Perinatal Stroke subtypes

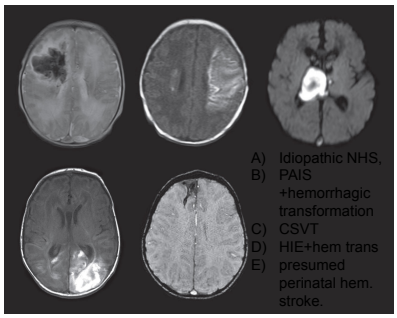
- **Haemorrhagic stroke**
- **Sinovenous Thrombosis CSVT 30%**
- **Arterial Ischemic Stroke PAIS 70%**

Clinical Characteristics, Risk Factors, and Outcomes Associated With Neonatal Hemorrhagic Stroke A Population-Based Case-Control Study.

Cole L et al; JAMA Pediatrics 2017

1 in 9500 live births

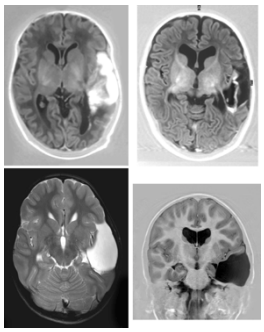
overall 1/6000



A) Idiopathic NHS,
B) PAIS +hemorrhagic transformation
C) CSVT
D) HIE+hem trans
E) presumed perinatal hem. stroke.

Intracranial hemorrhage in full-term newborns: a hospital-based cohort study.

Brouwer AJ et al; Neuroradiology 2010; 52(6):567-76



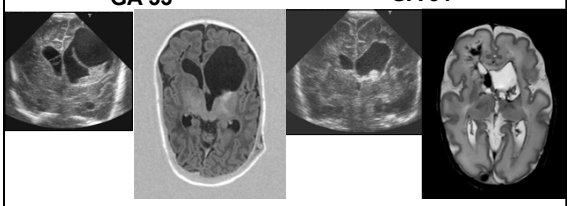
ICH with parenchymal involvement (n=53)
* mortality of 24.5% and CP in 8.6%.
* 30/ 34 survivors without CP (88.2%) had normal DQ on the Griffiths at 15 months.
* Developed ADHD

COL4A1 Mutation in Two Preterm Siblings with Antenatal Onset of Parenchymal Hemorrhage

Ann Neurol 2009;65:12–18

Linda S. de Vries, MD, PhD,[1] Corine Koopman, MD, PhD,[1] Floris Groenendaal, MD, PhD,[1] Mary Van Schooneveld, MD, PhD,[2] Frans W. Verheijen, PhD,[3] Elly Verbeek, BSc,[3] Theo D. Witkamp, MD,[4] H. Bart van der Worp, MD, PhD,[2] and Grazia M. S. Mancini, MD, PhD[3]

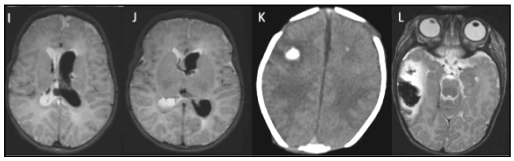
GA 33 **GA 31**



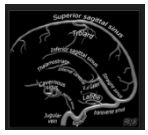
Haemorrhagic stroke in term and late preterm neonates.

CJ Bruno et al; Arch Dis Child Fetal Neonatal Ed. 2014

? ?

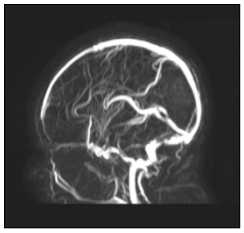


1) Neurologic deficits or death occurred in more than 50%.
2) Haemorrhagic transformation of infarction was the leading mechanism of HS.



Introduction CSVT

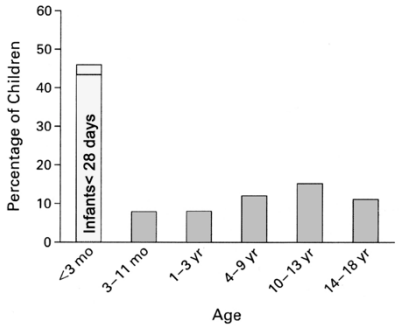
- veins
- Incidence in neonates estimated at 1-12 /100.000[1,2]
- Boys more at risk[3]
- Non specific presentation
- Mortality 2-19%[2]
- Adverse outcome up to 50%
- More routine use of MRI and newer techniques has led to increased recognition



1 2 3

Age distribution among 160 children with SVT

deVeber G; *N Eng J Med* 2001

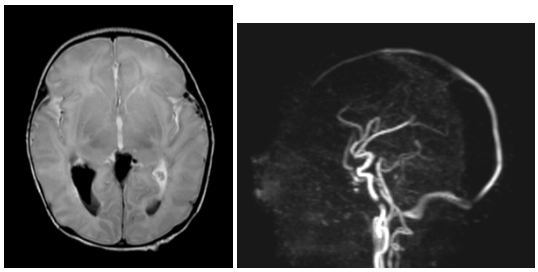


Case

- midline; lack of flow in straight sinus;
- Decided not to start ACT

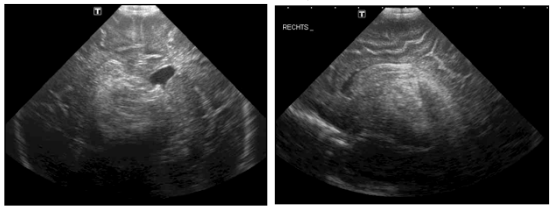
Guidelines say: repeat MRI 5 days later and start Rx when there is propagation of the thrombus

1st MRI

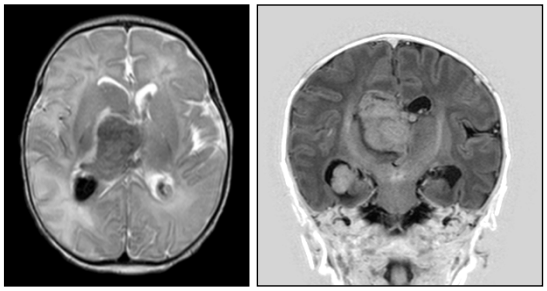


What happened after 1st MRI?

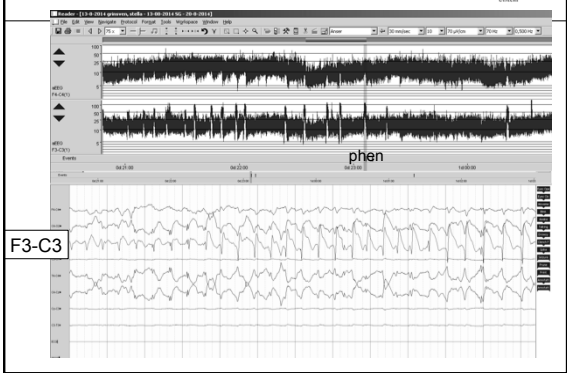
- LMWH; cUS did not show a thalamic haemorrhage
- Seizures: phenobarb; mida and levetiracetam
- Day 6: large thalamic haemorrhage;
- antiXa 0.27 (aim 0.5-1) next day



2nd MRI
what would you tell the parents re outcome?



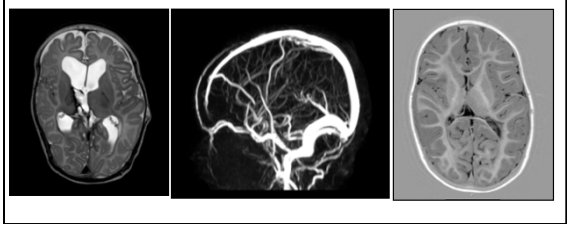
aEEG



Developed progressive ventricular dilatation.
Initially treated with punctures from a reservoir
No stabilisation. VP shunt

DQ 97 at 2 years

T2 and MRV at 3 months; T1 at 2 yrs



Clinical presentation

University Medical Center Utrecht

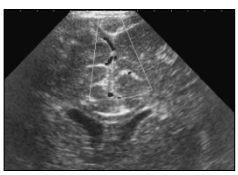
Neonatal Cerebral Sinovenous Thrombosis From Symptom to Outcome.

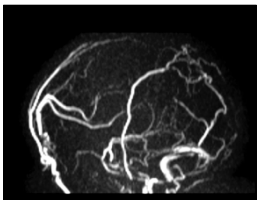
Berfelo F, Kersbergen KJ et al, Stroke 2010; 41:1382-88

Clinical symptoms (n=52)	No (%)	
Generalised seizures	18 (34.6%)	
Focal seizures	11 (21.2%)	**73.1**
Apneas	9 (17.3%)	
Asymptomatic (chance finding)	7 (13.4%)	
Agitated	3 (5.8%)	
Sepis like	2 (3.8%)	
Depressed consciousness	1 (2%)	
No data	1 (2%)	

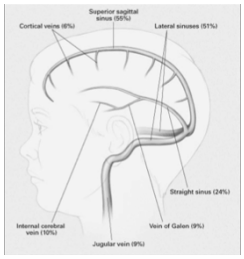
Diagnosis SVT

- Colour Doppler flow US, especially power Doppler
- CT and CTV with and without the use of contrast (empty delta sign)
- MRI with MRV (MR venography)

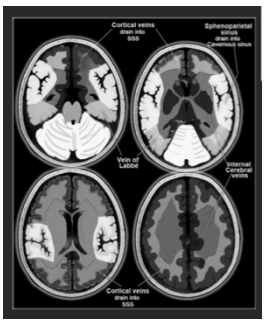




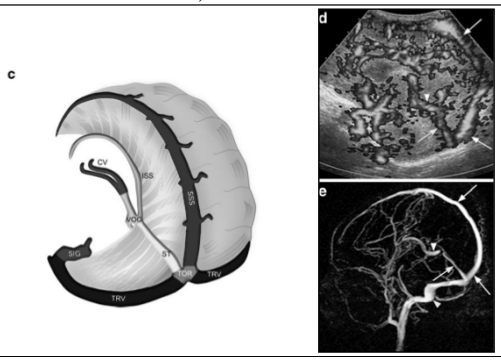
Most important sinuses and veins

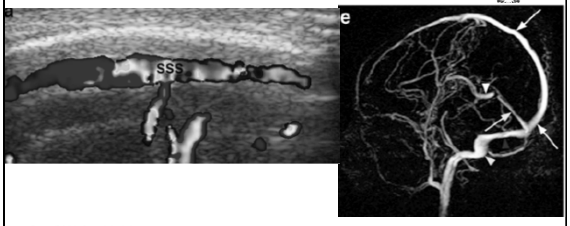


deVeber G;
NEJM 2001



Color Doppler US of normal cerebral venous sinuses in neonates: a comparison with MR venography.
Miller E et al 2012; Pediatr Radiol 42:1070–1079



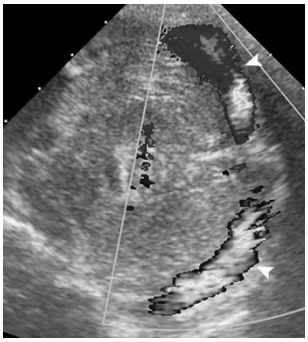


Pediatr Radiol (2012) 42:1070–1079
DOI 10.1007/s00247-012-2393-3

ORIGINAL ARTICLE

Color Doppler US of normal cerebral venous sinuses in neonates: a comparison with MR venography

Elka Miller · Alan Daneman · Andrea S. Doria · Susan Blaser · Jeffrey Traubici · Jose Jarrin · Rahim Moineddin · Aideen Moore · Manohar Shroff



Mastoid views of the transverse sinuses

Edelman M et al
Comparison of US and MRI
Pediatr Radiol (2010)
40:1640–1650

Radiographic findings:location in 42 infants

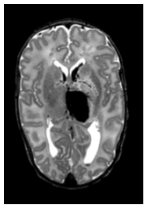
Fitzgerald, K. C. et al. Arch Neurol 2006;63:405-409.

Sinus	No. (%)*
Superior sagittal	28 (67)
Transverse (lateral)	23 (55)
Straight	14 (33)
Torcula	8 (19)
Jugular	7 (17)
Sigmoid	6 (14)
Vein of Galen	5 (12)

* Some infants were included in more than 1 category

IVH in term neonates caused by SVT,
Wu Y et al: Ann Neurol 2003;54:123

- - 9 (31%) had SVT
- 26 had CT or MRI
  - 4/5 with thalamic haemorrhage
  5/21 without thalamic haemorrhage had SVT (p=0.03)
- In case of unilateral thalamic haemorrhage, or IVH in a ***term*** infant, always consider SVT



Kersbergen KJ et al; Arch Dis Child 2011
Comparing preterm and full-term infants

Sinus	Preterm (n=6)	Term (n=18)
Superior sagittal sinus	3	8
Straight sinus	4 (67%)	13 (72%)
Transverse sinus	0	5
Sigmoid sinus	0	0
Deep venous system	0	4
Several sinuses affected	3	12
Pansinovenous thrombosis	2	2

Type of associated parenchymal injury depends on gestational age

Kersbergen KJ et al, Arch Dis Child 2011

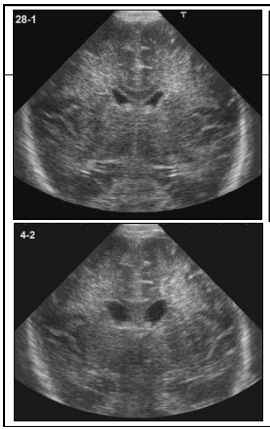
CSVT n=26

Preterm infant n=6

Full-term infant n=18

Severe WMI n=5
Thalamic haem n=2
IVH n=4

Thalamic haem n=10
IVH n=15
PWML n=14



GA 30 wks; 2 kg

UAC 3 days

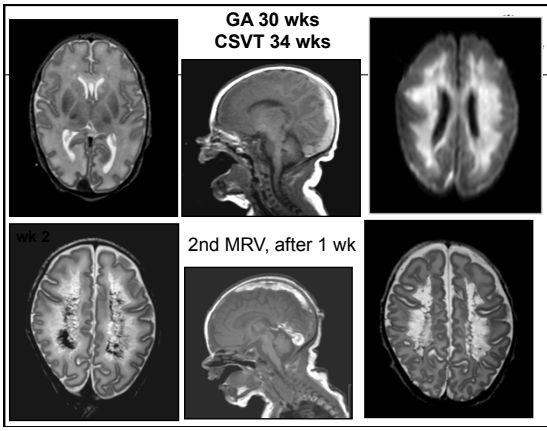
Readmitted at 34 wks, sodium 102 mmol/l

Renal artery thrombosis and

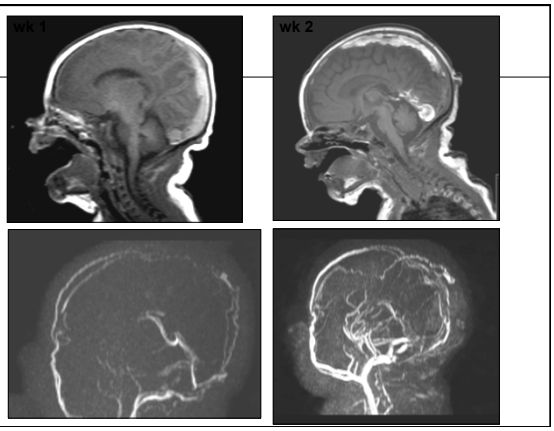
Cerebro-Sinovenous thrombosis

van Tellingen V et al; Int J Nephrol. 2011;2011:406515

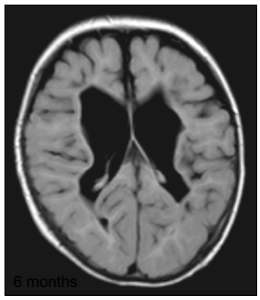
GA 30 wks
CSVT 34 wks



2nd MRV, after 1 wk



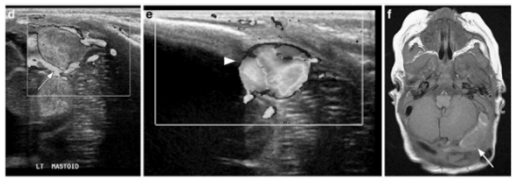
Outcome



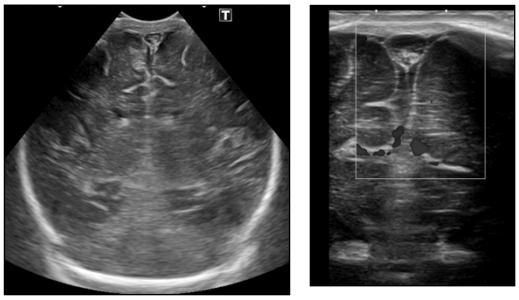
Outcome:
- Hypsarrhythmia
- Cerebral palsy
- Severe mental retardation

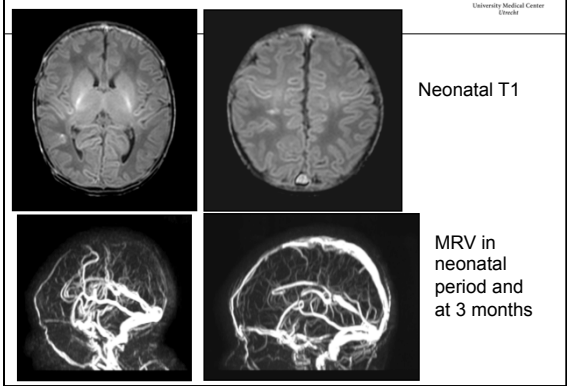
Color Doppler US of normal cerebral venous sinuses in neonates: a comparison with MR venography.

Miller E; Pediatr Radiology 2012; 42:1070–1079



Routine US following mild HIE in a full-term infant



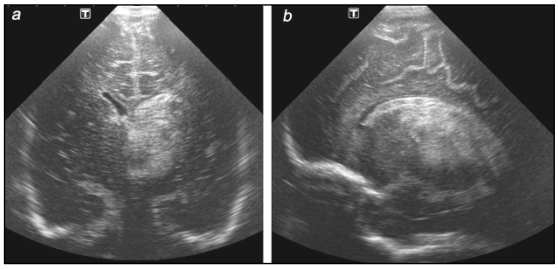


Neonatal T1

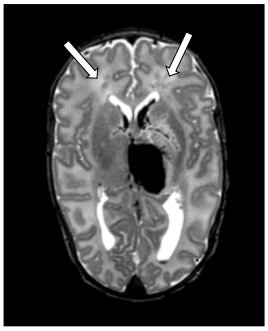
MRV in neonatal period and at 3 months

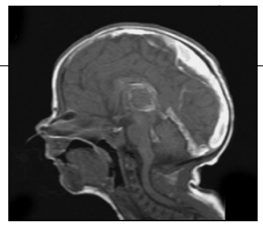
Typical ultrasound example with a thalamic haemorrhage in a full-term infant

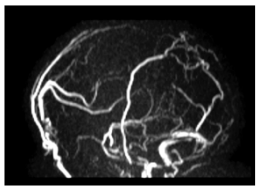
Day 18 very irritable and opisthotonic posture.



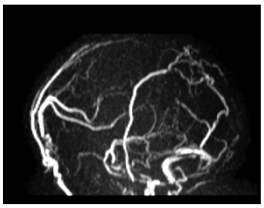
Typical example in a full-term infant

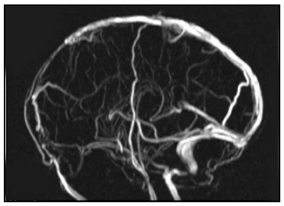




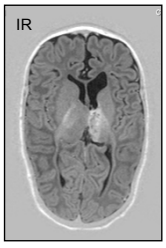


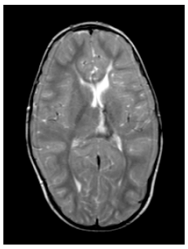
MRV at diagnosis and at 3 months following 3 months of LMWH treament



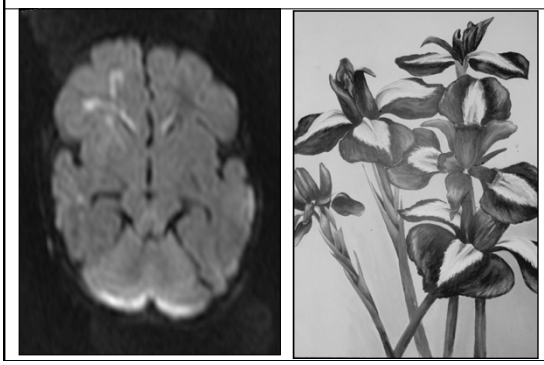


MRI at 3 months and at 24 months 1st clinical seizure at 4 years of age; development of ESES at 4 years



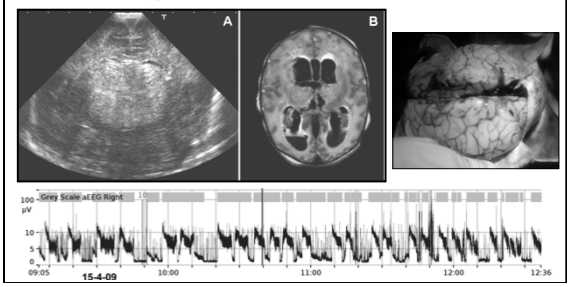


The "Iris sign"/venous tree



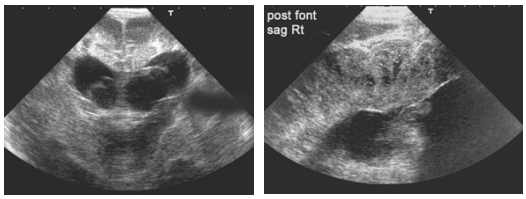
Extreme end of the spectrum: 1. preterm

G 35 wks; 2000 g; initially well;
tachycardia and suspected sepsis at 1 wk;
Homozygous MTHFR (C677T)

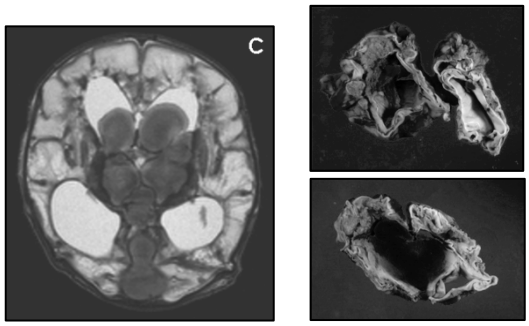


Extreme end of the spectrum: 2. term

GA 37 wks, delivered at home, loose nuchal cord with very long (>1m) umbilical cord with few coils
Apgarscores van 7/8/9; BW 2950 gram (P50), OFC 38 cm (>P98).
Referred because of full fontanelle and seizures



Extreme end of the spectrum: 2. term



Different patterns of associated lesions can be recognised in newborn infants with CSVT, depending on gestational age.

Preterm infant:	Full-term infants
Extensive white matter lesions cPVL-Mimick	IVH associated with thalamic haemorrhage and PWML

Neonatal Cerebral Sinovenous Thrombosis From Symptom to Outcome.

Berfelo F, Kersbergen KJ et al, Stroke 2010; 41:1382-88

Outcome 42 survivors	n (%)
Died	10 (19%)
Survived	42 (81%)
Normal	19/42 (45%)
Moderately abnormal	12/42 (29%)
Severely abnormal	8/42 (19%)
No follow/up data	3/42 (7%)
Follow up < 9 months	13/42 (36.1%)

Neonatal thalamic hemorrhage is strongly associated with electrical status epilepticus in slow wave sleep

Kersbergen KJ et al, Epilepsia 2013, 54(4):733-40

n=15
CSVT +
thalamic haemorrhage

↓

14 survived
One with bilateral thalamic haemorrhage

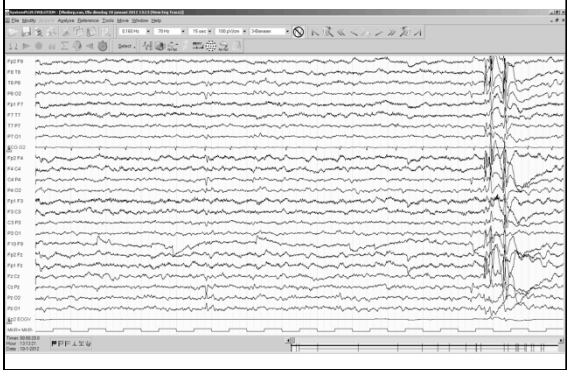
↓

all had EEG during sleep

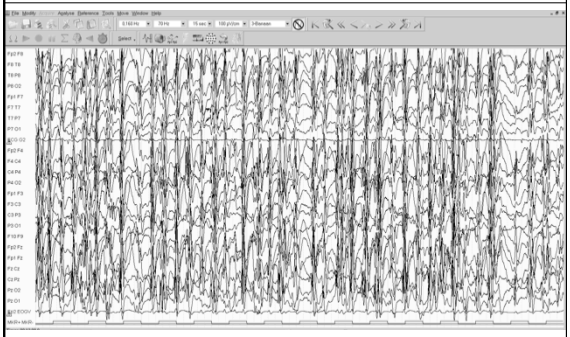
Aim:
To assess the prevalence of interictal epileptiform activity and calculate a sleep-induced spike and waves index (SWI).

ESES was defined as SWI exceeding 85%, ESES spectrum as a SWI 50% - 85%

Awake



Asleep (non-REM)



Results (with additional patients)

n=18
3-10 years

13 abnormal EEG

5 normal sleep deprivation EEG

2 focal epilepsy

9 ESES
2 > 50% Epilepsy in sleep

ESES (spectrum) seen so far in 61 % and epilepsy including ESES in 72%

Conclusions

- Children with a thalamic haemorrhage associated with straight sinus thrombosis are at high risk of developing ESES and/or other types of epilepsy.
- Electrographical findings were already present at a young age, in some cases even ***before*** cognitive deficits had occurred.
- Early recognition and subsequent treatment may prevent cognitive deterioration.
- Routine (once a year) sleep deprivation EEG recordings are therefore recommended in children with a neonatal thalamic haemorrhage often associated with CSVT from 2-3 yrs onwards

Conclusions CSVT

-
- seizures, especially in the context of
  - dehydration
  - post cardiac surgery
  - meningitis
  - IVH on US
- MRI-MRV should be performed whenever possible and therapy (LMWH) considered
- RCT for treatment to be carried out in the near future

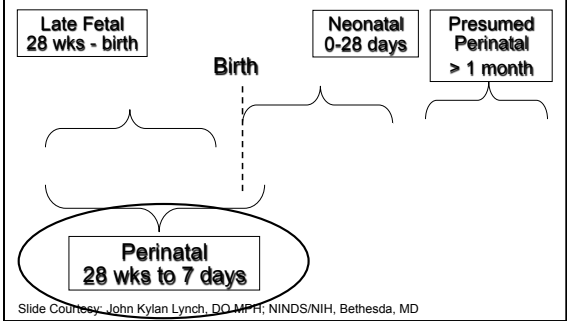
Perinatal arterial ischemic stroke

Linda de Vries, Nienke Wagenaar, Niek van der Aa, Floris Groenendaal, Manon Benders, Frank van Bel, Cobi Heinen, Cora Nijboer

University Medical Center Utrecht

NICHD

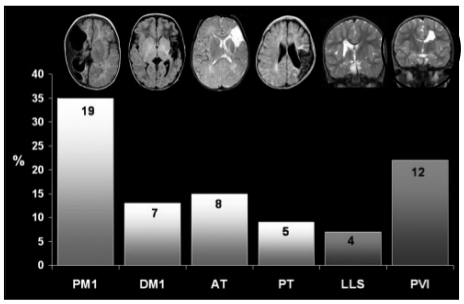
Perinatal Arterial Ischemic Stroke Definitions



Slide Courtesy: John Kylan Lynch, DO MPH; NINDS/NIH, Bethesda, MD

"Presumed" perinatal ischemic stroke (PPIS): vascular classification predicts outcomes.

Kirton A et al; Ann Neurol. 2008;63:436-443.



Predictive Value of Clinical and EEG Features in the Diagnosis of Stroke and HIE in Neonates With Seizures ;

Rafay MF et al; Stroke 2009

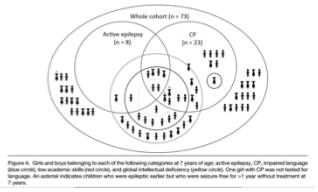
Table 1. Comparison of Clinical Characteristics of Neonates With Stroke and HIE

	n (Percentage)				
Clinical Characteristics	Stroke (n=27)	HIE (n=35)	OR (95% CI)	χ^2 Test	*P* Value
Neurological abnormalities*					<0.0001
Normal	15 (56)	0 (0)			
Diffuse	9 (33)	35 (100)			
Asymmetric†	3 (11)	0 (0)			
Sz. onset ≥12 hours after birth	22 (81)	5 (14)	26.4 (6.8, 102.5)	28.00	<0.0001
Duration of Sz (minutes±SD)	6.3±5.0	13.3±11.7	0.91 (0.84,0.99)	5.09	0.02
Focal motor Sz	13 (48)	4 (11)	7.2 (2.0, 26.0)	10.32	0.001
Response to single AED*	27 (100)	29 (83)	12.1 (0.7, 225.4)	…	0.03

n indicates number of patients; SD, standard deviation; AED, antiepileptic drug; Sz, seizure; OR, odds ratio; CI, confidence interval.
*Fisher exact test reported. All *P* values and OR represent univariate analysis, †*P* value 0.08, OR: 0.1 (0.0, 2.0).

What we tend to say about PAIS

- Incidence: 1 in 2300 live births
- Mortality: 3.5/1000 every year
- Risk of hemiplegia: about 30%

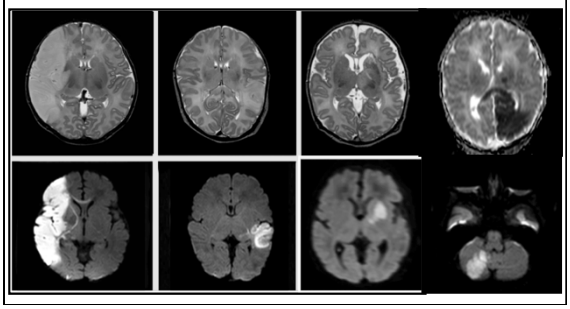


Chabrier S et al, J Pediatr 2016

Typical T2 and DWI images in PAIS

Harteman J et al, Arch Dis Child Fetal Neon Ed 2012

Main MCA | Post MCA | Lent striate | PCA/PICA

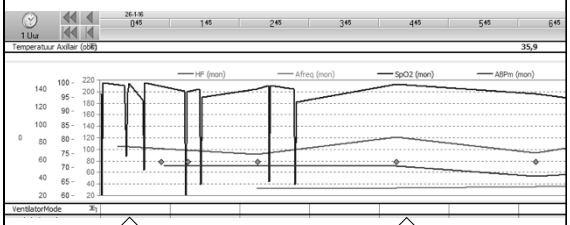


Actual management of PAIS

-
  - continuous EEG monitoring
    (at least 2 channel aEEG)
  - treatment of neonatal seizures
    often hemiconvulsions
    sometimes only apneas

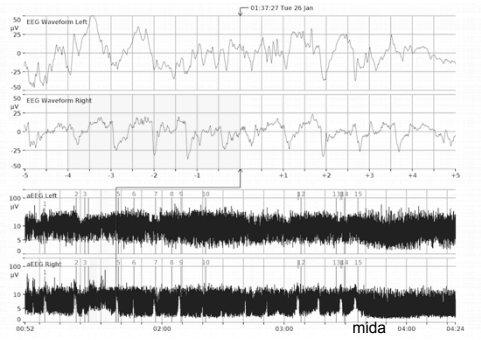
- Diagnosis
  - suspected with cranial ultrasound when:
    large and second half of the first week
  - confirmed with MRI, and especially with early DWI

Infant (GA 42 wks/ BW 3190) Admitted with apneas at 26 hrs

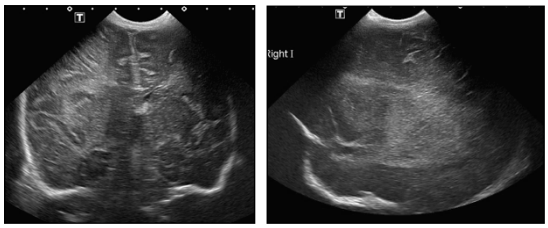


Phenob midazolam

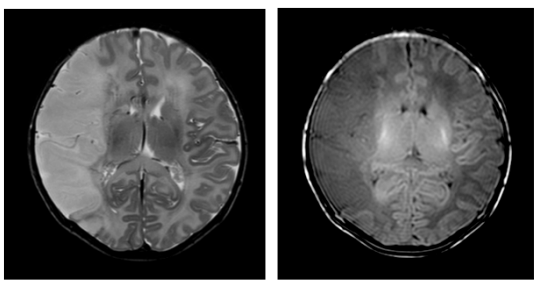
Ictal discharges – right hemisphere

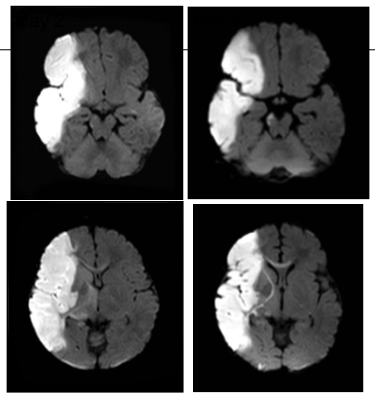


Cranial ultrasound on admission



Conventional T2 and T1 sequence day 2

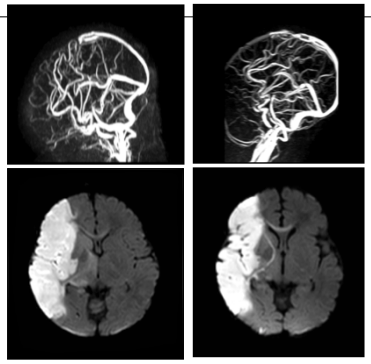




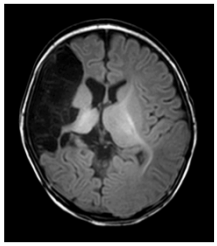
MRI day 2
and day 4

DWI abn
may take
time to
develop !

Delay in EPO administration in view of CSVT

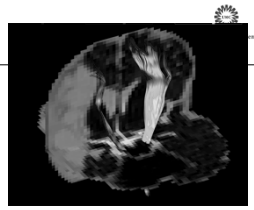


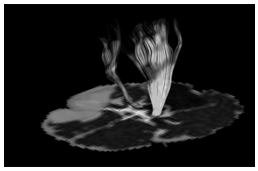
MRI at 3 months and clinical at 6 months

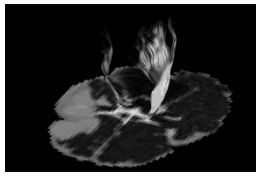


Tractography at 3 months

Tractography not possible on 1st MRI due to edema

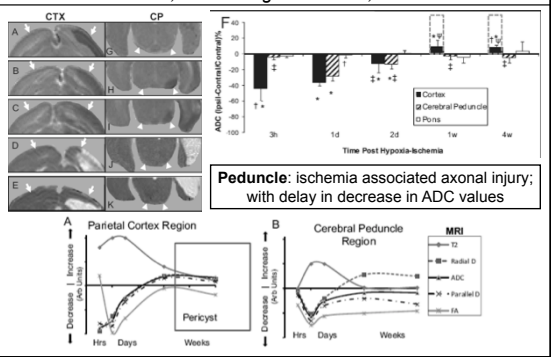






Cellular correlates of longitudinal DTI of axonal degeneration following HI cerebral infarction in neonatal rats.

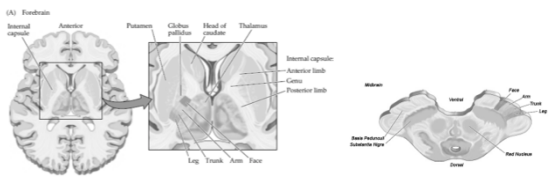
Tuor et al, Neuroimage Clin 2014; 6:32–42



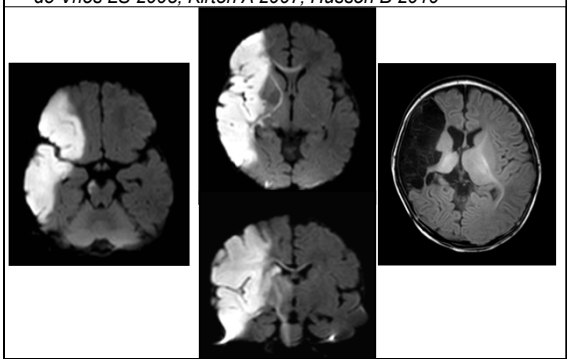
Peduncle: ischemia associated axonal injury; with delay in decrease in ADC values

Early DWI allows early prediction of motor outcome "Pre-Wallerian degeneration"

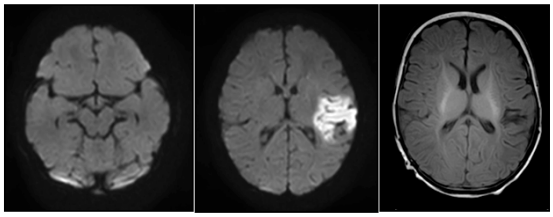
- Involvement of descending corticospinal tracts
  - level of the posterior limb of the internal capsule (PLIC)
  - level of the cerebral peduncles



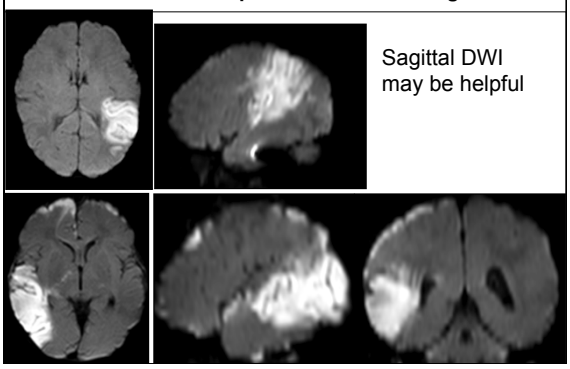
Neonatal DWI, and T1 at 3 months from 'pre-Wallerian' to Wallerian degeneration*de de Vries LS 2005; Kirton A 2007, Husson B 2010*



No involvement PLIC,
no involvement of peduncle
no hemiplegia



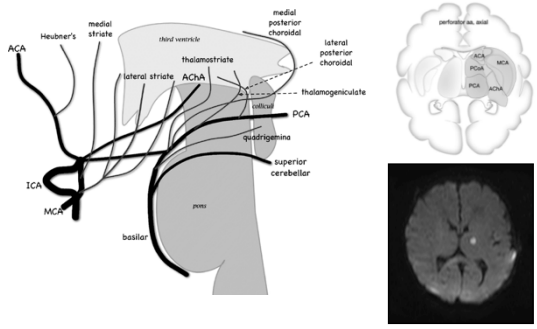
Top: posterior MCA branch stroke
Below: associated with pneumococcal meningitis



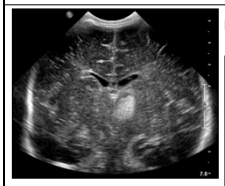
Sagittal DWI
may be helpful

Risk factors, clinical presentation, and neuroimaging findings of neonatal perforator stroke

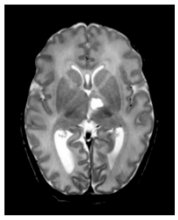
Abels L et al,Ped Radiol 2006; *Ecury-Goossen Get al,Stroke 2013*

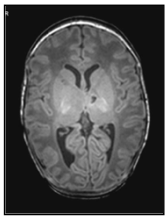


GA 34 wks; 2 normal cUS scans; lesion first seen day 12, PLIC not involved (PCoA)



US day 12





cUS day 12, T2SE day 14 T1 TEA

It is not only about motor outcome!

University Medical Center
Utrecht

Multimodal Outcome at 7 Years of Age after Neonatal Arterial Ischemic Stroke

Chabrier S et al, J Pediatr 2016

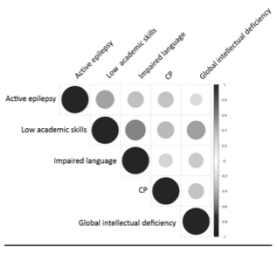
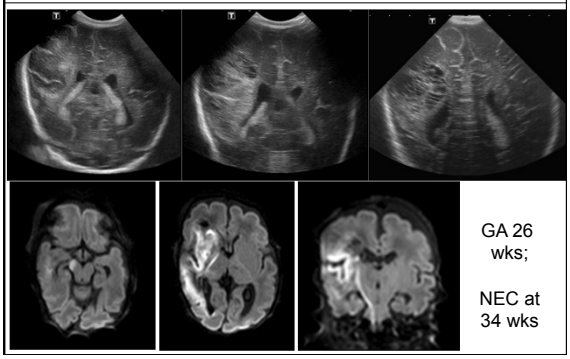


Figure 6. Heat map obtained with PCA of the 5 variables. The color of the circles indicates the direction (*blue*, positive) of the correlation, and the diameter of the circles indicates its strength.

Impaired language	49%
Cerebral Palsy	32%
Low academic skills	28%
Active epilepsy	11%
Global intellectual deficiency	8%

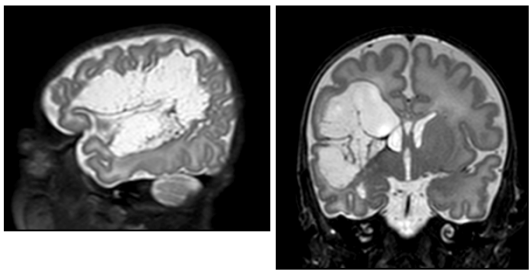
Cortical Sparing in Preterm Ischemic Arterial Stroke
van der Aa NE et al, Stroke 2016



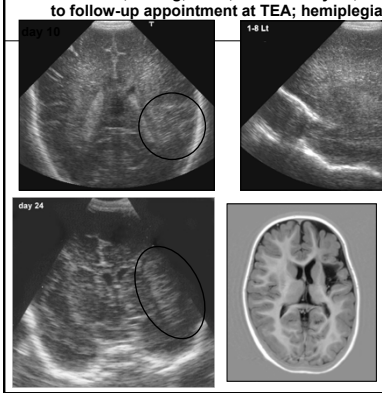
GA 26 wks;

NEC at 34 wks

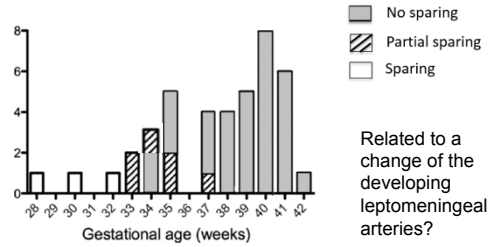
Cortical Sparing in Preterm Ischemic Arterial Stroke
van der Aa NE et al, Stroke 2016



GA 30 5/7 wk; 1435 g; IRDS; PVE US day 10; did not come to follow-up appointment at TEA; hemiplegia at 18m



Cortical Sparing in Preterm Ischemic Arterial Stroke
van der Aa NE et al, Stroke 2016



Related to a change of the developing leptomeningeal arteries?

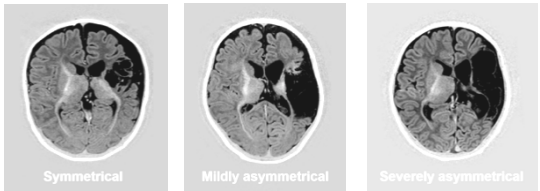
Cortical Sparing in Preterm Ischemic Arterial Stroke
van der Aa NE et al, Stroke 2016

Table. Clinical Characteristics and Neurodevelopmental Outcome

	Complete Sparing (n=3)	Partial Sparing (n=5)	No Sparing (n=32)	Significance
Gestational age, wk	$30^{5/7}$ [28–32]	$33^{4/7}$ [$33^{3/7}$–$37^{1/7}$]	$39^{5/7}$ [34–42]	<0.001
Sex (m/f)	1/2	2/3	20/12	n.s.
Side (l/r)	2/1	4/1	17/15	n.s.
Neonatal seizures	0 (0)	2 (40)	31 (97)	<0.001
Follow-up >18 months	3 (100)	4 (80)	29 (90)	
Griffiths' DQ	99 [66–114]	85 [52–98]	90 [55–112]	n.s.
USCP	3 (100)	3 (75)	25 (86)	n.s.
Epilepsy	2 (66)	1 (25)	9 (31)	n.s.

Data are depicted as median and [range] or as (percentage). Neurodevelopmental outcome, reported from the age of 18 months onwards, was available in 36 children. DQ indicates developmental quotients; l/r, left/right; m/f, male/female; and USCP, unilateral spastic cerebral palsy.

Prediction of visual field defects in newborn infants with perinatal arterial ischemic stroke using early MRI and DTI-based tractography of the optic radiation. *Koenraads Y et al; EJPN 2016*



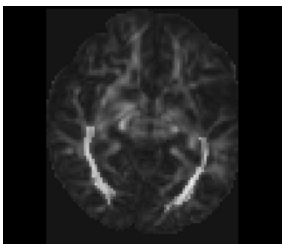
6
all normal peripheral VF

4
2 normal peripheral VF
1 quadrantanopia
1 inconclusive

9
1 normal peripheral VF
1 quadrantanopia
6 hemianopia
1 inconclusive

DTI: visualizing the radiatio optica

Koenraads Y et al, DMCN 2016



	OR asymmetry index				
n=17	myelination (MRI)	FA	λ_1	λ_{23}	MD
ROC curve *AUC	**0.92**	**0.96**	**0.78**	**0.93**	**0.90**

Early prediction of hemiplegia in PAIS allows selection of infants for neuroprotection and intervention

1) CIMT
2) Erythropoietin
3) Mesenchymal stem cells

Cerebral Palsy ALLIANCE RESEARCH FOUNDATION

University Medical Center Utrecht

Nienke Wagenaar

Improvements in bimanual hand function after baby-CIMT in two-year old children with unilateral cerebral palsy: A retrospective study. *Nordstrand L et al; Research Dev Dis 2015*

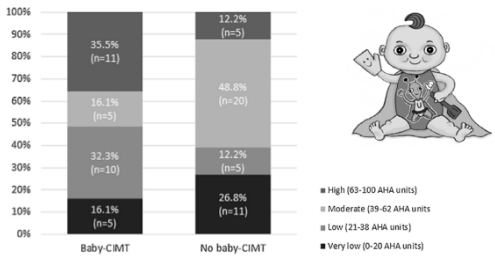


Fig. 1. Proportional distribution over the four AHA levels for children with and without baby-CIMT,

Erythropoietin- general

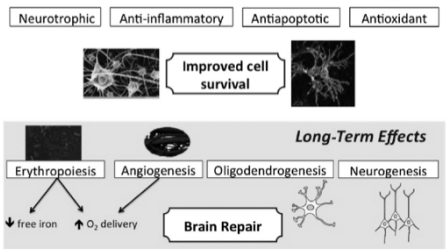
- erythropoiesis
- EPO is postnatally primarily produced in the kidney,
- EPO is also produced in developing brain, where it functions as both an important growth factor and neuroprotective agent for the central nervous system.
- EPO is produced in the brain by multiple cells types, including astrocytes, oligodendrocytes, neurons, and microglia.
- EPO production is stimulated by hypoxia

EPO-neuroprotective effect

- - (neonatal) hypoxia-ischemia-induced free radical formation,
  - inappropriate pro-inflammatory and apoptotic activity (Chong et al 2003).
- EPO stimulates
  - **neuroregeneration** via a trophic effect.
  - Experimental studies in neonatal stroke have shown a substantial **immunohistological reduction of infarct volume** (Sola et al 2005)
  - **neuronal differentiation** from neural progenitor cells (Shingo et al 2001, Wang et al 2004).

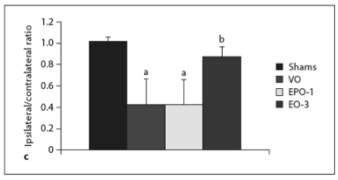
Erythropoietin and Neonatal Neuroprotection

Clinics Perinatology 2015; Juul SE, Pet GC.

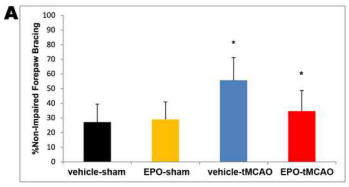


Erythropoietin Sustains Cognitive Function and Brain Volume after Neonatal Stroke.
Gonzalez FF et al; Dev Neurosci 2009;31:403–411

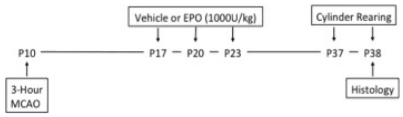
- A single dose of exogenous EPO immediately following transient MCAO did not preserve tissue volume in the long term
- 3 doses of EPO did improve histology, with increased regional and total hemispheric brain volumes as well as functional outcome (water maze test)



Delayed Erythropoietin Therapy Improves Behavioral and Histological Outcomes after Transient Neonatal Stroke.
Larpthaveesarp A et al, Neurobiol Dis 2016

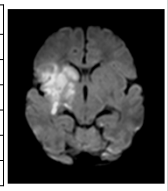


EPO given one week after tMCAO (at P17, P20, and P23).
- At four weeks after tMCAO, non-impaired forepaw use was similar to sham animals
- Volume loss was significantly reduced.



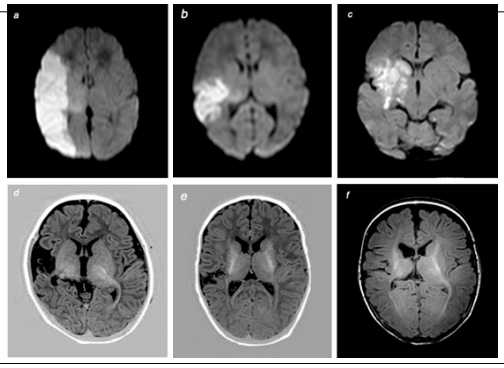
Rh-EPO for reduction of PAIS: A feasibility and safety study.
Benders M et al, J Ped 2014

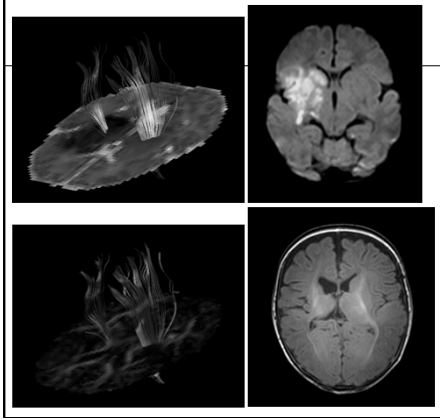
	N=20
Gestational age (wks)	39 ± 5
Birthweight (g)	3357 ± 483
Age (d) start Rh-EPO	4.4 ± 1.5
Stroke Left/Right (n)	14/6
Seizures Yes/No (n)	19/1
Gender M/F (n)	11/9



3 doses of Rh-EPO of 1000 IU/kg iv

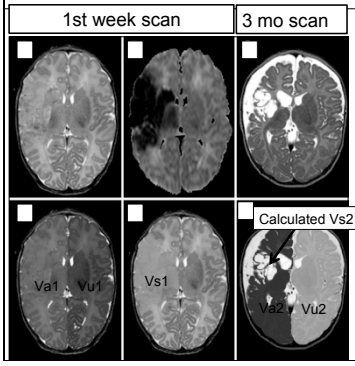
Neonatal DWI and 3mo T1 following EPO





AHA at 18mo
56, 52U
Walked 14mo

Reduction tissue loss after EPO?



Conventional MRI:
1. Infarct volume scan 1
2. Infarct volume scan 2
3. Compare these two scans
4. Assess brain growth
5. Relative tissue loss after 3 months = R

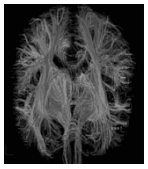
$$R = \frac{(V_{A2}+V_{S2})}{V_{S1}/V_{A1}}^{exp} * 100\%$$

R
3 months

Benders M et al, J Pediatr 2014

RCT - EPO

- Multicentre International study
- Eligible infants
  - Newborns ≥ 36 weeks gestation,
  - MRI confirmed diagnosis of acute PAIS
  - < 96 hours following presentation
  - 40 in each arm



- Primary outcome based on:
  - MRI neonatal period and at 6 wks (-3 months)
  - change in lesion size and brain growth that will be estimated using advanced volumetric MRI techniques
  - DTI based analysis

Early prediction of hemiplegia in PAIS allows selection of infants for neuroprotection and intervention

2) Mesenchymal stem cells

ZonMw

University Medical Center Utrecht

NICHD

Nienke Wagenaar

Annemieke Kavelaars, Cobi Heijnen and Cora Nijboer

University Medical Center Utrecht

Project- stages

Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8

Phase A1
Pre-clinical studies

Phase A2
Production CCMO

- Nasal administration route & migration
- Dose response
- Multiple dosing
- Therapeutic window
- Cognitive & motor improvements
- Long-term effect (14 mnth)
- Long-term safety (14 mnth)
- Working-mechanism

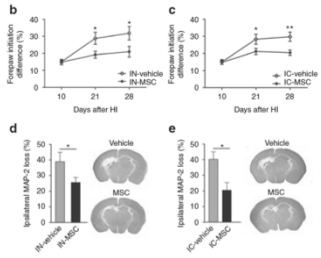
Phase B
Clinical trial

UMC Utrecht

Intranasal versus intracranial MSC
C.T. van Velthoven, Pediatr Res 2010;68:419–22

University Medical Center Utrecht

Intranasal Intracranial



Effect of intranasal and intracranial MSC treatment at 10 d post HI.

Brain sections 18 d after intranasal administration of MSCs

Intranasally administered MSC promote a regenerative niche for repair of neonatal ischemic brain injury.
Donega V et al, Exp Neurol 2014

NICHD

- Intranasally administered MSCs are present in the lesion site < 2hrs
- They remain within the lesion for a short period of time only
- MSCs induce a cascade of events leading to tissue repair

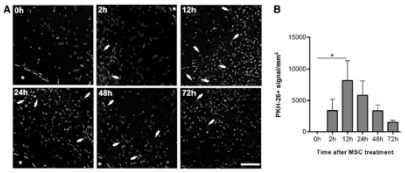
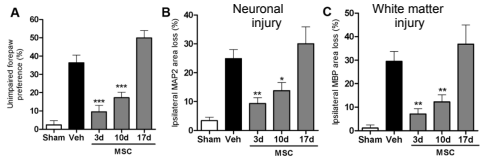


Fig. 2. MSCs reach the lesion site within 2 h after administration. 1 × 10⁵ PKH-26 labeled MSCs were administered intranasally 10 d post-HI. (A) Representative images of PKH-26⁺ cells (see arrows) at the lesion site at 2, 6, 12, 24, 48 and 72 h following MSC administration. (B) Quantification of PKH-26⁺ signal/mm² at 2, 6, 12, 24, 48 and 72 h. Data represent mean ± SEM. *p < 0.05 by ANOVA and Bonferroni post-hoc test (n = 5 per group). Red = PKH-26; blue = DAPI; asterisk = lesion; dashed line = lesion border. Scale bar = 50 μm.

Intranasal Administration of Human MSC for Ischemic Brain Injury in the Mouse: In Vitro and In Vivo Neuroregenerative Functions. *Donega V et al. PlosOne 2013; 8(1):e51253*

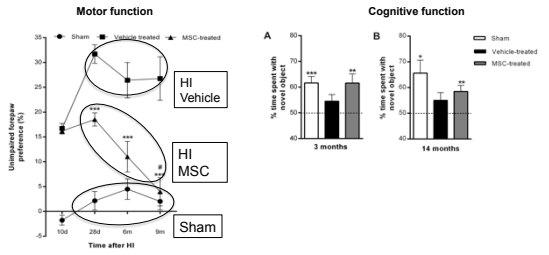
NICHD

- Therapeutic window at least 10d after HI
- MSC treatment started on day 17 after HI is not effective



Assessment of long term safety and efficacy of intranasal MSC treatment for neonatal brain injury in the mouse.

Donega V et al; Ped Res 2015; 78(5):520-6.



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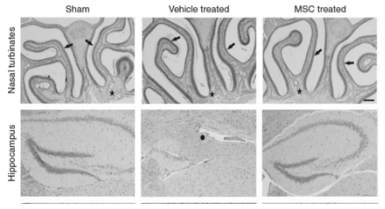

Figure 4.
or brain after intranasal MSC treatment. Hematoxylin–eosin staining of brain and nasal turbinates sections from sham-operated, HI-vehicle, and HI-MSC mice at 14 mo post-HI. No neoplasia or lesions were observed

Conclusions Experimental data UMCU

- hMSCs migrate towards the HI-induced cerebral lesion site
- Administered MSCs do not survive very long in the brain of the recipient, but long enough to stimulate endogenous repair processes.
- Stimulation of repair by MSCs is mediated via growth factors and is dependent on the bidirectional interplay between the administered MSCs and the ischemic environment in the brain.
- Intranasal hMSC treatment improves sensorimotor outcome, lesion volume and cognitive outcome after HI

Future plans

- Single center, open-label, prospective study
- Infants admitted to the NICU- Utrecht
- Inclusion:
  -
  -
  -
  -