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Joel Fluss, Mickaël Dinomais, Stéphane Chabrier

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4 **Perinatal stroke syndromes: similarities and diversities in aetiology, outcome and**  
5 **management**

6

7 Joel Fluss<sup>1</sup> MD, Mickaël Dinomais<sup>2,3</sup> MD-PhD, Stéphane Chabrier<sup>4,5</sup> MD

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12

13 1. Geneva University Hospital, Paediatric Neurology Unit, Geneva, Switzerland

14 2. Univ Angers, Laboratoire d'Ingénierie des Systèmes Automatisés (LISA), F-49000 Angers, France

15 3. LUNAM, CHU Angers, Physical and Rehabilitation Medicine Department, F-49000 Angers, France

16 4. CHU Saint-Étienne, French Centre for Paediatric Stroke, Paediatric Physical and Rehabilitation Medicine  
17 Department, INSERM, CIC 1408, F-42055 Saint-Étienne, France

18 5. INSERM, U1059 Sainbiose, Univ Saint-Étienne, Univ Lyon, F-42023 Saint-Étienne, France.

19

20 **Correspondence:** [stephane.chabrier@chu-st-etienne.fr](mailto:stephane.chabrier@chu-st-etienne.fr); **Tel:** (33)477120786; **Fax** (33)477127613.

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26 **Abstract (150 words)**

27

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

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

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

42

## 43 I. Introduction

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

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

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

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

77

## 78 **II. Neonatal arterial ischemic stroke (NAIS)**

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

82

### 83 **II.a Epidemiology**

84 According to the five available population-based studies specifically dedicated to NAIS, its  
85 birth-prevalence in term and near-term newborns varies from 6 to 17/100,000.[10] In the  
86 Swiss Paediatric Stroke Registry that collects longitudinally all paediatric ischemic strokes  
87 since 2000, the observed figure for NAIS is 13/100,000 (95% confidence interval 11-  
88 16/100,000) or 1/8000 live births.[11] [It must here highlighted that most studies on NAIS  
89 have excluded preterm newborns, in whom AIS is most often found incidentally by routine  
90 cranial ultrasound \(CUS\) screening in the absence of overt clinical manifestations. One  
91 single-centre study has estimated the birth-prevalence of perinatal AIS to be around 7/1000  
92 in newborns with a gestational age \(GA\) of less than 34 weeks.](#)[12,13]

93 NAIS cannot be reduced to a single determinant and numerous maternal, foetal and  
94 neonatal characteristics have been emphasized. Beyond this apparent diversity, case-  
95 control studies dedicated to NAIS (n=7; 353 patients) have identified with high consistency  
96 four sets of risk factors: (1) male sex, (2) obstetrical determinants (first pregnancy,  
97 caesarean section), and two perinatal complications: (3) perpartum hypoxia, and (4)  
98 foetal/neonatal inflammatory state.[14] Perinatal asphyxia concomitant to NAIS, reflected  
99 by perpartum markers, is demonstrated in all case-control studies as well as in one meta-  
100 analysis.[15] Current evidence suggests that although both conditions share similar  
101 determinants, hypoxic-ischemic encephalopathy (HIE) *per se* is rarely associated with true  
102 infarction.[16] Most studies emphasize the role of materno-foetal infection/inflammation  
103 that might be responsible for placental inflammatory and thrombotic modifications.[14,17]  
104 Much interest was focused initially on inherited or acquired prothrombotic states but their  
105 contribution to perinatal stroke is probably minor.[18] Furthermore, it does not seem to  
106 change the acute and long-term management or the outcome, notably the risk of  
107 recurrence.[19] As a consequence, a systematic screening of biological prothrombotic  
108 factors is no longer recommended in NAIS, except in specific circumstances such as  
109 multiple thrombosis, a thrombotic family history, or recurrent miscarriages suggestive of  
110 antiphospholipid syndrome.[20]

111 In summary, most studies seeking to identify risk factors associated with NAIS are  
112 converging to a multifactorial origin. Furthermore, the risk is dramatically increased when  
113 these factors (essentially perpartum events) are cumulative.[16] The onset of stroke in this  
114 narrow time-window might be increased by the physiological hypercoagulable state of the  
115 peripartum period. The implication of instrumental delivery and birth trauma has been a  
116 matter of medico-legal debates. Due to the high number of assisted deliveries and the rare  
117 occurrence of NAIS, it is assumed that forceps or vacuum's use is not causative. Yet one

118 cannot rule out that under specific circumstances such as macrosomia and shoulder  
119 dystocia, traumatic cervical arterial injury can lead to stroke. These cases are however  
120 exceptional and should be carefully investigated.[21,22]

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

128

## 129 **II.b Pathogenesis**

130 It is presumed that the main materno-foetal interface, namely the placenta, plays a key role,  
131 being furthermore the most plausible embolic source.[22,25] Due to foetal circulation  
132 characteristics, a clot migrating from the umbilical vein will indeed preferentially embolize to  
133 the left cerebral hemisphere through the foramen ovale, which is actually the main site of  
134 infarction observed *in vivo*. In addition, an elegant study has shown that multiple thrombi can be  
135 found on this direct route from placenta to brain and even in other systemic organs, thus  
136 endorsing the placenta-embolic hypothesis.[26] Some cases with carotid or middle cerebral  
137 artery (MCA) occlusion have been reported, but cerebral vessels are usually patent at the time  
138 of first imaging leading one to suspect that vessel recanalization has already occurred.[22]  
139 When available, a placental disorder is found in 80% of cases in the form of foetal  
140 placental thrombotic vasculopathy or chorioamnionitis with foetal endovasculitis.[17,27]  
141 Chorioamnionitis might lead to the release of cytokines, thus promoting diffuse foetal  
142 arteriopathy, thrombus formation and eventually in preclinical models, intracranial

143 arteritis.[14,28] Other potential embolic (e.g. cardiac) sources might exist.[29] When a  
144 traumatic birth injury is presumed, cervical artery dissection is theoretically plausible but has  
145 rarely been proven.[30] A carotid artery occlusion might be a warning sign.[22]  
146 The high propensity for seizures as leading manifestations of neonatal stroke rather than a  
147 neurological deficit is explained by specific characteristics and properties of the immature brain,  
148 including excitatory GABAergic neurons and bilateral corticospinal tracts projections.[31]

149

### 150 **III.c Clinical manifestations**

151 The prototypic scenario is characterised by: 1) unilateral repetitive clonic seizures, at Day  
152 1-3; 2) in a term baby who is otherwise well; and 3) whose imaging reveals an infarction  
153 with preferential involvement of the superficial left MCA territory. Seizures occurring  
154 <12 h after birth are uncommon in NAIS and point to HIE. Mixed patterns are however  
155 possible.[32]

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

163

### 164 **II.d Imaging**

165 CUS, a reliable bedside imaging tool in the neonatal intensive care unit, is often performed  
166 at first line. In cortical ischemic stroke, it may detect an area of triangular cortical-based  
167 hyperechogenicity within an arterial territory and coupled Doppler examination can

168 eventually detect a luxury perfusion. A recent Spanish study reports that CUS sensitivity to  
169 detect an acute NAIS might be higher than previously reported, if performed in  
170 experienced hands.[34] A similar conclusion was reached in the setting of perforator  
171 ischemic strokes that are captured by serial CUS screening in ill-newborns, notably  
172 preterm.[35] Nevertheless the main limit of CUS remains its low sensitivity in non-  
173 experience hands, for small lesions and stroke outside of the MCA territory.[36,37] In  
174 addition, crucial data regarding the precise localisation and extent of the infarct might not  
175 be identified.[25,38] Computed tomography (CT) is not recommended due to radiation and  
176 low sensitivity in the acute phase.[20]

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

186 The size and location of the infarct are better circumscribed if the MRI is postponed or  
187 repeated after a few days, and have important prognostic values. **Most newborns show an  
188 acute infarct within the MCA territory, but different patterns of involvement are associated  
189 with diverse outcome.**[41] Concomitant involvement of the cerebral cortex, the basal  
190 ganglia and the posterior limb of the internal capsule is strongly associated with the

191 development of a unilateral cerebral palsy (UCP).<sup>1</sup>[41,42] Restricted diffusion at the level  
192 of the cerebral peduncle or above, representing pre-Wallerian degeneration of the  
193 corticospinal tract (CST; visualized at best after Day 2-3), strongly predicts unfavourable  
194 motor outcome (Fig. 2a).[43,44] Cerebral peduncle atrophy, reflecting established  
195 degeneration of the motor tracts, can also be identified within a few weeks and is  
196 prognostic of UCP (Fig. 2b).[45] Other similar network injuries (also called diaschisis),  
197 remote from the infarct, are well described in the thalamus, the corpus callosum (Fig. 2c)  
198 [as well in the cerebellum](#). [46-49]. In addition, vessel occlusion at the level of the carotid  
199 artery or MCA is often associated with an extended stroke and unfavourable  
200 outcome.[22,50]

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

209

## 210 **II.e Management**

211 The treatment is largely supportive unless there is a treatable medical condition or complication.  
212 A baseline routine electroencephalogram (EEG) recording is often sufficient. Interictal focal  
213 sharp waves with preserved background activity in the healthy hemisphere are the typical

---

<sup>1</sup> 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.

214 finding. If available, early continuous EEG-video monitoring to detect subclinical seizures and  
215 to monitor responses treatment is advocated.[53,54] Seizures are often self-limited or controlled  
216 with phenobarbital but exceptions are described. As they rarely persist beyond the neonatal  
217 period, and given the potential neurotoxicity of antiepileptic drugs on the immature brain, the  
218 recommendation is now to shorten the duration of antiepileptic treatment. Most newborns can  
219 be discharged without medication, although practice varies widely across centres.[4,20] Some  
220 centres do even not start any antiepileptic drugs. If available, the placenta should be submitted  
221 for pathological evaluation.[17] The recurrence risk being very low, the use of antithrombotics  
222 is not recommended unless a persistent source of embolism or a severe thrombophilia is  
223 documented.

224 Similarly to adult stroke and other forms of perinatal brain injury (prematurity and HIE),  
225 neuroprotective approaches have been developed. Hypothermia has been found in a single-  
226 centre study to reduce the number of seizures in HIE newborns with coexisting NAIS, and is  
227 promising in preclinical models.[55] A pilot study with erythropoietin could not detect any  
228 beneficial effect in a small sample.[56] At this stage, the recommended neuroprotective measure  
229 is to maintain neonatal homeostasis (O<sub>2</sub>, temperature, hydration, glycaemia...), as in similar  
230 situations with neonatal distress, including acute forms of other perinatal stroke syndromes: see  
231 infra.

232

## 233 **II.f Outcome**

234 Beyond the neonatal period, regular surveillance all along the child development is needed to  
235 identify the occurrence of epilepsy and signs of motor and cognitive sequelae possibly  
236 amenable to intervention programs. Due to the multimodal form of impairments, a  
237 multidisciplinary approach is required and tailored to the patient's needs. Recent homogeneous  
238 cohorts have provided precious data regarding short- and medium-term outcome that are

239 important to share carefully with affected parents in the neonatal ward, where stress and anxiety  
240 can lead to misconceptions and unrealistic projections about future.[4,11,41,57,58] These data  
241 also serve to guide neurodevelopment surveillance and counselling. As a general rule, the larger  
242 the stroke, the higher the risk of sequelae is.[41]

243 *Neonatal mortality* is around 2%, and not directly related to stroke.[11,33,41] Stroke *recurrence*  
244 after NAIS has also been shown to be around 1-2% and affects predominantly those  
245 newborns with known risk factors, such as congenital heart disease.[16,19,59] Clinical  
246 experience shows that NAIS does not recur in siblings.

247 Earlier studies reported a rate of *epilepsy* up to 30-50% after perinatal stroke, but these were not  
248 exclusively focusing on NAIS. Recent prospective studies of term/near term NAIS  
249 populations give now more consistent data, with four main findings. (i) The risk of  
250 epilepsy is homogeneous, and lower than initially presumed: 9% at 2 years in the Swiss  
251 Neuropaediatric Stroke Registry data (n=74),[11] 13% at 2.5 years in a Philadelphian  
252 cohort (n=46),[60] 12% at 3.5 years in a pooled population of children from UK and the  
253 Netherlands (n=151),[41] 15% at 7 years in our experience (n=80) [58] and 16.4% at 8.5  
254 years in an Italian cohort (n=55).[61] Epilepsy being not necessarily permanent, the  
255 prevalence of active epilepsy in any given period is lower than the cumulative incidence  
256 over time. (ii) Most children received monotherapy.[11,58,60-62] This signifies that post-  
257 NAIS epilepsy is rarely refractory. (iii) Large, bilateral and multiple strokes are predictive  
258 factors, while maintenance of antiepileptic drugs beyond the neonatal period seems  
259 not.[11,41,60] (iv) Epilepsy tends to cluster with CP, poor academic performances and  
260 cognitive impairments.[41,58]

261 Recent data show that the rate of CP is close to 30% with the majority of affected children being

262 classified GMFCS<sup>2</sup> grade I or II.[41,58] In other words, all children walk independently. Upper  
263 limb is more affected. Poor hand function, seen in a minority of patients, often clusters with  
264 other forms of disabilities.[58,65] Motor outcome can be predicted above all by the  
265 involvement of the CST at any level.[41,52,66] This reliable prediction is explained by the  
266 limited plasticity of the sensorimotor system, whose maturation is achieved early in life. Hence,  
267 NAIS may trigger structural changes in both grey matter and white matter regions involved and  
268 remote from the infarct site. The atrophy in the remote white matter regions, notably in  
269 perilesional white matter close to the body of corpus callosum and cerebral peduncle, is related  
270 to controlesional, but also ipsilesional hand function.[66,67]

271 Whatever the side and the extent of the lesion, preserved *speech ability* is the rule, although the  
272 trajectory of early oral language milestones can be slightly delayed.[41,58,68] More subtle  
273 deficits might emerge in school years where sophisticated linguistic abilities need to be  
274 mastered.[69] Functional MRI studies have indeed shown that early injury of the language  
275 network in the dominant hemisphere can be partially compensated by a contralateral homotopic  
276 reorganization.[70] The right-hemispheric language reorganization after unilateral left  
277 hemispheric lesion appears particularly efficient in the neonatal period.[71] Data regarding  
278 written language are pending.

279 Three prospective studies have explored school-age *global cognitive* outcome after NAIS. Ricci  
280 et al. observed that children had global intelligence scores in the normal range.[72] Westmacott

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<sup>2</sup> Motor function was classified according to the Gross Motor Function Classification System (GMFCS) 63. 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**:214-223. 64. Palisano RJ, Rosenbaum P, Bartlett D, Livingston MH: **Content validity of the expanded and revised Gross Motor Function Classification System.** *Ibid.* 2008, **50**:744-750. 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.

281 et al. found in addition that NAIS preschoolers did not differ from controls, but cognitive  
282 deficits, notably in the non-verbal reasoning domain, may emerge later.[57] In the French  
283 cohort, despite preserved intellectual abilities in most children, a significant subset of children  
284 manifests low academic performance, which is well-correlated with language skills.[58]

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

294

### 295 **III. Perinatal haemorrhagic stroke (PHS): neonatal haemorrhagic stroke (NHS),** 296 **haemorrhagic transformation of a primary ischemic injury and presumed PHS**

#### 297 **III.a Epidemiology**

298 A recent population-based report found a term/near term birth-prevalence of primary NHS at  
299 10.5/100,000. In the same study, the overall birth-prevalence of PHS (i.e. including  
300 haemorrhagic transformation of ischemic injury and presumed PHS) was 16/100,000.[7] This is  
301 in line with previous data (6.2/100,000).[73] [It is important to stress that these figures do not](#)  
302 [include isolated subdural or subarachnoid haemorrhage, neither germinal-matrix related](#)  
303 [bleeding occurring in preterm newborns. \[6\] Therefore, the prevalence of PHS should be](#)  
304 [differentiated from previous data gathering all forms of neonatal intracranial haemorrhage,](#)  
305 [including asymptomatic ones.\[74\]](#)

306 Occasionally, a defined medical condition explains the stroke: haemostasis disorders (especially  
307 neonatal thrombocytopenia, with platelets count  $<30,000/\text{mm}^3$ ), cerebrovascular malformation,  
308 trauma, and congenital heart disease/procedure.[75] Those causes are usually readily identified  
309 but represent a minority.[7,73,74,76] Interestingly, in cryptogenic NHS, risk factors are close to  
310 those of NAIS, notably biomarkers of perpartum asphyxia, which suggest shared mechanisms  
311 between both entities. Whether the duration of labour, the mode of delivery or the use of  
312 assisting devices are additional independent factors, is controversial in PHS.[74,76] Many  
313 authors agree that pre-existing materno-foetal conditions are primarily associated with PHS  
314 rather than the mode of delivery.[7,74,77,78]

315

### 316 **III.b Clinical manifestations and imaging**

317 Manifestations during the neonatal period are often acute, with both focal and systemic  
318 symptoms, including seizures, unexplained apnoea, encephalopathy, feeding difficulties, fever  
319 and irritability.[7,74,76] A bulging fontanel or an excessive growth of the cranial vault is  
320 occasionally reported.

321 Due to its easy availability, CUS is often performed first and can detect significant  
322 supratentorial parenchymal lesions. It carries however some limitations for small lesions and  
323 hemorrhage involving the posterior fossa or the convexities.[6,79] Despite its good sensitivity  
324 for acute hemorrhage, the use of CT in neonatal brain imaging is not anymore recommended  
325 due to ionizing radiation. Including in the emergency setting, the preferential imaging modality  
326 is MRI. It must be carried out with appropriate sequences sensitive to blood content to better  
327 delineates the site of bleeding and associated ischemic areas, and will help to understand the  
328 underlying pathology (Fig. 3).[6] Especially in the context of unexplained intraventricular  
329 haemorrhage or mixed ischemic-haemorrhagic lesions, MR venography (MRV) is indicated to  
330 search for sinus venous thrombosis that can mimic a primary NHS.[76]

331 Presumed PHS are less commonly identified than their ischemic equivalent (see section V).  
332 Children might present with global developmental delay, seizures and early hand asymmetry.  
333 The detection on imaging of a circumscribed old brain lesion with haemosiderin deposits can  
334 lead to consider the diagnosis of presumed PHS (Fig. 4). Investigations should seek to identify a  
335 predisposing condition such as hereditary haemorrhagic telangiectasia or bleeding diathesis.[4]  
336 If associated features are present such as congenital cataracts, extensive white matter changes on  
337 imaging or in the presence of a suggestive family history, *COL4A1/2* mutations should be  
338 searched.[80,81]

339

### 340 **III.c Management and outcome**

341 Most often, the management is supportive and often requires a multidisciplinary approach:  
342 neonatology, haematology, neurology, and neurosurgery. Haemoglobin level should be  
343 monitored and blood products transfusion might necessary. Prompt haematological work-up is  
344 mandatory to identify a bleeding diathesis (immune thrombocytopenia, coagulopathy,  
345 extracorporeal membrane oxygenation-related haemostatic disturbances) that will require  
346 specific forms of treatment.[6,78] It is of interest to observe that PHS related to fetal/neonatal  
347 thrombocytopenia is often multicompartmental involving in particular the subarachnoid space,  
348 which might raise the suspicion.[82,83] Other exceptional causes of PHS that require  
349 specialised management include ruptured neonatal intracranial aneurysms and arteriovenous  
350 malformations.[84,85]

351 Acute decompressive craniectomy and/or hematoma evacuation is rarely performed in PHS and  
352 is reserved for cases with massive or infratentorial haemorrhage inducing herniation, brain stem  
353 compression or acute obstructive hydrocephalus when an external ventricular drain placement  
354 might be required.[7,74,86] The indication for surgery should be particularly weighed if the  
355 haemorrhage is thought to be secondary in order to avoid damage to an underlying preserved

356 [brain tissue](#).<sup>[87]</sup>

357 PHS is encumbered with significant mortality related to the extent of the initial haemorrhage.  
358 Long-term outcome for survivors is however often better than for its ischemic counterpart and  
359 more favourable than expected initially despite a dramatic presentation at onset.<sup>[74,78]</sup> This  
360 said, outcome is worst when PHS is associated with either NAIS, HIE or a chronic deleterious  
361 condition such as haemophilia.<sup>[7,78,88]</sup> The risk of *recurrence* is low and the occurrence of  
362 *epilepsy* varies from 10 to 15%.<sup>[7,89]</sup>

363

#### 364 **IV. Neonatal cerebral sinus venous thrombosis (CSVT)**

##### 365 **IV.a Epidemiology**

366 Newborns represent the most affected age-group of children affected by CSVT, with a birth-  
367 prevalence of 1.4-12/100,000 and a male predominance.<sup>[90]</sup> This is however likely to be  
368 underestimated due to heterogeneous non-specific manifestations, lack of clinicians' awareness,  
369 and difficulties in confirming the diagnosis.<sup>[90]</sup> Common materno-foetal determinants are  
370 gestational hypertension, chorioamnionitis, foetal distress and perpartum asphyxia. Although  
371 prothrombotic disorders are frequently reported, their contribution is probably minor.<sup>[90,91]</sup>  
372 Mechanical compression of the superior sagittal sinus in supine position might represent an  
373 easily prevented cause through adequate positioning.<sup>[92]</sup> As for NAIS and PHS, pathogenesis  
374 cannot be usually reduced to a single cause, but involves many of the factors mentioned above.

375

##### 376 **IV.b Clinical and imaging manifestations**

377 Most newborns with CSVT present at birth or within the first week with non-specific signs that  
378 explains the diagnostic delay. Seizures at onset (in approximately 60-70%) will prompt  
379 neuroimaging. CSVT as an incidental finding already occurs, either in severely ill-newborns  
380 (e.g. in case of bacterial meningitis) or in asymptomatic newborns, notably those with extremely

381 low birthweight.[90,93] In rare cases, newborns have been discharged home and a dramatic  
382 delayed presentation with seizures and encephalopathy may reflect the abrupt onset of  
383 intraventricular haemorrhage. This delayed presentation can also be mild and unspecific.[93,94]  
384 The goal of imaging is to detect a thrombus or an absent flow in the brain venous system and  
385 associated parenchymal injuries.[95] Conversely, the detection of an unexplained centrally  
386 located brain ischemic or haemorrhagic lesions raises the possibility of a CSVT and imaging  
387 modalities will confirm this suspicion.[91] Although CUS and CT venography may have a role,  
388 MRV is the gold standard.[90,93] Careful imaging interpretation is however mandatory in  
389 newborns where flow gaps in the venous system are frequent. Contrast-enhanced MRV might  
390 be required, particularly in the acute phase.[96] Multiple sinuses involvement is common and  
391 simultaneous involvement of both the superficial and the deep venous system is related to worse  
392 outcome. Parenchymal (often ischemic and haemorrhagic) injury is detectable in half of  
393 cases.[90,91,97] Intraventricular haemorrhage with a unilateral thalamic haemorrhage is a  
394 typical presentation of neonatal CSVT often caused by straight sinus thrombosis (Fig. 5a,b).[94]

395

#### 396 **IV.c Management**

397 In regard to significant long-term morbidities, and the tendency to observe thrombus  
398 propagation with a higher risk of brain damage, a number of paediatric stroke centres have  
399 addressed the necessity to plan clinical trials on the utility of anticoagulation therapy (ACT) in  
400 neonatal CSVT.[98,99] It appears indeed that low molecular-weighted heparin is safe in  
401 newborns, even in the setting of significant haemorrhage.[99] There is however insufficient data  
402 to determine if ACT is efficient and it remains indicated on a case-by-case basis.[91,98,100] A  
403 pragmatic attitude is to initiate ACT if there is thrombus propagation in order to prevent  
404 additional brain insults. Due to rapid sinus recanalization in infants, the duration should be  
405 shorter than in older children and radiological reassessment can be done already at 6-12

406 weeks.[91,97,101]

407

#### 408 **IV.d Outcome**

409 The high incidence of intracranial haemorrhage and of comorbid medical conditions might  
410 partly explain the *mortality* rate, which has been reported as 2-19%.[90,102] Most surviving  
411 children exhibit *neurodevelopmental impairment*, including *epilepsy*. [90,98,101,103] Adverse  
412 outcome is predicted by the presence of a parenchymal infarct, bilateral involvement and  
413 neurological comorbidities.[91,101] The subgroup of term newborns, with deep venous  
414 thrombosis and thalamic haemorrhage is at risk of developing late onset epilepsy with  
415 continuous spike and wave during sleep or related spectrum, that might lead to cognitive and  
416 behavioural sequelae.[94]

417

#### 418 **V. Presumed perinatal ischemic stroke: Arterial presumed perinatal ischemic stroke** 419 **(APPIS) and Periventricular venous infarction (PVI)**

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

422

#### 423 **V.a Epidemiology and pathogenesis**

424 Prevalence of APPIS is probably underestimated due to the difficulty to register all children  
425 whose presentation is subtle and delayed. The Estonian Paediatric Stroke Database brought a  
426 figure of birth-prevalence to be around 40/100,000.[8] Two-thirds are due to PVI and one-third  
427 to APPIS. The same ratio was found in Japan.[104]

428 Most of the materno-foetal risk factors already discussed with NAIS, PHS and CSVT have been  
429 incriminated and similar conclusions have been reached regarding the multifactorial origin of  
430 these perinatal vascular events.[105] Antepartum conditions such as pre-eclampsia, infections

431 and past history of miscarriage are found more frequently in PVI than in NAIS.[106,107]  
432 Interestingly, acute perpartum factors are found in the other way more often in APPIS vs. PVI,  
433 raising the question that some (most?) APPIS are occurring around birth, and are possibly  
434 missed paucisymptomatic NAIS.[107]  
435 Otherwise, antepartum conditions are in line with the presumed pathogenesis of PVI, which  
436 correspond to the well-recognised germinal matrix haemorrhage of the preterm, yet occurring  
437 here in utero. This haemorrhage leads to compression of the medullar veins that drain the  
438 periventricular white matter causing a venous infarction. Timing of insult corresponds therefore  
439 from 24 to 34 weeks' GA.[105]

#### 440 **V.b Clinical manifestations**

441 Early hand preference and asymmetric reaching can be already detected in the first months of  
442 life.[108] This usually becomes obvious after 4-6 months and is the main reason for referral, but  
443 the diagnosis is commonly delayed for many months after the first parental concern.[67]  
444 Neurological examination reveals a varied spectrum of impairment, from subtle differences in  
445 hand dexterity or arm neglect to major spasticity with limited hand and finger movements.  
446 Although there are in general no sensory complaints, deficit in tactile perception can be  
447 demonstrated.[109] According to the topography of the lesion, predominant upper limb  
448 impairment is typical in APPIS, while PVI tends to cause predominant lower limb  
449 spasticity.[104]  
450 A minority of infants with APPIS present with epileptic spasms or focal seizures rather than by  
451 motor features.[106,110] Finally, a small subset of children will present with non-specific signs  
452 such as developmental delay.

453

#### 454 **V.c Imaging**

455 MRI confirms the clinical suspicion, determines the mechanism and the extent of insults and

456 provides important data regarding prognosis.

457 In APPIS, the porencephalic cyst involves cortical and subcortical grey matter in the MCA  
458 territory.[111,112] Some visible remnant fibres can be functional.[113] In case of PVI, there is  
459 periventricular tissue loss, gliosis and eventually haemosiderin deposition while cortex and  
460 basal ganglia are spared.[111] PVI can be either very subtle with little deformation of the lateral  
461 ventricle and corpus callosum tissue loss or much larger extending to the subcortical layer (Fig.  
462 6a,b).

463 New MRI techniques coupled with diffusion tensor imaging, repetitive transcranial magnetic  
464 stimulation and functional MRI have enabled a better understanding of the reorganization of the  
465 motor and somatosensory cortex including related pathways, as well as the language areas after  
466 a focal perinatal brain injury.[114-116] These modalities, currently restricted for research  
467 purposes, might be important in the future to predict adverse outcome and to guide early  
468 intervention.[115,117] Numerous neuroimaging and neurophysiological data have highlighted  
469 the influence of timing, size, and location of early brain injury on the plasticity of the brain  
470 motor system and of the hand function.[118]

471 Briefly, unilateral injury to the developing brain can lead to different patterns of  
472 reorganization.[70,119] Many patients with pre- or perinatally acquired unilateral lesions to the  
473 motor cortex or the CST will develop ipsilateral cortico-spinal pathways that allow the  
474 unaffected hemisphere to partially control the paretic hand. This type of interhemispheric  
475 reorganization is often observed following unilateral periventricular lesions (as in PVI), which  
476 damage the CST in the periventricular white matter, but might also be seen following perinatal  
477 AIS. [120] Mirror movements are a clinical argument in favour of this interhemispheric  
478 reorganization of motor function.[121,122]

479 In contrast, in a group of patients with unilateral perinatal MCA stroke, primary motor cortex  
480 (M1) has been found to be represented in the ipsilesional precentral gyrus.[123] Functional MRI

481 studies, which enable visualization of cortical motor activity, corroborate these findings and  
482 show that active movements of the paretic hand activate areas in both the ipsi- and  
483 controlateral hemispheres.[124] Abnormal maintenance of these ipsilateral CST, that could  
484 seem, at first glance, a favourable condition, represents clinically a form of maladaptive model  
485 of plasticity inducing excessive mirror movements hindering proper rehabilitation and might  
486 restrict the use of constraint-induced movement therapy.[125-128]

487

#### 488 **V.d Management and outcome**

489 Being the main clinical manifestation, *UCP* is present in almost all cases.[129]. As evidence-  
490 based guidelines are lacking, there is much debate regarding the timing and the type of early  
491 intervention that can be implemented.[130-132]

492 The risk of associated *cognitive impairment* and *learning disabilities* should not be overlooked  
493 when the child enters school. Children with cortical involvement, i.e. with APPIS, have a higher  
494 risk.[104,111] Most of them have however normal-range intellectual abilities with perceptual  
495 non-verbal reasoning often lower than verbal abilities that tend to be better preserved whatever  
496 the side and the extent of the lesion.[133,134] Although there is no true cognitive decline, global  
497 impairment might appear more obvious as children are growing, due to insufficient intellectual  
498 resources to master more complex skills, including sophisticated linguistic knowledge.[135-  
499 137] Active epilepsy has been repeatedly reported to impact cognitive outcome, with a  
500 cumulative effect over time.[135,138]

501 Cognitive assessment should go beyond the simple assessment of intelligence by standardized  
502 tests. Many children with UCP will present with learning disabilities, visuo-spatial deficits, and  
503 weak executive and attention skills.[139-141] Mathematic learning disorder appears to be  
504 particularly prevalent among children with CP.[140] *Epilepsy*, more frequent in APPIS than in  
505 PVI, negatively impacts the degree of recovery and optimal plasticity.[104,111,142]

506

## 507 **VI. Conclusion and therapeutic perspectives**

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

512 Preclinical and epidemiological studies remain critical to better clarify the various predictive  
513 and prognostic determinants and their respective contributions in the distinct entities in order to  
514 plan meaningful management, as well as preventive and neuroprotective strategies. As shown in  
515 this review, most of the situations described cannot be reduced to a single causative link, but  
516 bring together numerous maternal, foetal and neonatal risk factors that culminate around the  
517 time of birth. *Despite significant progresses, these preventive and acute neuroprotective  
518 strategies for reducing the incidence and the impact of early brain injuries (including the  
519 various perinatal stroke syndroms) in the developing brain remain at the preclinical  
520 stage.[143,144]*

521 *Irrespective to the vascular type or time of perinatal stroke, infants with overt clinical signs  
522 of motor dysfunction should get early referral to a specialized child rehabilitation clinics.  
523 Although no interventions appear as the gold standard, some newly therapeutic approaches  
524 might soften the emerging motor deficit. The constraint induced movement therapy, the  
525 hand-arm bimanual intensive therapy and intensive therapy based on motor learning appear  
526 promising, but their effect remain small.[145,146]* Whether or not very early intervention  
527 soon after discharge can be beneficial and alter the developmental trajectory of children with  
528 perinatal stroke at risk of CP is still unclear.[130,145,147,148] In this setting, NAIS and other  
529 forms of perinatal stroke represent a unique opportunity not only to understand, but also to  
530 assess the effectiveness of early therapy pre-symptomatic based on the concept of

531 developmental brain plasticity. It is acknowledged that focal perinatal brain injury has  
532 differential effects on the sensorimotor, language and visual system.[114] While the latter two  
533 are exhibiting robust capacities of regional and contralateral reorganisation, the sensorimotor  
534 system is however already relatively mature at birth and less prone to plasticity.[149] This  
535 explains why lesions affecting predominantly the CST are highly predictive of CP.[66] This  
536 must be balanced with the fact that CST projections evolve dramatically during the 2 first years  
537 of life and that ipsilateral projections are normally progressively withdrawn to favour a  
538 contralateral hemispheric control. These data underpin the need not only to better assess both  
539 CST in perinatal stroke using clinical, radiological and neurophysiological measures, but also to  
540 target it in interventional approaches.[115] As such, safety data and promising results of  
541 transcranial magnetic as a tool to modulate neuroplasticity are now available in older children  
542 with UCP.[150] Whether or not similar type treatment could be applied in newborns after  
543 perinatal stroke at risk of CP, before the onset of any visible deficit is unknown.[151] [Beyond](#)  
544 [motor-targeted interventions, there is also a trend towards multifaceted program that promote all](#)  
545 [aspects of child development in close collaboration with the family and the caregivers. Mixed](#)  
546 [programs, integrating multiples approaches tailored to the child needs and regional availability](#)  
547 [will certainly continue to develop in the near future, hopefully in parallel with dedicated clinical](#)  
548 [research.](#)[152]

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968 **XII. Legends**

969

970 **Figure 1**

971 The various perinatal stroke syndromes according to timing and vascular mechanisms.

972 Haemorrhagic transformation of primary ischaemic lesion is not showed. W: weeks.

973

974 **Figure 2**

975

976 Diffusion Weight MRI of a 4-day-old neonate with hypotonia and right focal seizures. The

977 images are consistent with a left superficial left median cerebral artery infarct. a) Network

978 injury is visible at level of the pulvinar and the splenium of the corpus callosum (white

979 arrows); b) Restricted diffusion is present on the left cerebral peduncle suggesting early

980 wallerian degeneration (small arrow).

981

982 **Figure 3**

983

984 Term neonate with focal seizures and lethargy. a) On this coronal T2-weighted image, a

985 large area of low signal intensity (dark) in the right frontal cortex is identified

986 corresponding to a subpial hematoma. The underlying brain tissue is compressed and has

987 mixed low and high signal intensity corresponding to a swollen brain parenchyma with

988 haemorrhagic content. b) Susceptibility weighted imaging of the same neonate confirming

989 large area of brain haemorrhage in the right frontal region. Despite extensive work-up, no

990 underlying cause was found.

991 Figure 4

992

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

997

998

999 Figure 5

1000

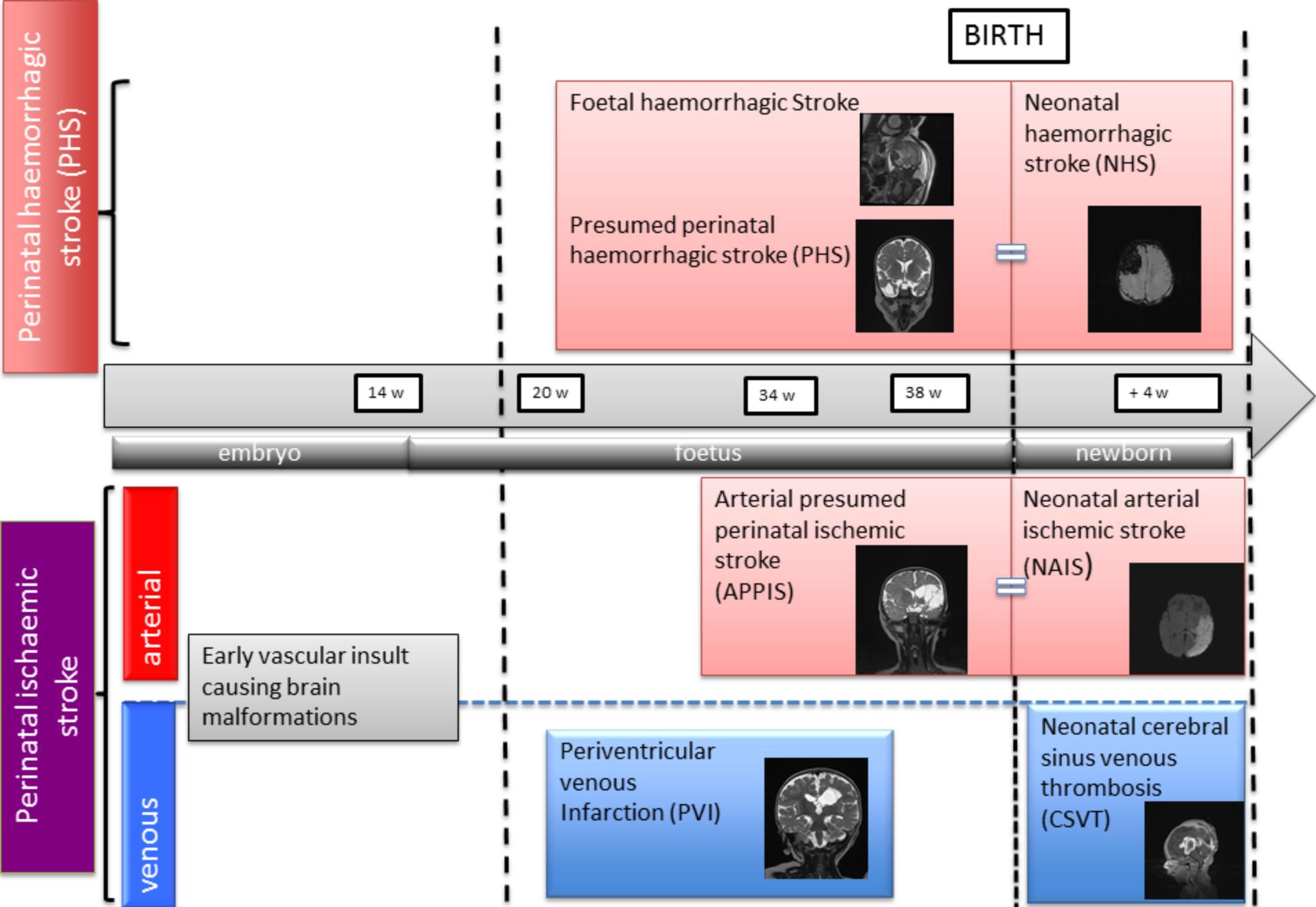
1001 Five-day-old term neonate who presented abruptly with lethargy and opisthotonus. A large  
1002 thalamic haemorrhagic stroke is seen on this axial T2-weighted image with contiguous  
1003 intraventricular haemorrhage. On contrast-enhanced MR venography, large filling defects  
1004 corresponding to extended thrombi are seen (double-arrow) along the superior sagittal  
1005 sinus and the straight sinus.

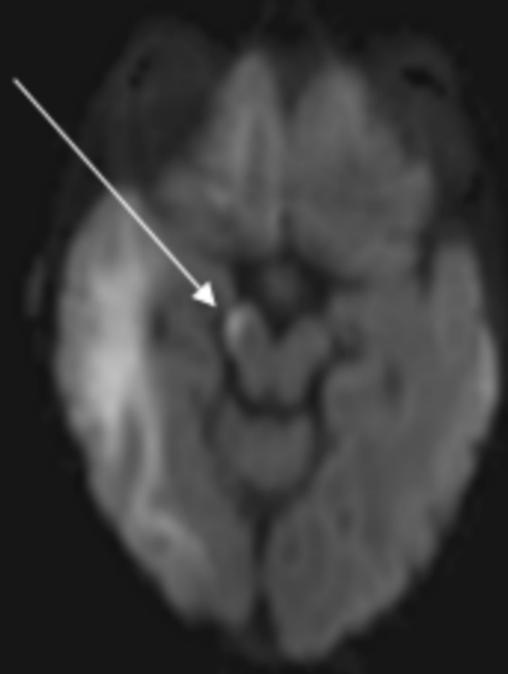
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1007 Figure 6

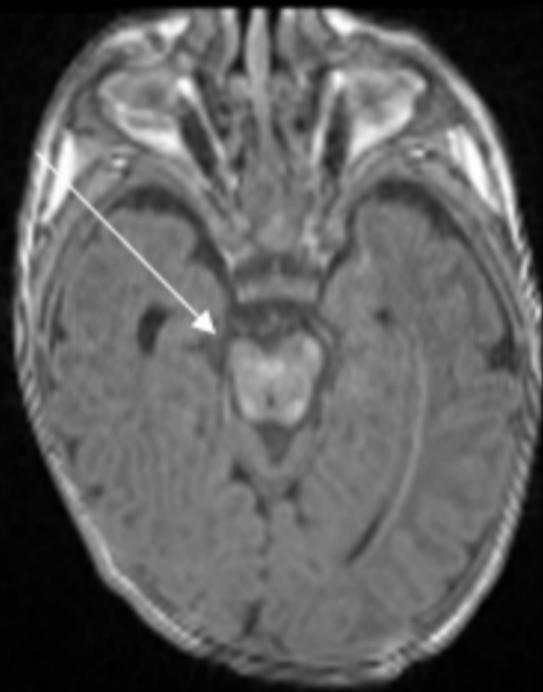
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1009 Coronal T2-weighted images of two children who presented with delayed onset. a) A large  
1010 porencephalic cavity in the left sylvian territory is seen in this 5-month-old boy who was seen  
1011 first in the emergency department with infantile spasms. Simultaneously, the parents were  
1012 reported diminished reaching and grasping of the right hand. (b) This child was referred due to  
1013 left hand preference at the age of 7 months. Left periventricular white matter loss is well visible.

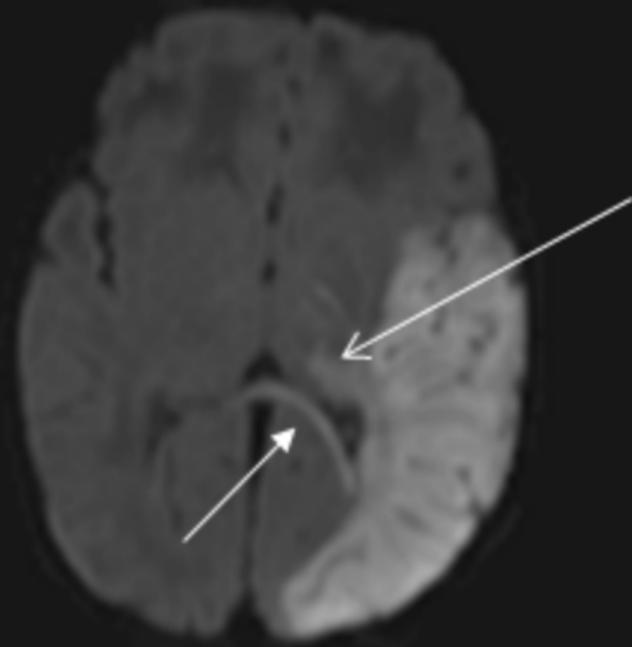




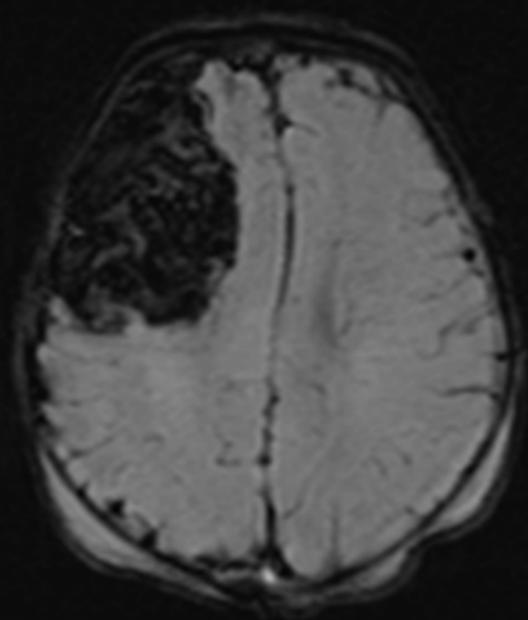
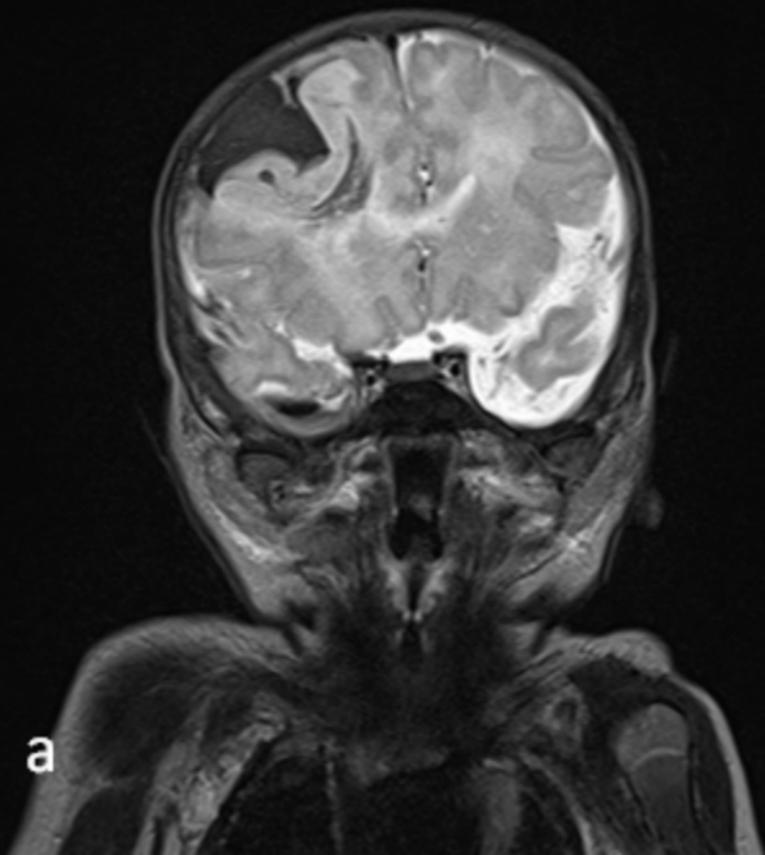
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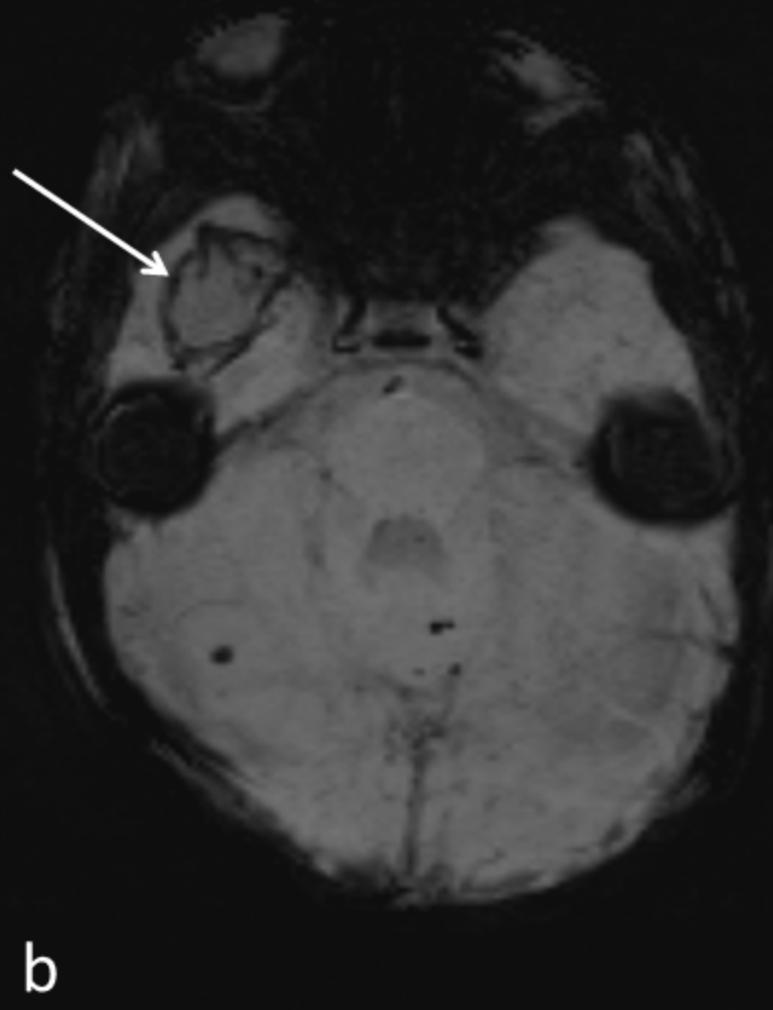
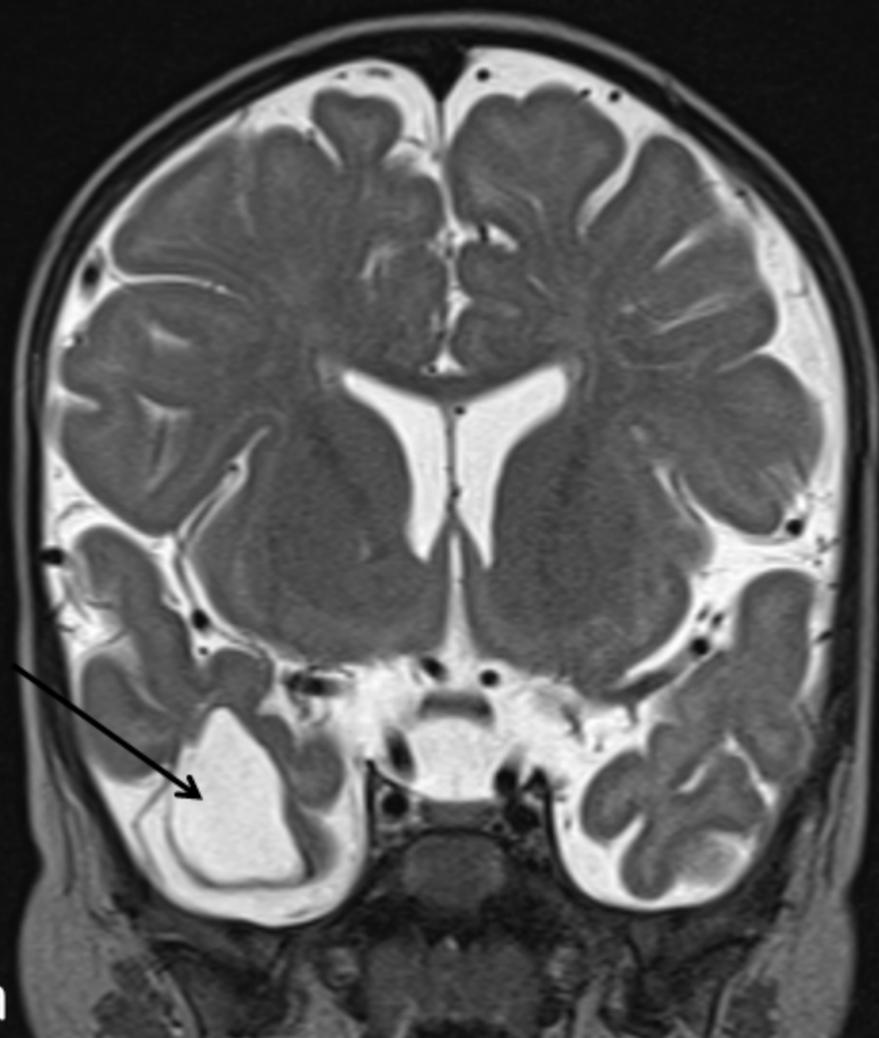


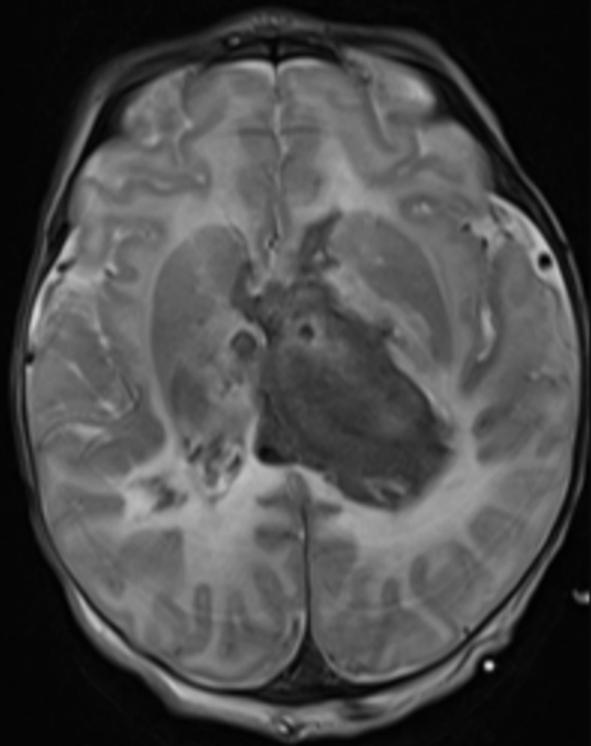
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c



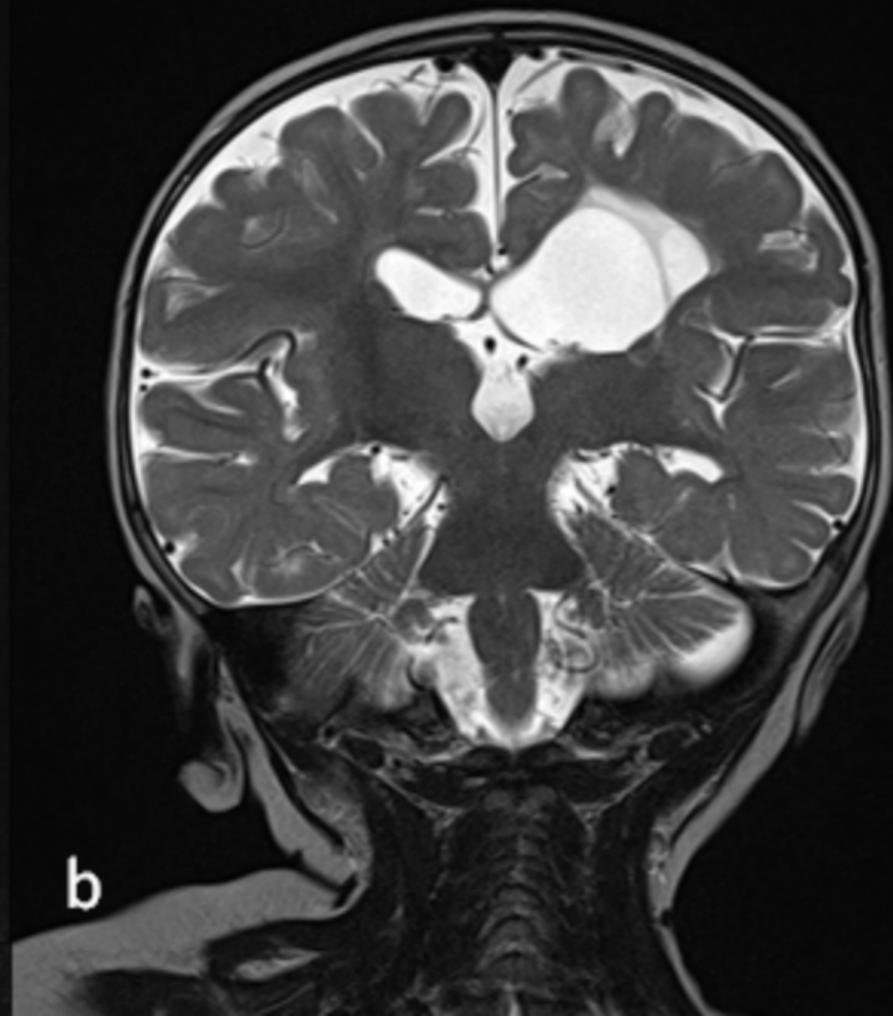
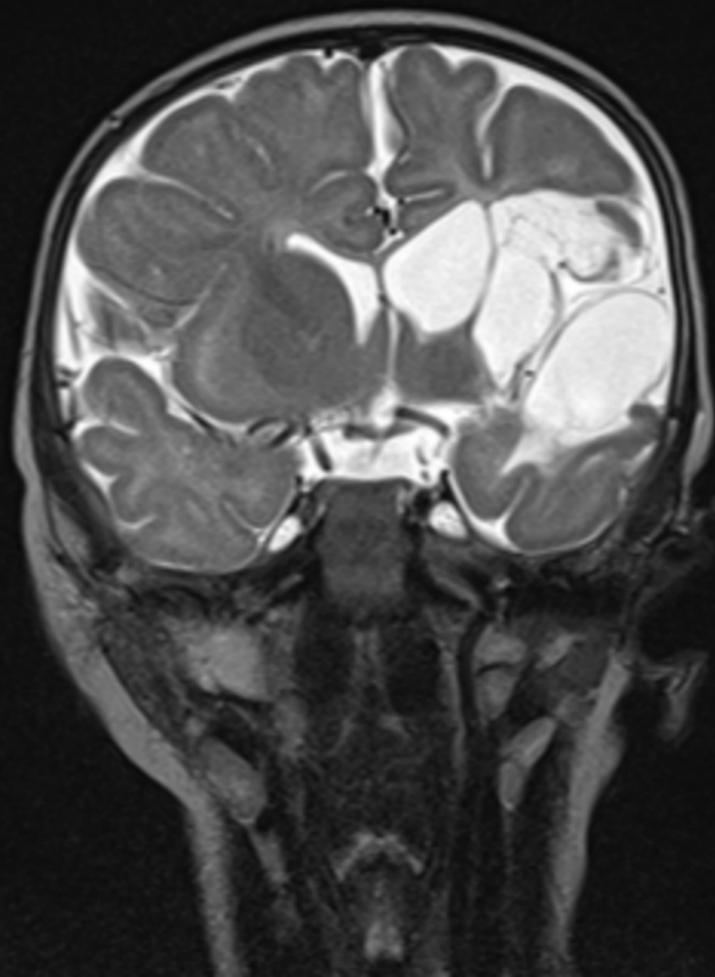




a



b



a

b

**Table**

Type of stroke	Birth-prevalence (37-67/100,000)	Causes and risk factors (often plural)	Mechanism	Main clinical findings	Outcome
<b>Neonatal arterial ischemic stroke (NAIS)</b>	- 6-17/100,000 in newborns $\geq 35$ GA  (670/100,000 $\leq 34$ GA with specific findings: see text)	<b>Symptomatic cases</b> - Bacterial meningitides - Cardiac disease/procedure - ECMO <b>Cryptogenic cases</b> - Chorioamnionitis - Perpartum asphyxia - Male sex and nulliparity	<b>Cryptogenic cases</b> - Placental cerebral embolism - Focal arteriopathy including cerebral vasculitis and (rarely) trauma	- Repeated focal seizures - In an otherwise healthy term/near term newborn	- <b>CP</b> : 1/3 (depending on the extend and localization of the infarct site) - <b>Epilepsy</b> : 15% - <b>Learning/behavioural difficulties</b> : ++ - <b>Recurrence</b> : exceptional
<b>Presumed perinatal ischemic stroke (APPIS + PVI)</b>	- 20-29/100,000	<b>APPIS</b> - similar to NAIS <b>PVI</b> - Preeclampsia, foetal hypotrophy	<b>APPIS</b> - Probably similar to NAIS <b>PVI</b> - In utero ( $\leq 34$ GA) germinal matrix haemorrhage leading to compression of the medullary veins and focal venous infarction of the periventricular white matter	<b>Delayed presentation</b> (by definition) - Most often through motor deficiency - Rarely with seizures, learning difficulties or systematic imaging	- <b>CP</b> : quasi systematic due to the mode of presentation - <b>Epilepsy and learning/behavioural difficulties</b> : higher than NAIS for APPIS and lower for PVI - <b>Recurrence</b> : exceptional
<b>Perinatal haemorrhagic stroke (PHS; restricted by definition to term/near term newborns)</b>	- 16/100,000	<b>Symptomatic (rare) cases</b> - Bleeding diathesis (thrombocytopenia) - Vascular malformation - Cardiac disease/procedure <b>Cryptogenic cases</b> - 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)	<b>Acute presentation</b> Similar to NAIS (seizures ++) and eventually more severe in case of intracranial hypertension <b>Delayed presentation</b> Similar to PPIS	- <b>Acute stage</b> More severe than NAIS (mortality risk up to 25 %) - <b>Long term</b> Depending on the extend and localization of the lesion and comorbid conditions (worse in symptomatic cases) - <b>Recurrence</b> : exceptional

<b>Neonatal cerebral sinus venous thrombosis (CSVT)</b>	- 1.4-12/100,000	<b>Symptomatic cases</b> - Severe neonatal condition: meningitis, dehydration, HIE... <b>Cryptogenic cases</b> - Gestational hypertension - Chorioamnionitis - Perpartum asphyxia	Virchow's triad	<b>Acute presentation</b> Similar to NAIS (seizures ++) <b>Discovered incidentally</b> in case of a severe disorder (e.g. meningitis) or as an incidental finding in case of systematic imaging survey (preterm, small for GA)	- <b>Long term</b> Depending on the association or with parenchymal injury and comorbid conditions - <b>Epilepsy</b> with continuous spike and wave during sleep - <b>Recurrence</b> : exceptional
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**GA**: gestational age; **ECMO**: extracorporeal membrane oxygenation; **HIE**: hypoxic ischemic encephalopathy; **CP**: cerebral palsy.