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# Neonatal stroke in premature neonates

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## ABSTRACT

There are many neuro-imaging studies on the presence of brain lesions in the preterm infant, using cranial ultrasound (cUS) and/or term equivalent age MRI (TEA-MRI). These studies however tend to focus on germinal matrix-intraventricular hemorrhage (GMH-IVH) and white matter injury. Data about perinatal arterial ischemic stroke (PAIS) or cerebral sinovenous thrombosis (CSVT) in the preterm infant are very limited. In fact, several large cohort studies on neuro-imaging in preterm infants do not even mention neonatal stroke.<sup>1-4</sup> Most studies about PAIS exclude preterm infants.<sup>5</sup> The aim of this review was to provide an update on neonatal stroke in the preterm infant, with a focus on neuro-imaging findings.

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## Perinatal arterial ischemic stroke

### Incidence

There are only a few studies that focus on PAIS in preterm infants and three of these report the incidence.<sup>2,6,7</sup> In a single NICU population of almost 3800 preterm infants with a gestational age (GA) below 35 weeks, 26 preterm infants were diagnosed to have PAIS with an incidence of 7 in 1000 admissions.<sup>2</sup> In the study by Ecury-Goossen the focus was on infants with perforator stroke.<sup>6</sup> It was mentioned that 25 of 55 infants were born preterm (<37 weeks) with 17 before 32 weeks' gestation, and an incidence for just perforator stroke of 0.5% for infants born preterm. In a German surveillance study, the incidence was significantly higher in preterm born infants [32 per 100.000 in preterm born infants (95% CI 15,49) and 21 (95% CI 16, 26) in full-term infants] (significant difference  $p = 0.001$ ).<sup>7</sup> In a study by Golomb et al. (2008) 23 infants with PAIS and a GA < 35 weeks were reported, but no incidence was given.<sup>8</sup> In a recent case control study by Sorg et al.

(2019) 16% of the 134 infants with PAIS were born preterm.<sup>9</sup> In their multivariable analysis, preterm birth was associated with a 1.57 (95% confidence interval 0.82–3.03) times higher risk for PAIS.

### Risk factors

One case control study reported risk factors for PAIS.<sup>2</sup> In a multivariable analysis twin-to-twin transfusion syndrome (TTTS), fetal heart rate abnormalities and hypoglycaemia were identified as independent risk factors. There was no difference in risk factors between preterm and term infants in the German surveillance study, but the number of risk factors was significantly higher in the preterm infants (mean 3.8 vs 2.9;  $p = 0.01$ ).<sup>7,10</sup> Golomb et al. did not perform a case control study.<sup>8</sup> Of their 23 infants, 6 had fetal distress, 2 had hypoglycaemia and 6 had meningitis. They had five twins in their cohort (22%), but only one was part of a twin pregnancy with TTTS. In the study of Ecury-Goossen et al. 25 / 55 infants studied were born preterm and 17 had a GA < 32 weeks.<sup>6</sup> Unfortunately, no distinction between the two groups was made

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when looking at risk factors. It is however striking that patent ductus arteriosus was diagnosed in 12 of the infants studied, presumably all preterm infants, but no mention was made of the time of PDA diagnosis and a possible relation of stroke with surgical closure. Follow-up was available in 17/25 preterm infants. Motor impairment was only seen in 2 and both had involvement of the posterior limb of the internal capsule (PLIC).<sup>11</sup>

### Imaging findings

Preterm infants admitted to a NICU will have serial cUS examinations during the neonatal period, even though the number of scans varies considerably across continents.

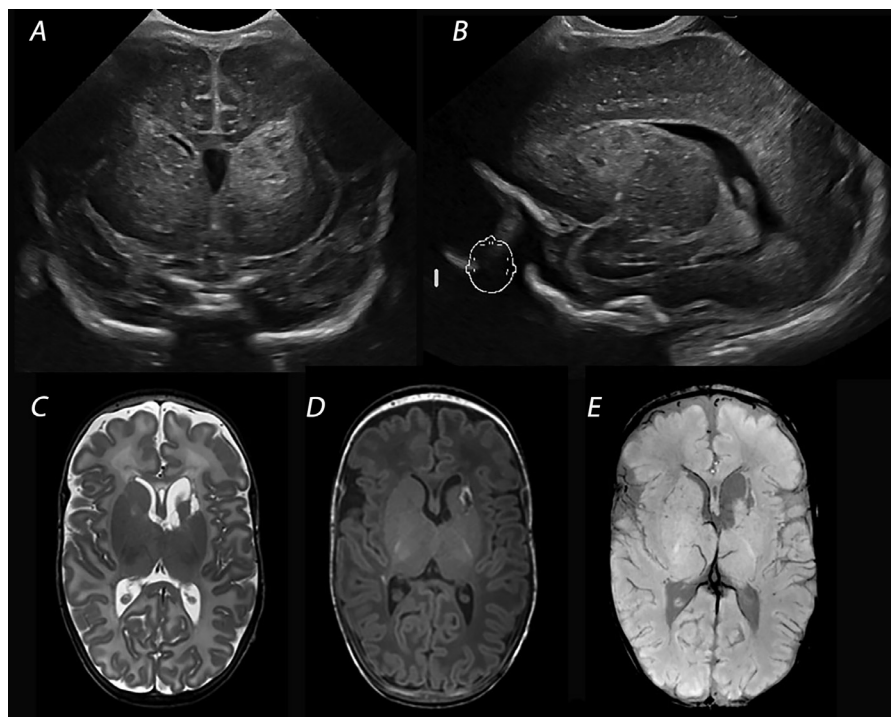
As *perforator strokes* are especially common in preterm infants with a GA < 32 weeks, cUS is an excellent diagnostic tool as this area is well within the field of view.<sup>2</sup> These centrally located infarcts tend to become apparent beyond the first postnatal week. They are typically wedge shaped and most lesions do not involve the PLIC. As the lesion tends to be unilateral, comparison with the contralateral side allows recognition of the area of increased echogenicity, which can initially be very subtle, but will become more marked over time (Fig. 1). A distinction between PAIS and a unilateral thalamic hemorrhage can only be made with MRI. Among those with perforator stroke, associated intracranial lesions were found in 4 cases, cystic PVL in 2 and a large GM-IVH in the other 2. Two other studies show helpful templates with examples of involvement of different branches of the anterior (Heubner's

artery) medial and lateral striate arteries of the middle cerebral artery (MCA) or thalamic branches of the posterior cerebral artery (PCA).<sup>3,6</sup>

While perforator strokes were most often seen (10/14) in infants with a GA < 32 weeks, involvement of the *main MCA branch* was seen in the majority (8/11) of those with a GA between 32 and 36 weeks.<sup>2</sup> PAIS was more often left-sided (61%), similar to what is seen in the full-term infant and bilateral PAIS was diagnosed in 7% of the infants.

Similar to what we see in the full-term infant with main branch MCA, echogenicity will take several days to develop and a linear demarcation line, if present, will become clear with time. Several weeks after recognition of the echogenicity, cavitation will become apparent. In contrast to the infants with perforator stroke, these infants often have clinical symptoms, apnea and/or seizures, and an MRI is therefore made acutely as well. Diffusion weighted imaging (DWI) will show the area of infarction as well as involvement of the corticospinal tracts and cerebral peduncle as 'pre-Wallerian' degeneration, allowing a better early prediction of motor outcome.

An interesting observation was made by van der Aa et al.,<sup>12</sup> referred to as 'cortical sparing'. In contrast to the full-term infant where there is no preserved cortex around the area of cavitation, in the preterm infant either partial or complete sparing of the cortex can be seen, with complete sparing seen only in infants with a GA < 32 weeks and partial sparing in infants with a GA of 33–37 weeks. This could be due to a regression of a large network of leptomeningeal arteries that initially show continuity of branches of these arteries arising



**Fig. 1** – Part of monozygous diamniotic twins with TAPS, born at 29 weeks/ birthweight 1250 g. cUS on day 2 shows a wedge shaped echogenic lesion on the left caudate nucleus region, A) coronal and B) sagittal view. The MRI at TEA shows cystic evolution with some ex-vacuo dilatation of the left ventricle (C) as well as a germinolytic cyst. On the T1 (D) the cyst has a high signal intensity rim. The SWI (E) does not show low signal intensity suggestive of a hemorrhage. Anterior cerebral artery perforator stroke.

from the MCA into branches of the anterior and posterior arteries. Beyond 30–32 weeks' gestation, a regression of the arterial system occurs, resulting in the formation of smaller anastomoses. When cortical sparing is seen on a childhood MRI, this may help to time stroke onset.

PAIS of the anterior and posterior cerebral arteries is even less often reported except for the thalamic branches of the PCA. PAIS of the anterior cerebral artery (ACA) territory should be recognized with cUS but PCA stroke may be easily missed and only noted with dedicated cUS through the posterior fontanel and routine term equivalent age MRI (TEA-MRI).

Two studies reported cerebellar infarcts. In the study by Golomb three infants were reported as having cerebellar infarcts possibly involving the posterior inferior cerebellar arteries: 2 unilateral and one bilateral.<sup>8</sup> The figure in this paper is however more suggestive of a preceding cerebellar hemorrhage, and it is therefore not entirely clear whether these 3 infants did indeed have cerebellar infarcts or sequelae of cerebellar haemorrhages. The same can be said for the study by Mercuri et al.,<sup>13</sup> where six cases with cerebellar infarcts were reported. The infarcts were not seen with cUS in the neonatal period, as mastoid window views were not yet routinely performed in those days and MRI was performed between 7 months to 8 years. The MR images do suggest prior hemorrhage and this would also be in agreement with the presence of additional supratentorial haemorrhagic lesions. Data on cerebellar infarcts are limited and without the use of neonatal MRI, including susceptibility weighted imaging (SWI) a distinction between cerebellar stroke and hemorrhage is challenging.<sup>14,15</sup>

### Periventricular hemorrhagic infarction

Periventricular venous infarction (PVI) is the second most common type of presumed perinatal stroke in infants who present with a hand preference in infancy.<sup>16</sup> As the appearance of this type of presumed perinatal stroke seen on MRI in infancy is very similar to the periventricular hemorrhagic infarction (PVHI) seen in the preterm infant who develops the lesion in the neonatal period, PVHI is also included in this review. This lesion is best referred to as PVHI rather than a grade IV hemorrhage and is considered to be due to impaired drainage of the medullary veins in the white matter. In those who are presenting later in infancy, remnants of hemorrhage can often still be seen, especially with the use of susceptibility-weighted imaging (SWI).

### Incidence

A decline of PVHI has been noted over the last few decades. In the most recent study by Yeo et al.<sup>17</sup> grade III and PVHI were taken together and the incidence was 5% among 21,606 infants born below 32 weeks' gestation. In another study PVHI was diagnosed in 163 out of 3764 (4.3%) preterm infants with a GA <32 weeks who were admitted to three participating centers during the study period.<sup>18</sup>

### Risk factors

Most studies looked at risk factors for all grades of GMH-IVH or just severe IVH, but not specifically for PVHI. Some well-known risk factors include lack of antenatal steroid exposure, low GA and birth weight, male sex, being outborn, 5 min Apgar scores below 7, intubation at birth and delivery room CPR.<sup>19,17</sup> One study looked at possible differences in risk factors for grade III and PVHI.<sup>20</sup> When comparing risk factors for 28 infants with a grade III, and 31 with PVHI, they found that infants with PVHI were significantly younger and weighed significantly less, but no other differences were found. If PVHI presentation is atypical (17 out of 62 preterm infants), being either present at birth or developing beyond 96 h after birth, it is recommended to assess factor V Leiden heterozygosity which was found in seven of these 17 infants.<sup>21</sup> PVHI can develop before birth and especially when there is also cerebellar involvement, mutations of the COL4A1 and COL4A2 gene should be investigated.<sup>22</sup>

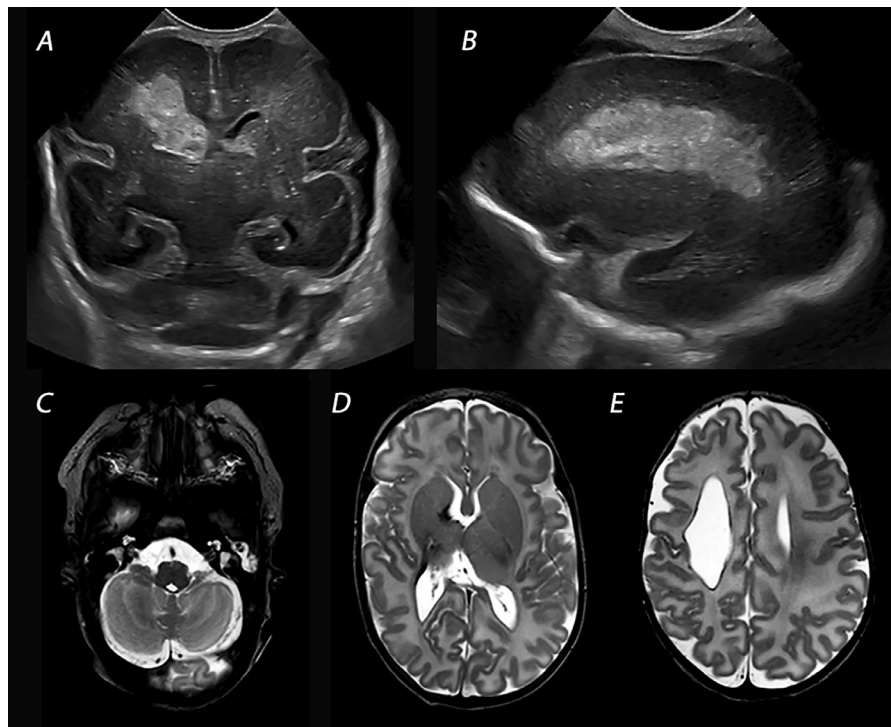
### Imaging findings

Performing several cUS examinations during the first week after birth will usually show an evolution from a GMH-IVH to PVHI due to impaired venous drainage of the medullary veins into the terminal vein. The area of echogenicity can be globular and continuous with the lateral ventricle and may extend over several lobes and even cause a midline shift.<sup>23</sup> The extent of the PVHI can be best assessed in the sagittal plane. In this view involvement of the trigone can be scored. The lesion can also be more triangular in shape with the apex of the lesion adjacent to, but not necessarily in communication with the lateral ventricle. On follow-up scans, the globular lesion will evolve into a single cyst communicating with the lateral ventricle (porencephaly) while in a triangular shaped lesion, multiple cysts may develop which are often not or partly communicating with the lateral ventricle and therefore misdiagnosed as c-PVL.<sup>24</sup>

An early MRI may show increased signal intensity on the T2 weighted sequence and reduced overlying cortical folding due to a pressure effect. The MRI provides more detail on the extent of associated white matter injury and also on additional injury of the contralesional hemisphere and the cerebellum. Using diffusion tensor imaging, the unmyelinated PLIC can be assessed, either visually on the direction encoded color map or by calculating fractional anisotropy (FA) values.<sup>25</sup> On the TEA-MRI asymmetry of myelination of the PLIC can be assessed as well as FA of the PLIC, both being predictive of motor outcome. In rare cases contralateral cerebello-cerebral diaschisis may be seen.<sup>26,27</sup>

### Neonatal cerebral sinovenous thrombosis

Neonatal cerebral sinovenous thrombosis (CSVT) is a rare but serious neurological disorder. Symptomatic CSVT has a high mortality and is associated with significant morbidity in multiple outcome domains, including epilepsy. Less severely affected and asymptomatic cases may remain undiagnosed unless targeted neuroimaging is performed. Greater clinical



**Fig. 2** – Preterm infant born at 26 weeks/ birthweight 809 g. cUS on day 2 shows globular shaped PVHI in a coronal (A) and parasagittal view (B) involving the frontal and parietal lobe. The TEA-MRI, axial T2 sequence, shows crossed cerebellar diaschisis (C), asymmetry of the PLIC (D) and the porencephalic cyst (E).

awareness, systematic cUS screening and MRI have improved the recognition of *preterm* CSVT. However, up to now little is known about the incidence, risk factors, management and outcome of preterm infants with CSVT.

### Incidence

Most registry studies on pediatric CSVT only discriminated between neonatal and childhood CSVT and did not mention how many neonatal cases were born preterm.<sup>28-31</sup> Therefore, the incidence of neonatal CSVT ranges from 2.6 to 12 per 100.000 *term-born* neonates per year but the true incidence of *preterm* CSVT is unknown.<sup>28,32</sup> In a recent German national surveillance study the incidence of both term and preterm CSVT was estimated 6.6 per 100.000 live births.<sup>10</sup> In this study and in other studies and case series specifically focussing on neonatal CSVT between 10 and 27% of the neonates were born preterm.<sup>30,32-35</sup> Moreover, in a prospective single-center cohort of 249 preterm infants the combination of serial cUS and MRI led to the detection of a high number of *asymptomatic preterm infants* (4.4%) with a partial or complete CSVT.<sup>36</sup> It is therefore likely that CSVT is not uncommon in the preterm infant and that a non-specific or asymptomatic presentation may have resulted in an underestimation of cases so far.

### Risk factors

It is important to realize that the risk factors for neonatal CSVT may vary between term and preterm infants due to differences in brain development and other prematurity related conditions. Up to now, only one study described both term

and preterm cases and reported data on the risk factors in preterm infants separately.<sup>35</sup> In this study, out of eight symptomatic preterm cases three were related to sepsis and another three to dehydration. In a prospective cohort of preterm infants including 11 cases with asymptomatic CSVT there was a trend towards more sepsis, patent ductus arteriosus, maternal risk factors, and a longer duration of mechanical ventilation in the cases with CSVT but none of these were significant.<sup>36</sup> Both cranial moulding during (complicated) delivery and compression of the occipital bone by lying in supine position may distort the underlying venous sinuses, compromise cerebral venous blood flow and have been associated with neonatal CSVT.<sup>32,37</sup> As preterm infants have a more compliant skull, they may be prone to mechanical compression by external factors including head position or even tight CPAP hats. In combination with other risk factors that induce a hypercoagulable state such as dehydration and sepsis this may be a contributing factor in the development of CSVT and deserves further attention.

### Presentation

The clinical presentation of neonatal CSVT has been described in cohorts of predominantly full-term infants. Presentation was most common within the first postnatal days and the main presenting symptoms consisted of generalized or focal seizures and/or apnea, especially in cases with associated brain lesions. Other symptoms included encephalopathy, lethargy, irritability, feeding problems and hyper- or hypotonia.<sup>29,32,33,38</sup> In the study by Kersbergen (2011) the mean postnatal age at presentation was slightly older in



preterm infants as compared to full-term infants (9 days; range 1–28 and 5 days; range 1–19, respectively).<sup>34</sup> In the study by Raets, all preterm infants with CSVT were asymptomatic and the postnatal age at diagnosis ranged from 5 to 34 days.<sup>36</sup> In the recent surveillance study by Sorg (2021) the median postnatal age at diagnosis was again higher in preterm infants, compared to term infants (12 versus 7 days). Overall there were no major differences in symptoms between term and preterm infants and seizures were the most common presenting symptom in both groups.<sup>10</sup>

Fig. 2.

### Neuroimaging

The neonatal venous system can be divided into a superficial and a deep venous system. The superficial venous system consists of the superior sagittal sinus, the transverse, torcular, and sigmoid sinuses; the deep system consists of the internal cerebral veins, vein of Galen and straight sinus (Fig. 3). Neonatal CSVT frequently involves the superficial venous system but thrombosis of multiple sinuses of both the superficial and deep venous system is also common.<sup>29,33,34,38,10</sup> There is no difference in site of involvement between symptomatic preterm and full-term infants but in asymptomatic preterm infants the transverse sinuses are more commonly affected.<sup>36</sup>

Both in newborns and older children the site and extent of thrombosis have been associated with the location of and severity of associated brain lesions.<sup>39</sup> Involvement of the straight sinus and complex multiple sinus thrombosis carry the highest risk of severe brain lesions.<sup>32</sup> Preterm infants have a different pattern of associated brain lesions than full-term infants. Where full-term infants have associated intraventricular hemorrhage (IVH), thalamic hemorrhage and punctate white matter lesions, preterm infants often present with extensive white matter injury.<sup>34</sup> The appearance of white matter injury resembles that of periventricular leukomalacia and extensive white matter cysts can develop later on. This often presents beyond the immediate neonatal period and occurs in combination with late onset IVH. It is therefore important to consider the diagnosis of CSVT in a preterm infant presenting with late onset white matter injury and unexpected late onset IVH.

Both cUS and MRI can be applied for the diagnosis of neonatal CSVT and are considered complementary as each has its own specific advantages. Serial imaging is used to assess the evolution of the thrombus (clot propagation, thrombus recanalization) and of associated lesions.

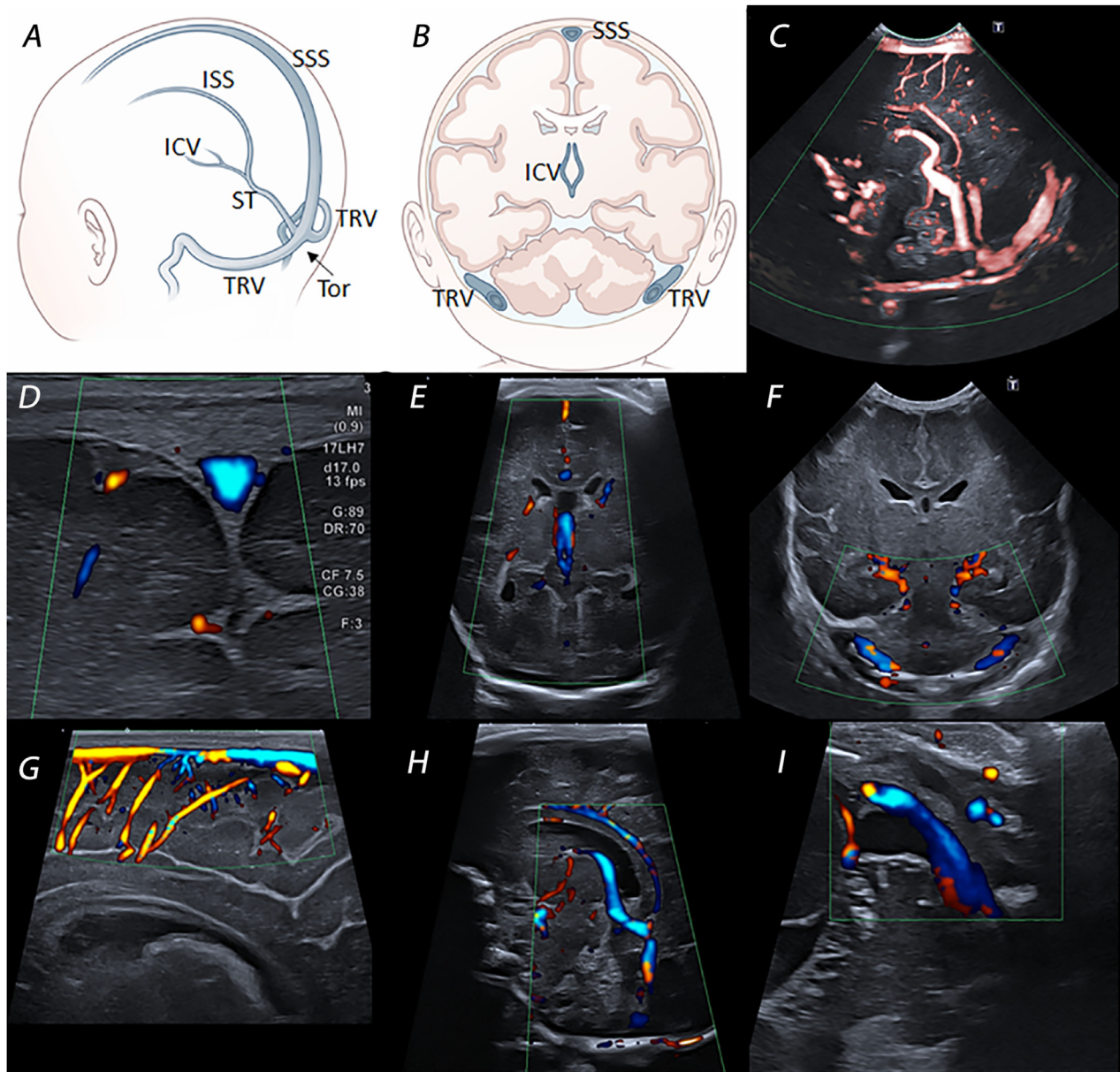
### Cranial ultrasound

In most neonatal intensive care units bedside, screening cUS examinations are performed in all very preterm infants. During cUS, Color Doppler can be applied to evaluate the patency of the venous sinuses and has a high specificity to rule out neonatal CSVT.<sup>40</sup> This is important because symptoms are often non-specific and an earlier diagnosis can provide a window for therapeutic intervention, before additional brain lesions occur.

Routine cUS is performed through the anterior fontanel (AF) in coronal and sagittal planes. In addition, posterior fontanel and mastoid fontanel views are used to visualize the occipital parts of the brain and the posterior fossa. In the AF coronal plane the superior sagittal sinus, internal cerebral veins and transverse sinuses can be visualized; in the AF midsagittal plane the anterior-middle and posterior parts of the superior sagittal sinus, the inferior sagittal sinus, internal cerebral veins and straight sinus. The posterior fontanel can be helpful to visualize the distal part of the straight sinus up to the Torcular Herophili and the mastoid fontanel can be used to further evaluate the transverse sinuses as they may be difficult to visualize from the AF view.<sup>40</sup> (Fig. 3). Color Doppler cUS can demonstrate partial or a total absence of flow in combination with a partial or complete occlusion of the affected sinus(es). Furthermore, cUS can depict associated brain lesions in the form of (late onset) IVH and white matter injury (Fig. 4). Although it is feasible to screen the venous system in neonates, previous retrospective studies reported only a moderate sensitivity of cUS for the detection of CSVT. In the study by Berfelo et al., 37% of cases were diagnosed with cUS and 63% solely on MRI and in another study approximately half of CSVT were detected with cUS.<sup>32, 41</sup> Nevertheless, the use of targeted cUS screening, including Color Doppler, high frequency linear transducers and additional mastoid fontanel views, has the potential to increase the diagnostic accuracy of cUS for the detection of CSVT.<sup>36</sup>

### Magnetic resonance imaging

MRI is not the initial preferred imaging modality in sick newborn infants, as it requires transportation to the scanner and is more expensive than cUS. However, MRI is a very sensitive technique to detect and exclude CSVT and should always be performed in neonates with a high suspicion of CSVT based on clinical symptoms and/or cUS. Because the symptoms of neonatal CSVT can be non-specific we also recommend to include MR venography (MRV) in all infants who undergo MRI because of seizures and/or an unusual presentation of (late onset) IVH or white matter injury. The MRI protocol for suspected CSVT preferably includes a combination of T1- and T2- weighted sequences, DWI, SWI, and MRV which can be acquired by both time-of-flight and phase contrast techniques. In general, the use of intravenous contrast agents is not necessary for the diagnosis of CSVT. The MRI appearance of the thrombus and associated brain lesions varies depending on the stage (acute, subacute or chronic). Ischemic parenchymal lesions can be depicted by DWI in the acute stage. Hemorrhagic lesions remain visible on the SWI for months. A potential pitfall of MRV is that there can be flow gaps in the venous sinuses, particularly in the posterior part of the superior sagittal sinus and the transverse sinuses, which can be attributed to a combination of a smaller caliber and consequently less venous flow, and compression of the sinuses in supine position.<sup>42</sup> The smaller inferior sagittal sinus can also be difficult to visualize by MRV. In these cases Doppler cUS with very low flow velocity settings can be helpful to demonstrate flow and exclude CSVT.<sup>40</sup>



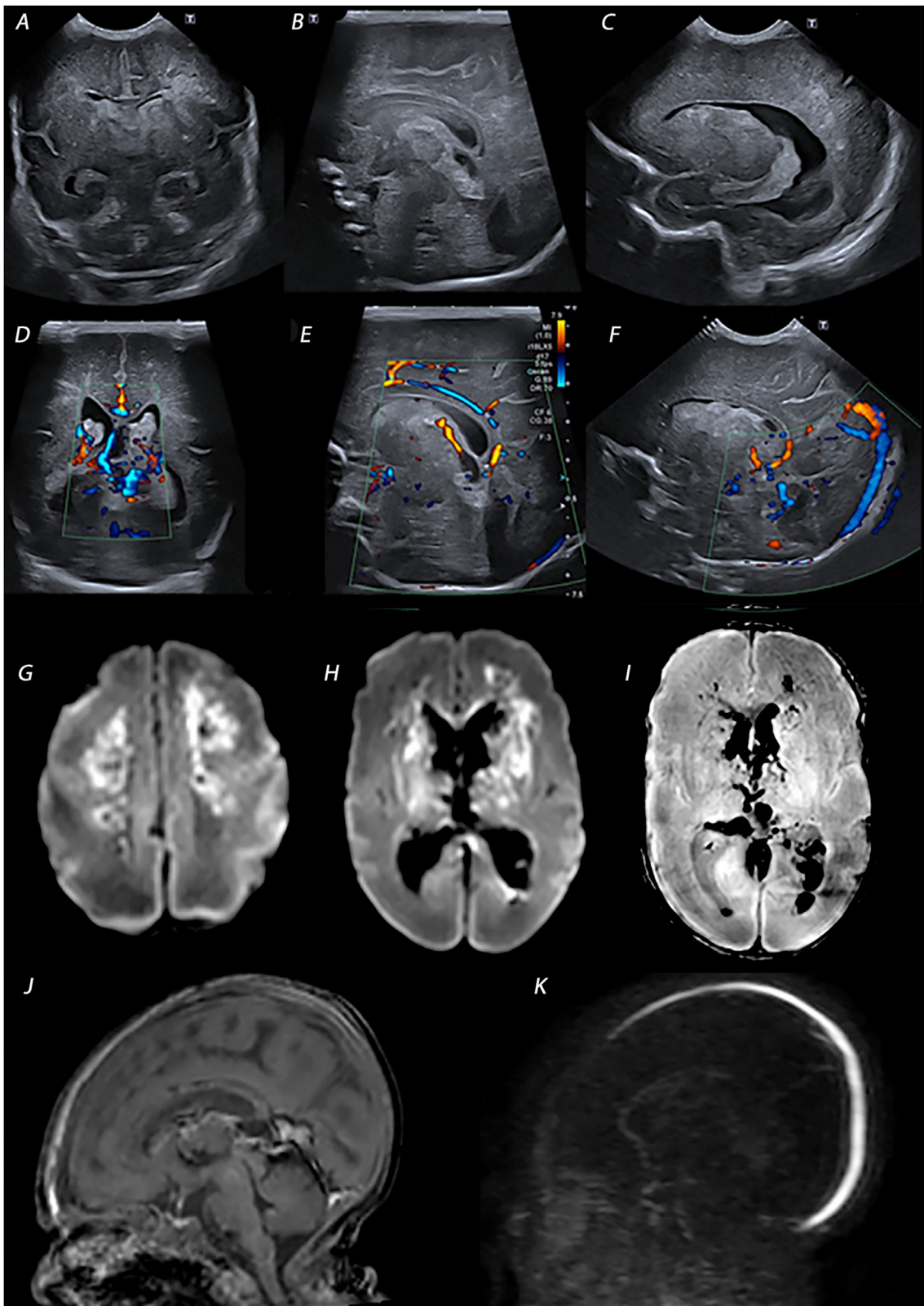
**Fig. 3**—(A) Lateral posterior and (B) coronal schematic views of the cerebral sinovenous system showing the superior sagittal sinus (SSS), inferior sagittal sinus (ISS), Torcular herophili (Tor), transverse sinuses (TRV), straight sinus (ST) and internal cerebral veins (ICV). (C–H) Cranial ultrasound images, obtained through the anterior fontanel using Superb microvascular imaging (C) and Color Doppler imaging (D–H). (C) Midsagittal view showing the anterior and posterior part of the SSS, the ISS, ST and ICV. (D–F) Coronal views showing the SSS (D), both ICVs (E) and both TRVs (F). (G–H) Midsagittal views with a detailed image of the SSS (G) and ISS, ST and ICV (H). (I) More detailed view of the TRV using the mastoid fontanel.

### Treatment and outcome

General treatment measures for neonatal CSVT are supportive and include rehydration, antibiotics for suspected sepsis/meningitis and medication for neonatal seizures.<sup>33</sup> There is only limited data available to guide the use of anticoagulant treatment (ACT) and the optimal approach in neonates with preexisting significant intracranial hemorrhage remains uncertain.<sup>43,44,45</sup> Preterm infants with a higher risk for IVH may not receive treatment because of fear for additional hemorrhagic complications.<sup>32</sup> Still, several retrospective case

series and one systematic review investigated the use of ACT in neonates with CSVT and none of them reported a significantly higher rate of hemorrhagic complications in neonates who received treatment.<sup>31–34,46</sup> The largest prospective study on treatment and outcome in neonatal CSVT reported a slightly higher rate of major intracranial hemorrhage in 6% of treated infants, as compared with 3% of untreated infants but in the same study an important benefit of ACT was a significant reduction in the risk of thrombus propagation and thereby prevention of subsequent (hemorrhagic) parenchymal venous infarction.<sup>30</sup>





**Fig. 4** – Preterm infant, born at 26 weeks' gestation with multiple sinus thrombosis. Anterior fontanel ultrasound images obtained 5 weeks after birth (31 weeks' gestation) after sudden clinical deterioration showing bilateral intraventricular hemorrhages, inhomogeneous periventricular white matter, and increased echogenicity in the trajectory of the straight sinus (ST) (A-C). Color Doppler ultrasound images demonstrate absence of flow in the left ICV (D) and ST (E-F). MRI images (G-K) were performed the following day. (G-H) Diffusion weighted MR images demonstrating extensive diffusion restriction in the periventricular white matter and deep gray matter. Susceptibility weighted MR image demonstrating the bilateral intraventricular hemorrhages and smaller areas of hemorrhagic infarction in the frontal lobes. (J-K) Midsagittal MRI images, T1-weighted image demonstrating a clot in the straight sinus (J) and MR venography demonstrating absence of flow in the deep venous system (K).



Neonatal CSVT carries a significant risk of a poor outcome.<sup>34</sup> The risk of impaired outcome depends on the extent of CSVT and the presence and severity of associated parenchymal brain injury.<sup>29,32,33,38</sup> Therefore, it is likely that reported outcomes will also depend on the clinical presentation and threshold of performing neuroimaging. Adequate long-term follow-up studies in preterm infants with CSVT, incorporating both symptomatic and asymptomatic cases and the whole spectrum of brain lesions are still urgently needed. These studies should also address the risks and benefits of ACT treatment in relation to mortality and long-term outcome.

### Conclusion

In the preterm infant, both PAIS and CSVT are still underreported in the literature. With the use of serial cUS, including Doppler Ultrasound, these diagnoses will be made more often. This will improve our understanding of risk factors and provide information about neurodevelopmental outcome.

### Declaration of Competing Interest

The authors have no potential conflicts to disclose

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