to the vascular type or time of perinatal stroke, infants with overt clinical signs of motor dysfunction should get early referral to a specialized child rehabilitation clinics. Although no interventions appear as the gold standard, some newly therapeutic approaches might soften the emerging motor deficit. The constraint induced movement therapy, the hand-arm bimanual intensive therapy and intensive therapy based on motor learning appear promising, but their effect remain small.[146,147] Whether or not very early intervention soon after discharge can be beneficial and alter the developmental trajectory of children with perinatal stroke at risk of CP is still unclear.[131,146,148,149] In this setting, NAIS and other forms of perinatal stroke represent a unique opportunity not only to understand, but also to assess the effectiveness of early therapy pre-symptomatic based on the concept of developmental brain plasticity. It is acknowledged that focal perinatal brain injury has differential effects on the sensorimotor, language and visual system.[115] While the latter two are exhibiting robust capacities of regional and controlateral reorganisation, the sensorimotor system is however already relatively mature at birth and less prone to plasticity.[150] This explains why lesions affecting predominantly the CST are highly predictive of CP.[67]

This must be balanced with the fact that CST projections evolve dramatically during the 2 first years of life and that ispilateral projections are normally progressively withdrawn to favour a controlateral hemispheric control. These data underpin the need to better assess both CST in perinatal stroke using clinical, radiological and neurophysiological measures and also to target it in interventional approaches.[116] As such, safety data and promising results of transcranial magnetic as a tool to modulate neuroplasticity are now available in older children with UCP.[151] Whether or not similar type of treatment could be applied in newborns after perinatal stroke at risk of CP, before the onset of any visible deficit is unknown.[152] Beyond motor-targeted interventions, there is also a trend towards multifaceted program that promote all aspects of child development in close collaboration with the family and the caregivers. Mixed programs, integrating multiples approaches tailored to the child needs and regional availability will certainly continue to develop in the near future, hopefully in parallel with dedicated clinical research.[153]

Sources of funding

None.

Conflicts of interest

None.

Disclosures

None.

Acknowledgments

The authors would like to thanks the Pediatric Radiology Unit at the Geneva's Children Hospital and Mr Sev Fluss for editorial assistance.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2019.02.013.

REFERENCES

1. Longo LD, Ashwal S. William Osler, Sigmund Freud and the evolution of ideas concerning cerebral palsy. *J Hist Neurosci* 1993;**2**:255–82.
2. Raju TN, Nelson KB, Ferriero D, Lynch JK. Participants N-NPSW: Ischemic perinatal stroke: summary of a workshop sponsored by the National Institute of child health and human development and the National Institute of neurological disorders and stroke. *Pediatrics* 2007;**120**:609–16.
3. Kirton A, Deveber G. Life after perinatal stroke. *Stroke* 2013;**44**:3265–71.
4. Dunbar M, Kirton A. Perinatal stroke: mechanisms, management, and outcomes of early cerebrovascular brain injury. *Lancet Child Adolesc Health* 2018;**2**:666–76.
5. Benders MJ, Groenendaal F, De Vries LS. Preterm arterial ischemic stroke. *Semin Fetal Neonatal Med* 2009;**14**:272–7.
6. Tan AP, Svrckova P, Cowan F, Chong WK, Mankad K. Intracranial hemorrhage in neonates: a review of etiologies, patterns and predicted clinical outcomes. *Eur J Paediatr Neurol* 2018;**22**:690–717.
7. Cole L, Dewey D, Letourneau N, Kaplan BJ, Chaput K, Gallagher C, Hodge J, Floer A, Kirton A. Clinical characteristics, risk factors, and outcomes associated with neonatal hemorrhagic stroke: a population-based case-control study. *JAMA Pediatr* 2017;**171**:230–8.
8. Laugesaar R, Kolk A, Tomberg T, Metsvaht T, Lintrop M, Varendi H, Talvik T. Acutely and retrospectively diagnosed perinatal stroke: a population-based study. *Stroke* 2007;**38**:2234–40.
9. Kirkham FJ, Zafeiriou D, Howe D, Czarpran P, Harris A, Gunny R, Vollmer B. Fetal stroke and cerebrovascular disease: advances in understanding from lenticulostriate and venous imaging, alloimmune thrombocytopaenia and monochorionic twins. *Eur J Paediatr Neurol* 2018;**22**:989–1005.
10. Darmency-Stamboul V, Cordier AG, Chabrier S. Neonatal arterial ischemic stroke in term or near-term newborns: prevalence and risk factors. *Arch Pediatr* 2017;**24**. 9S3-S11.
11. Grunt S, Mazenauer L, Buerki SE, Boltshauser E, Mori AC, Datta AN, Fluss J, Mercati D, Keller E, Maier O, et al. Incidence and outcomes of symptomatic neonatal arterial ischemic stroke. *Pediatrics* 2015;**135**:e1220–8.
12. Benders MJ, Groenendaal F, Uiterwaal CS, Nikkels PG, Bruinse HW, Nievelstein RA, de Vries LS. Maternal and infant characteristics associated with perinatal arterial stroke in the preterm infant. *Stroke* 2007;**38**:1759–65.
13. Benders MJ, Groenendaal F, Uiterwaal CS, de Vries LS. Perinatal arterial stroke in the preterm infant. *Semin Perinatol* 2008;**32**:344–9.
14. Giraud A, Guiraut C, Chevin M, Chabrier S, Sebire G. Role of perinatal inflammation in neonatal arterial ischemic stroke. *Front Neurol* 2017;**8**:612.
15. Luo L, Chen D, Qu Y, Wu J, Li X, Mu D. Association between hypoxia and perinatal arterial ischemic stroke: a meta-analysis. *PLoS One* 2014;**9**:e90106.
16. Martinez-Biarge M, Cheong JL, Diez-Sebastian J, Mercuri E, Dubowitz LM, Cowan FM. Risk factors for neonatal arterial ischemic stroke: the importance of the intrapartum period. *J Pediatr* 2016 Jun;**173**. 62–69.e1.
17. Bernson-Leung ME, Boyd TK, Meserve EE, Danehy AR, Kapur K, Trenor 3rd CC, Lehman LL, Rivkin MJ. Placental pathology in neonatal stroke: a retrospective case-control study. *J Pediatr* 2018;**195**:39–47. e35.
18. Curtis C, Mineyko A, Massicotte P, Leaker M, Jiang XY, Floer A, Kirton A. Thrombophilia risk is not increased in children after perinatal stroke. *Blood* 2017;**129**:2793–800.
19. Lehman LL, Beaute J, Kapur K, Danehy AR, Bernson-Leung ME, Malkin H, Rivkin MJ, Trenor 3rd CC. Workup for perinatal stroke does not predict recurrence. *Stroke* 2017;**48**:2078–83.
20. Debillon T, Ego A, Chabrier S. Clinical practice guidelines for neonatal arterial ischaemic stroke. *Dev Med Child Neurol* 2017;**59**:980–1.
21. Kirton A, Armstrong-Wells J, Chang T, Deveber G, Rivkin MJ, Hernandez M, Carpenter J, Yager JY, Lynch JK, Ferriero DM, et al. Symptomatic neonatal arterial ischemic stroke: the International pediatric stroke study. *Pediatrics* 2011;**128**:e1402–10.

22. Fluss J, Garcia-Tarodo S, Granier M, Villega F, Ferey S, Husson B, Kossorotoff M, Muehlethaler V, Lebon S, Chabrier S. Perinatal arterial ischemic stroke related to carotid artery occlusion. *Eur J Paediatr Neurol* 2016 Jul;**20**(4):639–48.
23. van der Aa NE, Dudink J, Benders MJ, Govaert P, van Straaten HL, Porro GL, Groenendaal F, de Vries LS. Neonatal posterior cerebral artery stroke: clinical presentation, MRI findings, and outcome. *Dev Med Child Neurol* 2013;**55**:283–90.
24. Govaert P. Neonatal brain arteriopathies. *Dev Med Child Neurol* 2010;**52**:117–8.
25. Chabrier S, Husson B, Dinomais M, Landrieu P, Nguyen The Tich S. New insights (and new interrogations) in perinatal arterial ischemic stroke. *Thromb Res* 2011;**127**:13–22.
26. Arnaez J, Garcia-Alix A. Extracerebral thrombosis in symptomatic neonatal arterial ischemic stroke. *Eur J Paediatr Neurol* 2017;**21**:687–8.
27. Elbers J, Viero S, MacGregor D, DeVeber G, Moore AM. Placental pathology in neonatal stroke. *Pediatrics* 2011;**127**:e722–9.
28. Guiraut C, Cauchon N, Lepage M, Sebire G. Perinatal arterial ischemic stroke is associated to materno-fetal immune activation and intracranial arteritis. *Int J Mol Sci* 2016;**17**.
29. Amlie-Lefond CM, Basir MA, Franciosi RA. Fatal neonatal stroke from a prenatal cardiac thrombus. *Pediatr Neurol* 2008;**38**:140–2.
30. Lequin MH, Peeters EA, Holscher HC, de Krijger R, Govaert P. Arterial infarction caused by carotid artery dissection in the neonate. *Eur J Paediatr Neurol* 2004;**8**:155–60.
31. Katsarou AM, Galanopoulou AS, Moshe SL. Epileptogenesis in neonatal brain. *Semin Fetal Neonatal Med* 2018;**23**:159–67.
32. Lehman LL, Rivkin MJ. Perinatal arterial ischemic stroke: presentation, risk factors, evaluation, and outcome. *Pediatr Neurol* 2014;**51**:760–8.
33. Chabrier S, Saliba E, Nguyen The Tich S, Charollais A, Varlet MN, Tardy B, Presles E, Renaud C, Allard D, Husson B, et al. Obstetrical and neonatal characteristics vary with birthweight in a cohort of 100 term newborns with symptomatic arterial ischemic stroke. *Eur J Paediatr Neurol* 2010;**14**:206–13.
34. Olive G, Agut T, Echeverria-Palacio CM, Arca G, Garcia-Alix A. Usefulness of cranial ultrasound for detecting neonatal middle cerebral artery stroke. *Ultrasound Med Biol* 2019 Mar;**45**(3):885–90.
35. Ecury-Goossen GM, Raets MM, Lequin M, Feijen-Roon M, Govaert P, Dudink J. Risk factors, clinical presentation, and neuroimaging findings of neonatal perforator stroke. *Stroke* 2013;**44**:2115–20.
36. Cowan F, Mercuri E, Groenendaal F, Bassi L, Ricci D, Rutherford M, de Vries L. Does cranial ultrasound imaging identify arterial cerebral infarction in term neonates? *Arch Dis Child Fetal Neonatal Ed* 2005;**90**:F252–6.
37. Lee S, Mirsky DM, Beslow LA, Amlie-Lefond C, Danehy AR, Lehman L, Stence NV, Vossough A, Wintermark M, Rivkin MJ, et al. Pathways for neuroimaging of neonatal stroke. *Pediatr Neurol* 2017;**69**:37–48.
38. Rutherford MA, Ramenghi LA, Cowan FM. Neonatal stroke. *Arch Dis Child Fetal Neonatal Ed* 2012;**97**:F377–84.
39. van der Aa NE, Benders MJ, Groenendaal F, de Vries LS. Neonatal stroke: a review of the current evidence on epidemiology, pathogenesis, diagnostics and therapeutic options. *Acta Paediatr* 2014;**103**:356–64.
40. van der Aa NE, Benders MJ, Vincken KL, Groenendaal F, de Vries LS. The course of apparent diffusion coefficient values following perinatal arterial ischemic stroke. *PLoS One* 2013;**8**:e56784.
41. Wagenaar N, Martinez-Biarge M, van der Aa NE, van Haastert IC, Groenendaal F, Benders M, Cowan FM, de Vries LS. Neurodevelopment after perinatal arterial ischemic stroke. *Pediatrics* 2018;**142**.
42. Boardman JP, Ganesan V, Rutherford MA, Saunders DE, Mercuri E, Cowan F. Magnetic resonance image correlates of hemiparesis after neonatal and childhood middle cerebral artery stroke. *Pediatrics* 2005;**115**:321–6.
43. Husson B, Hertz-Pannier L, Renaud C, Allard D, Presles E, Landrieu P, Chabrier S, Group AV. Motor outcomes after neonatal arterial ischemic stroke related to early MRI data in a prospective study. *Pediatrics* 2010;**126**:912–8.
44. Kirton A, Shroff M, Visvanathan T, deVeber G. Quantified corticospinal tract diffusion restriction predicts neonatal stroke outcome. *Stroke* 2007;**38**:974–80.
45. Dudink J, Mercuri E, Al-Nakib L, Govaert P, Counsell SJ, Rutherford MA, Cowan FM. Evolution of unilateral perinatal arterial ischemic stroke on conventional and diffusion-weighted MR imaging. *AJNR Am J Neuroradiol* 2009;**30**:998–1004.
46. Dudink J, Counsell SJ, Lequin MH, Govaert PP. DTI reveals network injury in perinatal stroke. *Arch Dis Child Fetal Neonatal Ed* 2012;**97**:F362–4.
47. Okabe T, Aida N, Niwa T, Nozawa K, Shibasaki J, Osaka H. Early magnetic resonance detection of cortical necrosis and acute network injury associated with neonatal and infantile cerebral infarction. *Pediatr Radiol* 2014;**44**:597–604.
48. Craig BT, Carlson HL, Kirton A. Thalamic diaschisis following perinatal stroke is associated with clinical disability. *Neuroimage Clin* 2019:101660.
49. Craig BT, Olsen C, Mah S, Carlson HL, Wei XC, Kirton A. Crossed cerebellar atrophy in perinatal stroke. *Stroke* 2018. https://doi.org/10.1161/STROKEAHA.118.022423 [Epub ahead of print].
50. Husson B, Hertz-Pannier L, Adamsbaum C, Renaud C, Presles E, Dinomais M, Kossorotoff M, Landrieu P, Chabrier S. MR angiography findings in infants with neonatal arterial ischemic stroke in the middle cerebral artery territory: a prospective study using circle of Willis MR angiography. *Eur J Radiol* 2016;**85**:1329–35.
51. Muhlbacher T, Bohner G, Buhrer C, Dame C. Cerebellar infarction: unusual manifestation with facial palsy, focal seizures, and secondary generalization. *Neonatology* 2018;**113**:33–6.
52. Ecury-Goossen GM, van der Haer M, Smit LS, Feijen-Roon M, Lequin M, de Jonge RC, Govaert P, Dudink J. Neurodevelopmental outcome after neonatal perforator stroke. *Dev Med Child Neurol* 2016 Jan;**58**(1):49–56.
53. Shellhaas RA, Chang T, Tsuchida T, Scher MS, Riviello JJ, Abend NS, Nguyen S, Wusthoff CJ, Clancy RR. The American clinical neurophysiology Society's guideline on continuous electroencephalography monitoring in neonates. *J Clin Neurophysiol* 2011;**28**:611–7.
54. Nguyen The Tich S. Place of EEG in the management of arterial ischemic stroke newborn. *Arch Pediatr* 2017;**24**. 9S41-S45.
55. Harbert MJ, Tam EW, Glass HC, Bonifacio SL, Haeusslein LA, Barkovich AJ, Jeremy RJ, Rogers EE, Glidden DV, Ferriero DM. Hypothermia is correlated with seizure absence in perinatal stroke. *J Child Neurol* 2011;**26**:1126–30.
56. Chevin M, Guiraut C, Maurice-Gelinas C, Deslauriers J, Grignon S, Sébire G. Neuroprotective effects of hypothermia in inflammatory-sensitized hypoxic-ischemic encephalopathy. *Int J Dev Neurosci* 2016;**55**:1–8.
57. Benders MJ, van der Aa NE, Roks M, van Straaten HL, Isgum I, Viergever MA, Groenendaal F, de Vries LS, van Bel F. Feasibility and safety of erythropoietin for neuroprotection after perinatal arterial ischemic stroke. *J Pediatr* 2014;**164**:481–6. e481-482.
58. Westmacott R, Askalan R, MacGregor D, Anderson P, Deveber G. Cognitive outcome following unilateral arterial

ischaemic stroke in childhood: effects of age at stroke and lesion location. *Dev Med Child Neurol* 2010;**52**:386–93.
59. Chabrier S, Peyric E, Drutel L, Deron J, Kossorotoff M, Dinomais M, Lazaro L, Lefranc J, Thebault G, Dray G, et al. Multimodal outcome at 7 Years of age after neonatal arterial ischemic stroke. *J Pediatr* 2016;**172**:156–61. e153.
60. Kurnik K, Kosch A, Strater R, Schobess R, Heller C, Nowak-Gottl U, Childhood Stroke Study G. Recurrent thromboembolism in infants and children suffering from symptomatic neonatal arterial stroke: a prospective follow-up study. *Stroke* 2003;**34**:2887–92.
61. Billinghurst LL, Beslow LA, Abend NS, Uohara M, Jastrzab L, Licht DJ, Ichord RN. Incidence and predictors of epilepsy after pediatric arterial ischemic stroke. *Neurology* 2017;**88**:630–7.
62. Suppiej A, Mastrangelo M, Mastella L, Accorsi P, Grazian L, Casara G, Peruzzi C, Carpanelli ML, Janes A, Traverso A, et al. Pediatric epilepsy following neonatal seizures symptomatic of stroke. *Brain Dev* 2016;**38**:27–31.
63. Wusthoff CJ, Kessler SK, Vossough A, Ichord R, Zelonis S, Halperin A, Gordon D, Vargas G, Licht DJ, Smith SE. Risk of later seizure after perinatal arterial ischemic stroke: a prospective cohort study. *Pediatrics* 2011;**127**:e1550–7.
64. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;**39**:214–23.
65. Palisano RJ, Rosenbaum P, Bartlett D, Livingston MH. Content validity of the expanded and revised gross motor function classification system. *Dev Med Child Neurol* 2008;**50**:744–50.
66. Sreenan C, Bhargava R, Robertson CM. Cerebral infarction in the term newborn: clinical presentation and long-term outcome. *J Pediatr* 2000;**137**:351–5.
67. Dinomais M, Hertz-Pannier L, Groeschel S, Chabrier S, Delion M, Husson B, Kossorotoff M, Renaud C, Nguyen The Tich S, Group AVS. Long term motor function after neonatal stroke: lesion localization above all. *Hum Brain Mapp* 2015;**36**:4793–807.
68. Dinomais M, Hertz-Pannier L, Groeschel S, Delion M, Husson B, Kossorotoff M, Renaud C, Chabrier S, The Tich SN, Group AVS. Does contralesional hand function after neonatal stroke only depend on lesion characteristics? *Stroke* 2016;**47**:1647–50.
69. Trauner DA, Eshagh K, Ballantyne AO, Bates E. Early language development after peri-natal stroke. *Brain Lang* 2013;**127**:399–403.
70. Reilly JS, Wasserman S, Appelbaum M. Later language development in narratives in children with perinatal stroke. *Dev Sci* 2013;**16**:67–83.
71. Staudt M. Reorganization after pre- and perinatal brain lesions. *J Anat* 2010;**217**:469–74.
72. Lidzba K, Kupper H, Kluger G, Staudt M. The time window for successful right-hemispheric language reorganization in children. *Eur J Paediatr Neurol* 2017;**21**:715–21.
73. Ricci D, Mercuri E, Barnett A, Rathbone R, Cota F, Haataja L, Rutherford M, Dubowitz L, Cowan F. Cognitive outcome at early school age in term-born children with perinatally acquired middle cerebral artery territory infarction. *Stroke* 2008;**39**:403–10.
74. Armstrong-Wells J, Johnston SC, Wu YW, Sidney S, Fullerton HJ. Prevalence and predictors of perinatal hemorrhagic stroke: results from the kaiser pediatric stroke study. *Pediatrics* 2009;**123**:823–8.
75. Brouwer AJ, Groenendaal F, Koopman C, Nievelstein RJ, Han SK, de Vries LS. Intracranial hemorrhage in full-term newborns: a hospital-based cohort study. *Neuroradiology* 2010;**52**:567–76.
76. Jhawar BS, Ranger A, Steven D, Del Maestro RF. Risk factors for intracranial hemorrhage among full-term infants: a case-control study. *Neurosurgery* 2003;**52**:581–90. discussion 588-590.
77. Bruno CJ, Beslow LA, Witmer CM, Vossough A, Jordan LC, Zelonis S, Licht DJ, Ichord RN, Smith SE. Haemorrhagic stroke in term and late preterm neonates. *Arch Dis Child Fetal Neonatal Ed* 2014;**99**:F48–53.
78. Towner D, Castro MA, Eby-Wilkens E, Gilbert WM. Effect of mode of delivery in nulliparous women on neonatal intracranial injury. *N Engl J Med* 1999;**341**:1709–14.
79. Gupta SN, Kechli AM, Kanamalla US. Intracranial hemorrhage in term newborns: management and outcomes. *Pediatr Neurol* 2009;**40**:1–12.
80. van Wezel-Meijler G, Steggerda SJ, Leijser LM. Cranial ultrasonography in neonates: role and limitations. *Semin Perinatol* 2010;**34**:28–38.
81. Shah S, Ellard S, Kneen R, Lim M, Osborne N, Rankin J, Stoodley N, van der Knaap M, Whitney A, Jardine P. Childhood presentation of COL4A1 mutations. *Dev Med Child Neurol* 2012;**54**:569–74.
82. Zagaglia S, Selch C, Nisevic JR, Mei D, Michalak Z, Hernandez-Hernandez L, Krithika S, Vezyroglou K, Varadkar SM, Pepler A, et al. Neurologic phenotypes associated with COL4A1/2 mutations: expanding the spectrum of disease. *Neurology* 2018;**91**:e2078–88.
83. Govaert P, Bridger J, Wigglesworth J. Nature of the brain lesion in fetal allo-immune thrombocytopenia. *Dev Med Child Neurol* 1995;**37**:485–95.
84. Becocci A, Felice-Civitillo C, Laurent M, Boehlen F, De Luca R, Fluss J. Intracranial hemorrhage and autoimmune thrombocytopenia in a neonate: a rare "unpredictable" event. *Child Neurol Open* 2018;**5**. 2329048X18768693.
85. Mohotti JE, Carter NS, Zhang VJW, Lai LT, Xenos C, Asadi H, Chandra RV. Neonatal intracranial aneurysms: case report and review of the literature. *J Neurosurg Pediatr* 2018;**21**:471–7.
86. Sachet M, Tardieu M, Durand P, Ozanne A, Soubrier F, Tissieres P, Chevret L, Husson B, Adamsbaum C, Bellesme C, et al. Medical care of brain malformative vascular diseases discovered during the pre- or neonatal period. *Arch Pediatr* 2013;**20**:74–81.
87. Blauwblomme T, Garnett M, Vergnaud E, Boddaert N, Bourgeois M, Dirocco F, Zerah M, Sainte-Rose C, Puget S. The management of birth-related posterior fossa hematomas in neonates. *Neurosurgery* 2013;**72**:755–62. discussion 762.
88. Sandberg DI, Lamberti-Pasculli M, Drake JM, Humphreys RP, Rutka JT. Spontaneous intraparenchymal hemorrhage in full-term neonates. *Neurosurgery* 2001;**48**:1042–8. discussion 1048-1049.
89. Jhawar BS, Ranger A, Steven DA, Del Maestro RF. A follow-up study of infants with intracranial hemorrhage at full-term. *Can J Neurol Sci* 2005;**32**:332–9.
90. Venkatesan C, Millichap JJ, Krueger JM, Nangia S, Ritacco DG, Stack C, Nordli DR. Epilepsy following neonatal seizures secondary to hemorrhagic stroke in term neonates. *J Child Neurol* 2016;**31**:547–52.
91. Berfelo FJ, Kersbergen KJ, van Ommen CH, Govaert P, van Straaten HL, Poll-The BT, van Wezel-Meijler G, Vermeulen RJ, Groenendaal F, de Vries LS, et al. Neonatal cerebral sinovenous thrombosis from symptom to outcome. *Stroke* 2010;**41**:1382–8.
92. Yang JY, Chan AK, Callen DJ, Paes BA. Neonatal cerebral sinovenous thrombosis: sifting the evidence for a diagnostic plan and treatment strategy. *Pediatrics* 2010;**126**:e693–700.
93. Tan M, Deveber G, Shroff M, Moharir M, Pontigon AM, Widjaja E, Kirton A. Sagittal sinus compression is associated with neonatal cerebral sinovenous thrombosis. *Pediatrics* 2011;**128**:e429–35.

94. Nwosu ME, Williams LS, Edwards-Brown M, Eckert GJ, Golomb MR. Neonatal sinovenous thrombosis: presentation and association with imaging. *Pediatr Neurol* 2008;**39**:155–61.
95. Merlini L, Hanquinet S, Fluss J. Thalamic hemorrhagic stroke in the term newborn: a specific neonatal syndrome with non-uniform outcome. *J Child Neurol* 2017;**32**:746–53.
96. Ramenghi LA, Govaert P, Fumagalli M, Bassi L, Mosca F. Neonatal cerebral sinovenous thrombosis. *Semin Fetal Neonatal Med* 2009;**14**:278–83.
97. Bracken J, Barnacle A, Ditchfield M. Potential pitfalls in imaging of paediatric cerebral sinovenous thrombosis. *Pediatr Radiol* 2013;**43**:219–31.
98. Kersbergen KJ, Groenendaal F, Benders MJ, de Vries LS. Neonatal cerebral sinovenous thrombosis: neuroimaging and long-term follow-up. *J Child Neurol* 2011;**26**:1111–20.
99. Jordan LC, Rafay MF, Smith SE, Askalan R, Zamel KM, deVeber G, Ashwal S, International Pediatric Stroke Study G. Antithrombotic treatment in neonatal cerebral sinovenous thrombosis: results of the International pediatric stroke study. *J Pediatr* 2010;**156**:704–10. 710 e701-710 e702.
100. Moharir MD, Shroff M, Stephens D, Pontigon AM, Chan A, MacGregor D, Mikulis D, Adams M, deVeber G. Anticoagulants in pediatric cerebral sinovenous thrombosis: a safety and outcome study. *Ann Neurol* 2010;**67**:590–9.
101. Rossor T, Arichi T, Bhate S, Hart AR, Raman Singh R. Anticoagulation in the management of neonatal cerebral sinovenous thrombosis: a systematic review and meta-analysis. *Dev Med Child Neurol* 2018 Sep;**60**(9):884–91.
102. Moharir MD, Shroff M, Pontigon AM, Askalan R, Yau I, Macgregor D, Deveber GA. A prospective outcome study of neonatal cerebral sinovenous thrombosis. *J Child Neurol* 2011;**26**:1137–44.
103. Fitzgerald KC, Williams LS, Garg BP, Carvalho KS, Golomb MR. Cerebral sinovenous thrombosis in the neonate. *Arch Neurol* 2006;**63**:405–9.
104. Grunt S, Wingeier K, Wehrli E, Boltshauser E, Capone A, Fluss J, Gubser-Mercati D, Jeannet PY, Keller E, Marcoz JP, et al. Cerebral sinus venous thrombosis in Swiss children. *Dev Med Child Neurol* 2010;**52**:1145–50.
105. Kitai Y, Haginoya K, Hirai S, Ohmura K, Ogura K, Inui T, Endo W, Okubo Y, Anzai M, Takezawa Y, et al. Outcome of hemiplegic cerebral palsy born at term depends on its etiology. *Brain Dev* 2016 Mar;**38**(3):267–73.
106. Kirton A, deVeber G. Advances in perinatal ischemic stroke. *Pediatr Neurol* 2009;**40**:205–14.
107. Kirton A, Shroff M, Pontigon AM, deVeber G. Risk factors and presentations of periventricular venous infarction vs arterial presumed perinatal ischemic stroke. *Arch Neurol* 2010;**67**:842–8.
108. Ilves P, Laugesaar R, Loorits D, Kolk A, Tomberg T, Loo S, Talvik I, Kahre T, Talvik T. Presumed perinatal stroke: risk factors, clinical and radiological findings. *J Child Neurol* 2016;**31**:621–8.
109. Chen CY, Tafone S, Lo W, Heathcock JC. Perinatal stroke causes abnormal trajectory and laterality in reaching during early infancy. *Res Dev Disabil* 2015;**38**:301–8.
110. Gordon AM, Bleyenheuft Y, Steenbergen B. Pathophysiology of impaired hand function in children with unilateral cerebral palsy. *Dev Med Child Neurol* 2013;**55**(Suppl. 4):32–7.
111. Wu YW, March WM, Croen LA, Grether JK, Escobar GJ, Newman TB. Perinatal stroke in children with motor impairment: a population-based study. *Pediatrics* 2004;**114**:612–9.
112. Kirton A, Deveber G, Pontigon AM, Macgregor D, Shroff M. Presumed perinatal ischemic stroke: vascular classification predicts outcomes. *Ann Neurol* 2008;**63**:436–43.
113. Golomb MR, MacGregor DL, Domi T, Armstrong DC, McCrindle BW, Mayank S, deVeber GA. Presumed pre- or perinatal arterial ischemic stroke: risk factors and outcomes. *Ann Neurol* 2001;**50**:163–8.
114. Staudt M. Imaging cerebral palsy. *Handb Clin Neurol* 2013;**111**:177–81.
115. Fiori S, Guzzetta A. Plasticity following early-life brain injury: insights from quantitative MRI. *Semin Perinatol* 2015;**39**:141–6.
116. Jaspers E, Byblow WD, Feys H, Wenderoth N. The corticospinal tract: a biomarker to categorize upper limb functional potential in unilateral cerebral palsy. *Front Pediatr* 2015;**3**:112.
117. Liegeois F, Connelly A, Cross JH, Boyd SG, Gadian DG, Vargha-Khadem F, Baldeweg T. Language reorganization in children with early-onset lesions of the left hemisphere: an fMRI study. *Brain* 2004;**127**:1229–36.
118. Arnfield E, Guzzetta A, Boyd R. Relationship between brain structure on magnetic resonance imaging and motor outcomes in children with cerebral palsy: a systematic review. *Res Dev Disabil* 2013;**34**:2234–50.
119. Krageloh-Mann I. Imaging of early brain injury and cortical plasticity. *Exp Neurol* 2004;**190**(Suppl. 1):S84–90.
120. Holmstrom L, Vollmer B, Tedroff K, Islam M, Persson JK, Kits A, Forssberg H, Eliasson AC. Hand function in relation to brain lesions and corticomotor-projection pattern in children with unilateral cerebral palsy. *Dev Med Child Neurol* 2010;**52**:145–52.
121. van der Aa NE, Verhage CH, Groenendaal F, Vermeulen RJ, de Bode S, van Nieuwenhuizen O, de Vries LS. Neonatal neuroimaging predicts recruitment of contralesional corticospinal tracts following perinatal brain injury. *Dev Med Child Neurol* 2013;**55**:707–12.
122. Staudt M, Grodd W, Gerloff C, Erb M, Stitz J, Krageloh-Mann I. Two types of ipsilateral reorganization in congenital hemiparesis: a TMS and fMRI study. *Brain* 2002;**125**:2222–37.
123. Klingels K, Jaspers E, Staudt M, Guzzetta A, Mailleux L, Ortibus E, Feys H. Do mirror movements relate to hand function and timing of the brain lesion in children with unilateral cerebral palsy? *Dev Med Child Neurol* 2016;**58**:735–42.
124. Staudt M, Gerloff C, Grodd W, Holthausen H, Niemann G, Krageloh-Mann I. Reorganization in congenital hemiparesis acquired at different gestational ages. *Ann Neurol* 2004;**56**:854–63.
125. Van de Winckel A, Klingels K, Bruyninckx F, Wenderoth N, Peeters R, Sunaert S, Van Hecke W, De Cock P, Eyssen M, De Weerdt W, et al. How does brain activation differ in children with unilateral cerebral palsy compared to typically developing children, during active and passive movements, and tactile stimulation? An fMRI study. *Res Dev Disabil* 2013;**34**:183–97.
126. Staudt M, Berweck S. Is constraint-induced movement therapy harmful in unilateral spastic cerebral palsy with ipsilateral cortico-spinal projections? *Dev Med Child Neurol* 2014;**56**:202–3.
127. Kirton A. Modeling developmental plasticity after perinatal stroke: defining central therapeutic targets in cerebral palsy. *Pediatr Neurol* 2013;**48**:81–94.
128. Islam M, Nordstrand L, Holmstrom L, Kits A, Forssberg H, Eliasson AC. Is outcome of constraint-induced movement therapy in unilateral cerebral palsy dependent on corticomotor projection pattern and brain lesion characteristics? *Dev Med Child Neurol* 2014;**56**:252–8.
129. Staudt M. Should mirror movements modify therapeutic strategies for unilateral spastic cerebral palsy? *Dev Med Child Neurol* 2017;**59**:114–5.
130. Nordstrand L, Eliasson AC, Holmefur M. Longitudinal development of hand function in children with unilateral

spastic cerebral palsy aged 18 months to 12 years. *Dev Med Child Neurol* 2016 Oct;**58**(10):1042–8.
131. Ward R, Reynolds JE, Bear N, Elliott C, Valentine J. What is the evidence for managing tone in young children with, or at risk of developing, cerebral palsy: a systematic review. *Disabil Rehabil* 2016:1–12.
132. Novak I. Evidence-based diagnosis, health care, and rehabilitation for children with cerebral palsy. *J Child Neurol* 2014;**29**:1141–56.
133. Novak I, McIntyre S, Morgan C, Campbell L, Dark L, Morton N, Stumbles E, Wilson SA, Goldsmith S. A systematic review of interventions for children with cerebral palsy: state of the evidence. *Dev Med Child Neurol* 2013;**55**:885–910.
134. Gonzalez-Monge S, Boudia B, Ritz A, Abbas-Chorfa F, Rabilloud M, Iwaz J, Berard C. A 7-year longitudinal follow-up of intellectual development in children with congenital hemiplegia. *Dev Med Child Neurol* 2009;**51**:959–67.
135. Goodman R, Yude C. IQ and its predictors in childhood hemiplegia. *Dev Med Child Neurol* 1996;**38**:881–90.
136. Ballantyne AO, Spilkin AM, Hesselink J, Trauner DA. Plasticity in the developing brain: intellectual, language and academic functions in children with ischaemic perinatal stroke. *Brain* 2008;**131**:2975–85.
137. Ballantyne AO, Spilkin AM, Trauner DA. Language outcome after perinatal stroke: does side matter? *Child Neuropsychol* 2007;**13**:494–509.
138. Anderson V, Spencer-Smith M, Wood A. Do children really recover better? Neurobehavioural plasticity after early brain insult. *Brain* 2011;**134**:2197–221.
139. Vargha-Khadem F, Isaacs E, van der Werf S, Robb S, Wilson J. Development of intelligence and memory in children with hemiplegic cerebral palsy. The deleterious consequences of early seizures. *Brain* 1992;**115**(Pt 1):315–29.
140. Lidzba K, Staudt M, Wilke M, Krageloh-Mann I. Visuospatial deficits in patients with early left-hemispheric lesions and functional reorganization of language: consequence of lesion or reorganization? *Neuropsychologia* 2006;**44**:1088–94.
141. Frampton I, Yude C, Goodman R. The prevalence and correlates of specific learning difficulties in a representative sample of children with hemiplegia. *Br J Educ Psychol* 1998;**68**(Pt 1):39–51.
142. Murias K, Brooks B, Kirton A, Iaria G. A review of cognitive outcomes in children following perinatal stroke. *Dev Neuropsychol* 2014;**39**:131–57.
143. Fitzgerald KC, Williams LS, Garg BP, Golomb MR. Epilepsy in children with delayed presentation of perinatal stroke. *J Child Neurol* 2007;**22**:1274–80.
144. Baud O, Auvin S, Saliba E, Biran V. Therapeutic management of neonatal arterial cerebral infarction and neuroprotection perspectives. *Arch Pediatr* 2017;**24**. 9S46-S50.
145. Hagberg H, David Edwards A, Groenendaal F. Perinatal brain damage: the term infant. *Neurobiol Dis* 2016;**92**:102–12.
146. Morgan C, Darrah J, Gordon AM, Harbourne R, Spittle A, Johnson R, Fetters L. Effectiveness of motor interventions in infants with cerebral palsy: a systematic review. *Dev Med Child Neurol* 2016 Sep;**58**(9):900–9.
147. Gordon AM. To constrain or not to constrain, and other stories of intensive upper extremity training for children with unilateral cerebral palsy. *Dev Med Child Neurol* 2011;**53**(Suppl. 4):56–61.
148. Hadders-Algra M, Boxum AG, Hielkema T, Hamer EG. Effect of early intervention in infants at very high risk of cerebral palsy: a systematic review. *Dev Med Child Neurol* 2017;**59**:246–58.
149. Herskind A, Greisen G, Nielsen JB. Early identification and intervention in cerebral palsy. *Dev Med Child Neurol* 2015;**57**:29–36.
150. Dubois J, Hertz-Pannier L, Cachia A, Mangin JF, Le Bihan D, Dehaene-Lambertz G. Structural asymmetries in the infant language and sensori-motor networks. *Cerebr Cortex* 2009;**19**:414–23.
151. Kirton A. Advancing non-invasive neuromodulation clinical trials in children: lessons from perinatal stroke. *Eur J Paediatr Neurol* 2014 Sep 24;**5**:185.
152. Kirton A. Can noninvasive brain stimulation measure and modulate developmental plasticity to improve function in stroke-induced cerebral palsy? *Semin Pediatr Neurol* 2013;**20**:116–26.
153. Hadders-Algra M. Early diagnosis and early intervention in cerebral palsy. *Front Neurol* 2014;**5**:185.