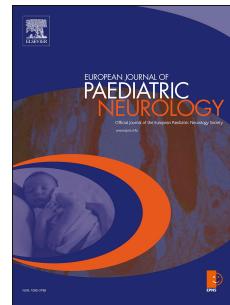


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MR Imaging for accurate Prediction of Outcome after Perinatal Arterial Ischemic Stroke: Sooner not Necessarily Better

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## MR Imaging for accurate Prediction of Outcome after Perinatal Arterial Ischemic Stroke: Sooner not Necessarily Better

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**ABSTRACT**

Two full-term infants with perinatal arterial ischemic stroke (PAIS), with cerebral sinovenous thrombosis of the superior sagittal sinus in one of them, are reported. Diffusion weighted imaging (DWI)-MRI, performed within 24 hours following onset of seizures and repeated 48 hours later, clearly showed restricted diffusion within the middle cerebral artery territory on both MRIs, but clear patterns of signal intensity changes in the descending corticospinal tracts on the second MRI only. Since involvement of these structures is essential for prediction of motor outcome, we may need to reconsider optimal timing of MR imaging for prediction of neurodevelopmental outcome after PAIS.

**Key words:** MRI; neonate; stroke; PAIS; Wallerian; corticospinal tract

**Highlights:**

- Early MRI is increasingly used to predict neurodevelopmental outcome of newborn infants with PAIS.
- Signal intensity changes in the descending corticospinal tracts are predictive of adverse motor development.
- This case series shows delayed onset of “pre-Wallerian” degeneration.
- Optimal timing of MRI imaging in PAIS patients for diagnosis and prognosis may be different

## 1. INTRODUCTION

Perinatal stroke consists of perinatal arterial ischemic stroke (PAIS) and cerebral sinovenous thrombosis (CSVT), and both are associated with unfavourable neurodevelopmental outcome. Adverse sequelae of PAIS include unilateral spastic cerebral palsy (USCP) cognitive dysfunction, epilepsy and speech problems. In 40-75% of infants, PAIS or CCSV lead to abnormal neuromotor and -developmental outcome.(1-3) Early MRI is used for diagnostic purposes, and for dating PAIS, but is also increasingly emphasized as an important prognostic value to predict the neurodevelopmental outcome of the infant.(4,5)

PAIS, and especially middle cerebral artery (MCA) infarction, often involves the descending corticospinal tracts (CST).(4-6) MRI and especially diffusion weighted imaging (DWI) offers the advantage of evaluating the posterior limb of the internal capsule (PLIC) and the cerebral peduncles, i.e. the presence of “pre-Wallerian” degeneration. Involvement of these structures is strongly correlated with adverse motor outcome.(4-9) CCSV is often associated with neurological comorbidity, such as hypoxic-ischemic encephalopathy, venous infarction and thalamic haemorrhage.(2,10) The presence of such neurological comorbidity at diagnosis predicts poor outcome in patients with CCSV.(2)

The aim of this short communication is to describe two newborns with PAIS who both had two early MRIs showing delayed onset of “pre-Wallerian” degeneration on sequential MRIs performed within 72 hours after onset of symptoms.

## 2. CASE DESCRIPTIONS

### 2.1 Case 1

This boy was born at  $40^{+4}$  weeks of gestation after an uncomplicated pregnancy by secondary caesarean section due to slow dilatation of the cervix and meconium stained amniotic fluid. His birth weight was 3570 gram (p15), length 53 cm (p50), head circumference 36 cm (p50). He had good Apgar scores of at 9, 10 and 10 at 1, 5 and 10 minutes, respectively. He was admitted to the neonatal unit in a level II hospital for observation, where he developed fluctuations in temperature, frequent apneas and lethargy, suspected for seizures. Amplitude integrated EEG (aEEG) showed epileptic activity originating from the left hemisphere. Cranial ultrasound and an early CT-scan showed an area of decreased attenuation in the distribution of the left MCA. He received phenobarbital to control seizure activity, and antibiotics and anti-viral medication until meningitis was ruled out by negative cerebrospinal fluid cultures, and he was transferred to our level III neonatal intensive care unit.

The first MRI was performed on the third day of life, around 20 hours after the onset of apneas (figure 1). In the complete left MCA territory, DWI and T2 weighed imaging showed increased signal intensity in the cortex and white matter. The basal ganglia including globus pallidus and putamen were also mildly affected. The left PLIC showed only very mild highlighting on DWI and T2 imaging, while some asymmetry was found laterally in the cerebral left peduncle (figure 1D-E). A small cortical lesion was also found in the upper right hemisphere, not affecting the corticospinal tracts. Reduced flow of the left MCA was seen on MR Angiography (MRA). The infant was included in an imaging study and the MRI was repeated on day 5, around 72 hours after the onset of clinical seizures and 48 hours after the first scan, to additionally perform arterial spin labeling.(11) DWI and T2WI showed the same area of increased signal intensity in the main left MCA territory. DWI hyperintensity in the PLIC had extended, showing a clear

asymmetrical pattern. Additionally, on DWI, the left cerebral peduncle now also clearly showed restricted diffusion, including the middle part.

The aEEG did not show any seizure activity, but the background pattern showed a continuous normal voltage with sleep-wake cycling on the right, while there was discontinuous normal voltage pattern on the left.

After the second MRI, the child was included in a pilot trial and treated with erythropoietin (EPO) 1000 U/kg per day for three days to improve neuroregeneration.(12) The infant improved clinically, could be fully breastfed and was discharged home one week after onset of seizures. A thrombophilia screen was performed, showing normal clotting time and homocysteine, no MTHFR, factor V Leiden or prothrombin mutation.

Repeat MRI at the age of three months showed cysts in the left hemisphere, especially in the region of the anterior branch of the MCA, and Wallerian degeneration of the left descending CST (Figure 1). On neurological assessment there was a hand preference for his left hand, suggestive of development of USCP, which was subsequently confirmed at two years of age, with Manual Ability Classification System score of 2, Gross Motor Function Classification System score of 1 and Hand Assessment for Infants (HAI) of 83% (whereas 0% equals no asymmetry).(13)

## 2.2 Case 2

This male infant was born at  $42^{+1}$  weeks' gestation after a secondary caesarean section because of slow dilatation of the cervix, meconium stained amniotic fluid, and fetal heart rate abnormalities following induction of labor. His birth weight was 3190 gram (<p5), length 51 cm (p3-p50), head circumference 35 cm (p3-p50). Apgar scores were 4, 7 and 9 at 1, 5 and 10

minutes, respectively. He recovered quickly after stimulation, insufflation breaths and CPAP (with max 40% O<sub>2</sub>) and no longer needed respiratory support after 5 minutes. He was admitted to the neonatal unit in a level II hospital, where he developed frequent apneas and desaturations 26 hours after birth, suggestive of seizures. He was transferred to our neonatal intensive care unit and was intubated because of respiratory insufficiency. Cranial ultrasound (9 hours after onset of apneas) showed a large wedge shaped area of increased echogenicity in the distribution of the right MCA, and reduced flow in the superior sagittal sinus. aEEG showed epileptic activity originating from the right hemisphere.

The first MRI was performed at 50 hours of age, 24 hours after the onset of apneas (Figure 2). DWI and T2 weighed imaging showed increased signal intensity in the cortex and white matter of the complete MCA territory in the right hemisphere. The basal ganglia including globus pallidus, putamen and part of the thalamus were also mildly affected. Very subtle restricted diffusion of the PLIC and right peduncle were noted (Figure 2D-E). On MRA there was interrupted flow of the right MCA. MR Venography (MRV) showed no flow in the anterior part of the superior sagittal sinus, suggestive of CSVT.

The infant was started on low molecular weight heparin (Dalteparin, 200 U/kg subcutaneously) to prevent propagation of the thrombus. Clinical seizures were controlled following administration of phenobarbital and midazolam and subsequently lidocaine on day 2 that controlled ongoing subclinical seizures on aEEG. There was a persistent asymmetry in background activity due to decreased activity on the right side. On day 2, activity on the right side was still mildly suppressed, but sleep-wake cycling had returned.

To assess the effect of therapy on CSVT, the MRI was repeated around 72 hours after the onset of clinical seizures and 48 hours after the first scan. DWI and T2WI showed the same area of increased signal intensity in the main MCA territory, including parts of the thalamus. In contrast, on DWI, the PLIC, anterior limb of the internal capsule and right cerebral peduncle now also clearly showed restricted diffusion. MRV showed recurrence of flow in the superior sagittal sinus.

After the second MRI, the child was treated with EPO.(12) The infant improved clinically, was extubated, started to bottle feed, and was discharged home on day 10 after birth. A thrombophilia screen was performed, showing a transient increase in homocysteine (13.7  $\mu$ mol/L, normal upper level 10  $\mu$ mol/L), but no MTHFR, factor V Leiden or prothrombin mutation.

At the age of three months, the infant returned for a repeat MRI, which showed a large area of cavitation in the right MCA region and Wallerian degeneration (Figure 1). On neurological assessment, he showed a clear preference for using his right hand, with intermittent fisting of the left hand, suggestive of a development of unilateral spastic cerebral palsy (USCP). The HAI at three months of age was 58%.

### 3. DISCUSSION

In this case report on two PAIS patients with main branch MCA stroke, DWI showed different patterns of CST involvement at 24 and 72 hours after the onset of clinical seizures. Also, the unusual combination of PAIS and CSVT is reported in the second infant, with recurrence of flow across the superior sagittal sinus on the second scan.

CT was performed in the level II hospital, but this neuro-imaging technique is not recommended as radiation is involved and CT will provide less information than MR imaging which is considered the gold standard.(14) Within the first week after PAIS, especially T2WI and DWI are most useful for detection and prediction of motor outcome. T2WI will show high signal intensity in the affected cortex and white matter, which can first be observed from 24 to 48 h onwards.(7) Changes on DWI can precede those on conventional T2WI and are often seen more clearly during the first 24–72 h as high signal intensity on DWI or low signal intensity on the derived apparent diffusion coefficient (ADC) map.(14) The lowest ADC can be observed around day 3, followed by a slow increase and pseudonormalisation of ADC values.(7,15) Clinicians are inclined to perform an MRI as quickly as possible in order to make a diagnosis in an infant presenting with neonatal seizures.(16) However, MR imaging also plays an important role in the prediction of motor outcome, especially in the development of USCP, and the cases presented have shown that “pre-Wallerian” degeneration may take time to develop and may not yet be present 1-2 days after onset of PAIS.

Wallerian degeneration was first described by Augustus Waller in 1850 and refers to anterograde degeneration of axons and their myelin sheaths, secondary to proximal axonal or cell body injury.(17) Wallerian degeneration of the descending CST and cerebral peduncle is first seen several weeks after cortical injury, and is associated with development of USCP. This was shown by Bouza et al. in a group of 20 infants and later by Kirton et al. (4,18) They described that the degree of Wallerian degeneration in the CSTs shown with MRI, well beyond the neonatal period, was correlated with the presence and severity of USCP later in life. Therefore, a follow-up MRI after several weeks is recommended for optimal prognosis of motor outcome. DW imaging is sensitive to early changes of cytotoxic edema and therefore able to depict acute

injury. Several studies have now shown that DWI can show subsequent axonal ischemia to the descending CST and the term “pre-Wallerian” degeneration was coined.(4,5,19,20) The presence of these DW changes in the CST, in particular the PLIC and the middle part of the cerebral peduncle, were found to be predictive of developing USCP.(4)

Our second infant presented with an unusual combination of main branch MCA infarction and CSVT. We performed a second MRI shortly after the first scan to evaluate the recurrence of flow in the sinus. This gave us the opportunity to obtain two early MRI scans, within the first week after birth. The first scan was performed at 24 hours after onset of seizures. Although DW imaging clearly showed acute injury in the MCA region, we could hardly find DW changes in the descending CST. This absence of early “pre-Wallerian” degeneration was also shown by Kang et al. in 2 adult patients and suggested by Husson et al.(6,21) On a repeat MRI at 72 hours after seizure onset, we found clear signal changes in the PLIC and cerebral peduncle. The increase of DWI abnormalities was also found in the first case. This delay in “pre-Wallerian” degeneration is in agreement with experimental data of Tuor et al. who showed in neonatal rats a delay of 24 hours for the decline in apparent diffusion coefficient (ADC) values and concomitant cellular correlates of degenerating neurons in the cerebral peduncle compared to the ADC values in the affected cortex. They proposed associated axonal ischemia as an explanation for this delay, induced by ischemic cell bodies of the axons in the descending motor pathways that lie within the primary motor cortex in the ischemic region. Subsequently, diffusivity reductions in the cerebral peduncle increase in magnitude over the first few days, but might not be visible on DWI or not yet involve the middle part of the peduncle the first day after hypoxia-ischemia.(20,21) However, these findings are important for prognosis of an adverse outcome.(4,5) This supports the different DWI findings in our two newborn infants with PAIS. It is of interest and rather

unexpected that an increase in signal intensity was already present in the mesencephalon on the T2 weighted sequence on the first MRI in the first patient.

In summary, we have shown that early DWI-MRI, performed within 24 following onset of seizures and repeated 48 hours later, clearly showed restricted diffusion within the MCA territory, but showed different patterns of signal intensity changes at the level of the PLIC and cerebral peduncles. When infants present with clinical seizures, an MRI scan is usually performed as soon as possible in order to make a diagnosis.(16) However, MR imaging in suspected PAIS may even be more important to predict neurodevelopmental outcome and its timing should depend on when it is most sensitive to see “pre-Wallerian” degeneration. As our data suggest that for accurate prediction of outcome ‘sooner is not necessarily better’, as early MRI may underestimate the full extent of the injury and one might underestimate or even miss “pre-Wallerian” degeneration, in the PLIC and cerebral peduncle. In case of suspected PAIS, timing of the MRI therefore needs to be well considered to optimize prediction of neurodevelopmental outcome.

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**Figure 1 – MRI of Case 1.**

MRI of a newborn (case 1) with a left sided MCA PAIS who had three MRIs: the first within 24 hours (upper row), the second at 72 hours after onset of symptoms (middle row) and the last at three months of age (bottom row). At 72 hours there was an increase in signal intensity in the right cerebral peduncle (A versus E) and PLIC (B versus F) on axial T2 weighted imaging compared to the first scan. On early axial DW imaging mild lateral signal changes can be observed in the cerebral peduncle (C), while a profound hyperintense signal was seen at 72 hours after onset of seizures (G). Signal changes in the PLIC on DW imaging were very clear after 72 hours (H), but not on the first MRI (D). Repeat MRI (bottom row) at the age of three months showed cysts in the left hemisphere, especially in the region of the anterior branch of the MCA (I-J). On Inversion Recovery T1 weighted imaging (axial view) Wallerian degeneration of the left descending CST, involving the cerebral peduncle (K) and PLIC (L) is noted.

**Figure 2 – MRI of Case 2.**

MRI of a newborn (case 2) with a rare combination of PAIS and CSVT who had three MRIs: the first at 24 hours (upper row) and the second at 72 hours after onset of symptoms (middle row) and the third at three months of age (bottom row). Compared to the first scan there was an increase in signal intensity in the right cerebral peduncle (A versus G) and PLIC (B versus H) on axial T2 weighted imaging at the second scan. On early axial DW imaging very little signal intensity changes were observed in the cerebral peduncle (C), while a hyperintense signal was seen at 72 hours after onset of seizures (I). Signal changes in the PLIC on DW imaging were clear after 72 hours (J), but not on the first MRI (D). MRV (sagittal view) showed initially no flow in the anterior part of the superior sagittal sinus (E), and recurrence of flow in the sinus on the second MRV after treatment with low molecular weight heparin (K). On MR angiography (axial view) there was persistent hypoperfusion of the right MCA until 72 hours after onset of seizures (F and L). At the age of three months a large cyst had developed in the right hemisphere (M-N). Additionally, there was Wallerian degeneration seen in the descending right CST involving both the cerebral peduncle (O) and the PLIC (P). On MRV flow in the superior sagittal sinus had restored completely (Q).

