

MRI and US in the preterm infant

Linda S de Vries, Margaretha Brouwer,
Karina Kersbergen, Kristin Keunen,
Floris Groenendaal, Manon Benders



Choosing Wisely in Newborn Medicine: Five Opportunities to Increase Value.

T Ho et al. *Pediatrics* 2015; 136(2):e482-9.



TABLE 2 Choosing Wisely Top Five List for Newborn Medicine

1. Avoid routine use of antireflux medications for treatment of symptomatic GERD or for treatment of apnea and desaturation in preterm infants.
2. Avoid routine continuation of antibiotic therapy beyond 48 hours for initially asymptomatic infants without evidence of bacterial infection.
3. Avoid routine use of pneumograms for predischarge assessment of ongoing and/or prolonged apnea of prematurity.
4. Avoid routine daily chest radiographs without an indication for intubated infants.
5. Avoid routine screening term-equivalent or discharge brain MRIs in preterm infants.

GERD, gastroesophageal reflux disease.

There is insufficient evidence that the routine use of TEA or discharge screening brain MRIs in preterm infants improves long-term outcome

ACTA PÆDIATRICA
(NOURISHING THE FUTURE)

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2012 101:1013-5

A DIFFERENT VIEW

Term MRI for small preterm babies: do parents really want to know and why has nobody asked them?

Rebecca Pearce, Jason Baardnes (jason.baardnes@nrc-nrc.gc.ca)
Life Sciences, NRC Human Health Therapeutics Portfolio, National Research Council Canada, Montreal, QC, Canada

Survivor of twin (GA 25 wks)
TEA-MRI: moderate cerebellar damage from an unrecognized bleed

Reply: *Acta Paediatr.*
2012 101:1016-7.
Janvier A, Barrington K.



Incidental findings on routine brain MRI scans in preterm infants

Malova et al; *Arch Dis Child Fetal Neonatal Ed* 2017;102:F73

- IFs were detected in 28 out of 276 VLBW infants (10.1%).
- In total, 21 cases (7.6%) required an intervention, which was only diagnostic in 16 cases, and both diagnostic and therapeutic in 5 cases.

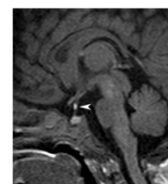
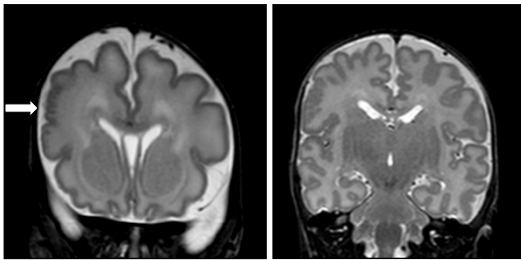


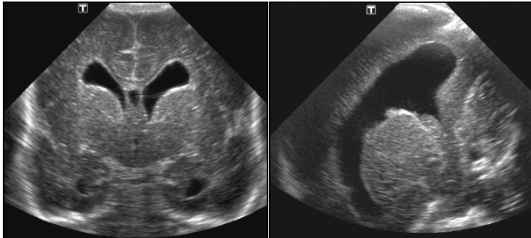
Figure 2 In a female born at 25 weeks, sagittal T1-weighted image shows echogenic (hyperintense) bright spot (arrowhead) along the inferior pole. Endocrine work-up revealed hypoparathyroidism that was treated with thyroid hormone and hypocalcaemia.

GA 27 2/7 wk/BW 1100g
PMG chance finding on routine MRI at 30 and 41 weeks

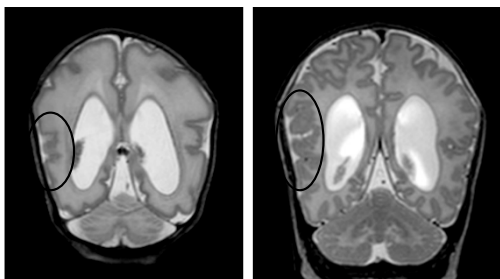


MRI raised concern;
Normal outcome (BSID 100) at 2 yrs

GA 28 3/7 wk, 685 gram; SC because of HELLP
Odd shaped VM from day 1



MRI at 30 wks PMA and at TEA: PMG

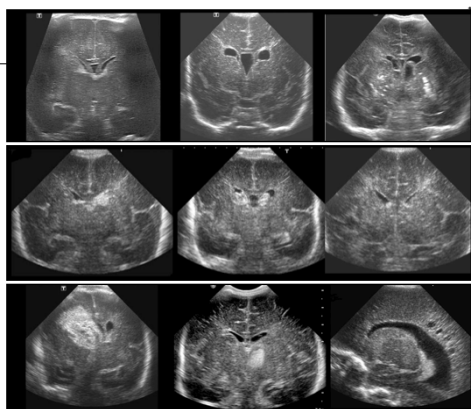


Megalencephaly-Polydactyly-Polymicrogyria-Hydrocephalus (MPPH) syndromes with capillary malformation.

Mirzaa GM et al, Am J Med Gen 2012



MRI helped to make the diagnosis



Sequential cUS identifies lesions which are predictive of cerebral palsy, if:



-
-
- at TEA
- The mastoid window is used as well to identify larger cerebellar haemorrhages (>4mm)
- Those doing the cUS have sufficient expertise

However: cPVL (and thus CP) is becoming less common

Trends in cerebral palsy among infants of VLBW (<1500 g) or born prematurely (<32 weeks) in 16 European centres: a database study. Platt MJ et al; Lancet, 2007; 6;369:43-50.

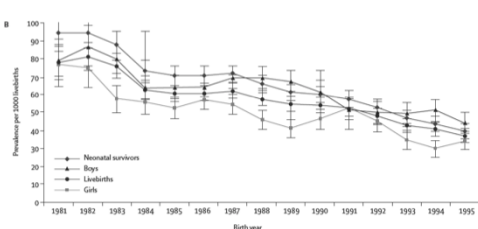
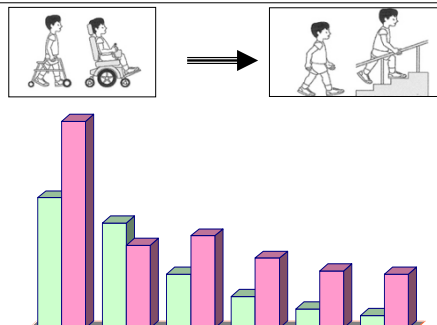
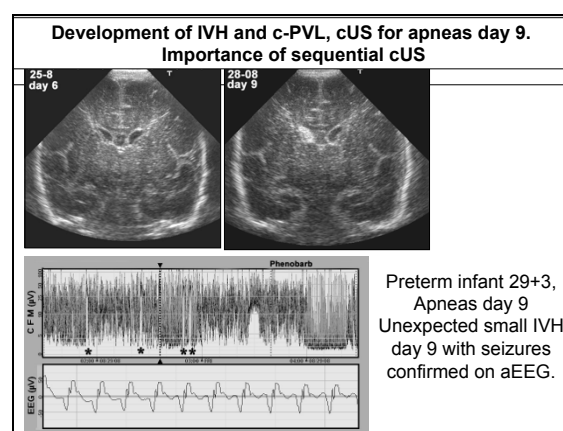
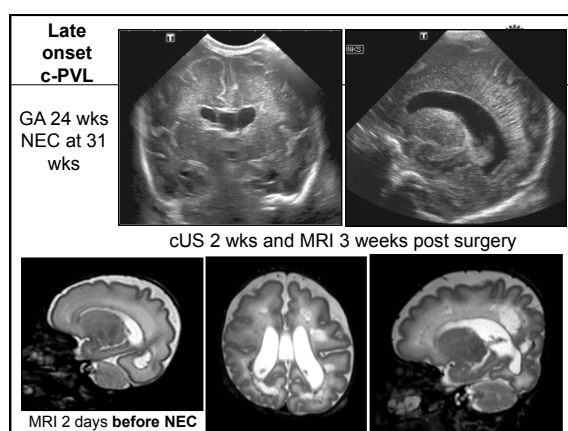
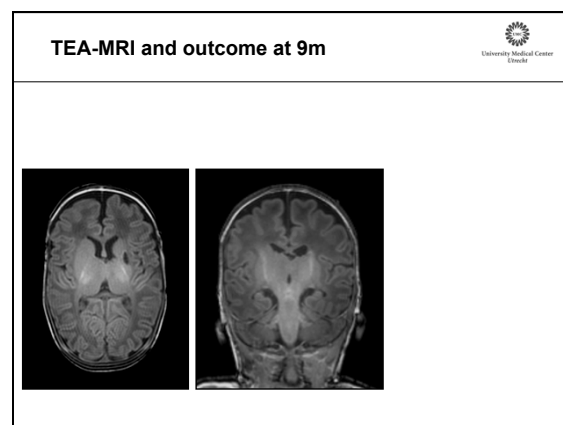
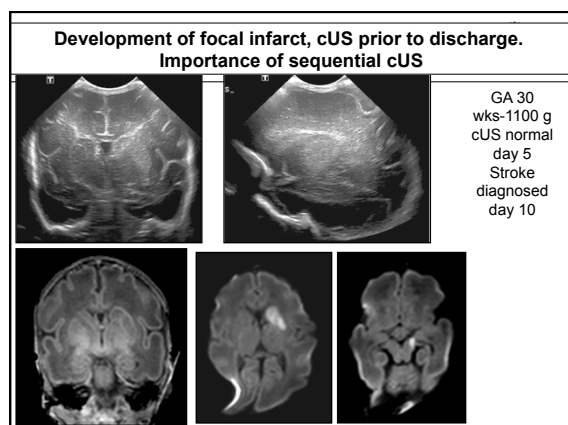
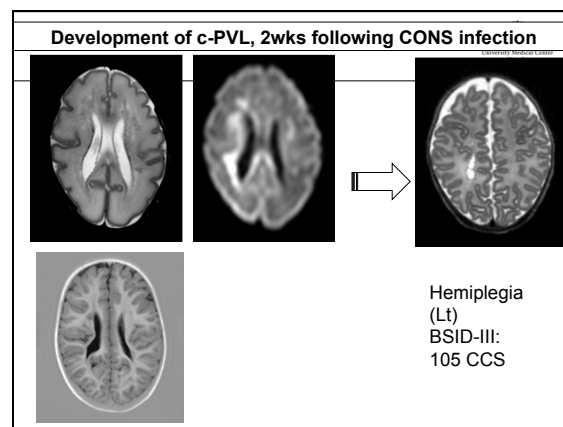
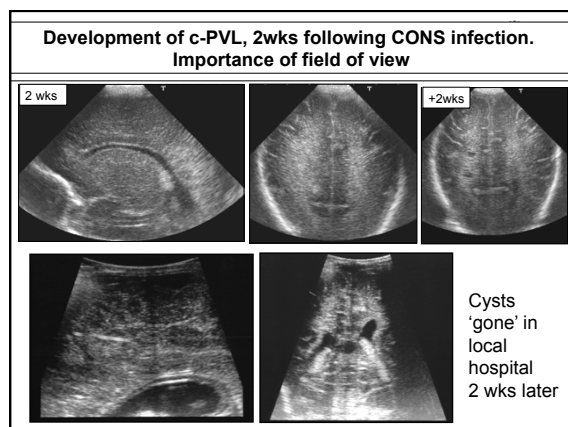


Figure 3: Cerebral palsy rates (3-year moving average) among infants of birthweight <1000 g (A) and 1000-1499 g (B) from nine European centres, 1980-96. Error bars=SE.

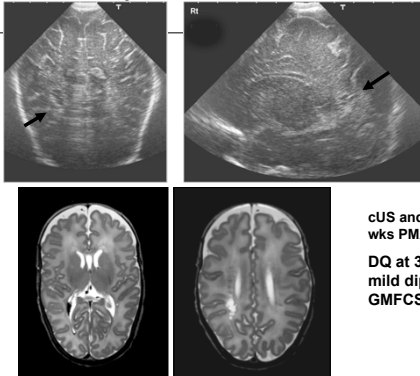
Change in incidence c-PVL and CP GA ≤ 32 wks

Van Haastert et al I-C et al, J Ped 2011





Importance of cUS at TEA



cUS and MRI at 41 wks PMA
DQ at 3 ½ yrs 100, mild diplegia, GMFCS level I

Time of occurrence of major US abnormalities, *Vries LS et al, J Pediatr 2004*

US/day	n	1-7	8-14	15-21	22-28	29-35	36-42	43-49	40 wks
IVH grade III	32	31	1	-	-	-	-	-	-
IVH grade III + cPVL	6	0	1	2	1	2	-	-	-
IVH grade IV	36	35	-	-	-	-	-	-	1
PVL grade I	303	303	-	-	-	-	-	-	-
PVL grade II	17	-	-	3	5	6	1	1	1
PVL grade III	18	1	2	5	3	1	1	1	4
Focal Infarction	12	1	6	3	2	-	-	-	-

19 infants developed "cysts" beyond day 28
12/19 : cysts were detected on their weekly US
6/19 first showed at 40 wks PMA
17/19 developed CP

Screening Cranial Imaging at Multiple Time Points Improves Cystic Periventricular Leukomalacia Detection. *Sarkar et al, Am J Perinatol 2015*

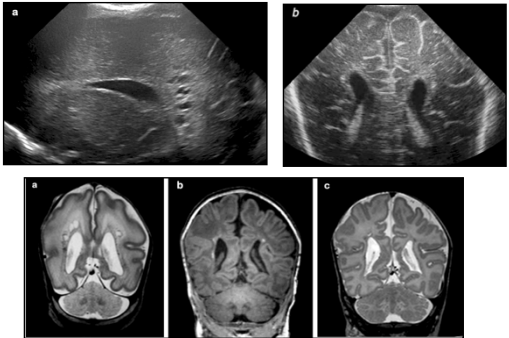
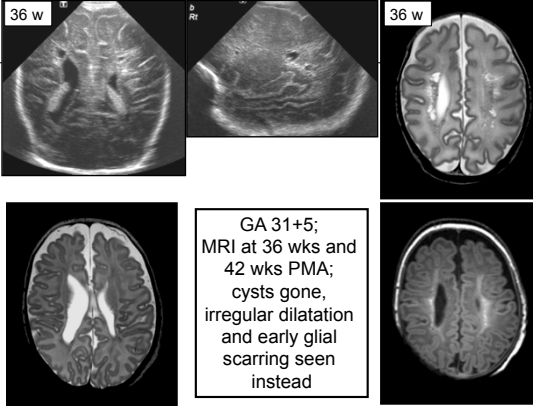
Table 1 Cystic PVL in infants of < 1,000 g birth weight or < 29 wks' gestational age who had neuroimaging at both within 28 d and closest to 36 wks

cPVL—28 d	cPVL—36 wks		Total
	No	Yes	
No	12,075	414	12,489
Yes	95	155	250
Total	12,170	569	12,739

Abbreviations: cPVL, cystic periventricular leukomalacia; PVL, periventricular leukomalacia.

95 (14.3%) of 664 cPVL cases seen on early imaging were no longer visible on repeat screening closest to 36 weeks PMA. Such disappearance of cPVL was more common in infants < 26 weeks' gestation versus infants of 26 to 28 weeks' gestation (18.5 vs. 11.5%; $p = 0.013$).

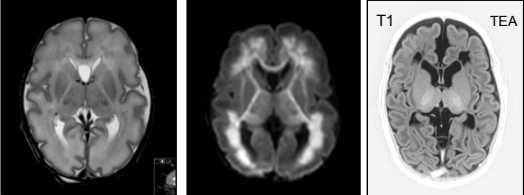
Cysts resolve!! Sequential imaging is very important to get the full picture.

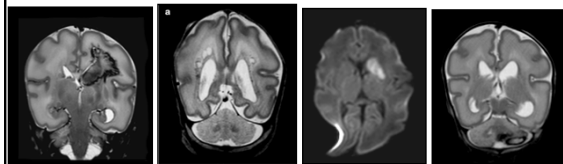
GA 31+5; MRI at 36 wks and 42 wks PMA; cysts gone, irregular dilatation and early glial scarring seen instead

New MRI - White matter score *Martinez-Biarge M et al, PLoS ONE 2016*

	First 2 wks after birth/insult	2-6 wks after birth/insult	TEA
Grade III	Extensive (confluent) DWI abnormalities	Extensive periventricular cysts	Extensive periventricular cysts, and/or at least 2 of the following: Decreased WM volume and mild-moderate VM (>10mm), irregular in shape Extensive increased SI WM lesions on T1 No/abn myelination of the PLIC



Major cUS abnormalities predictive of abnormal (mostly) motor outcome, well visualised with sequential cUS, similar to MRI	
Type of cUS lesion	Likely Outcome
Unilateral PVHI	Unilateral spastic CP
Bilateral c-PVL	Bilateral spastic CP
Unilateral stroke	Unilateral spastic CP
Cerebellar haemorrhage	Rarely ataxia



Cranial ultrasound and MRI at term age in extremely preterms

Horsch S et al, Arch Dis Child Fetal Neonatal Ed 2010;95:F310

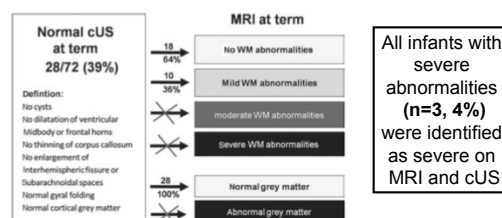
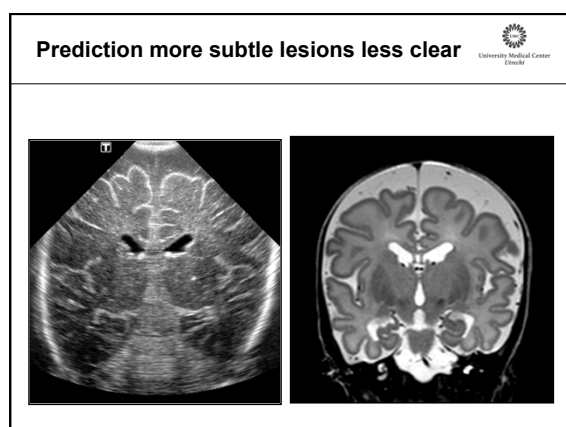
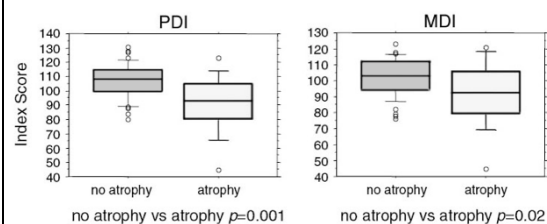


Figure 3 MRI results of infants with normal cranial ultrasound (cUS) at term (n=28). WM, white matter.



Ultrasound diagnosis of brain atrophy is related to neurodevelopmental outcome in preterm infants.

Horsch S. et al; Acta Paediatr 2005; 94:1815



Brain atrophy and results of Bayley scales at 3 years

The relationship between ventricular size at 1 month and outcome at 2 years in infants less than 30 weeks' gestation.

Fox LM et al, Arch Dis Child Neon and Fetal Ed 2014

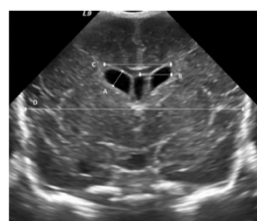
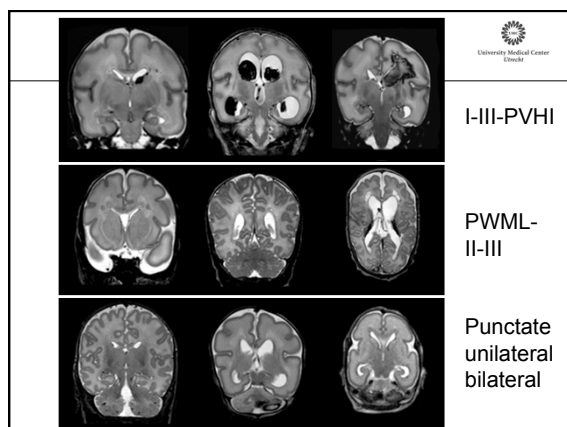


Figure 1 Coronal view, (A) anterior horn width, (B) ventricular index, (C) ventricular transverse width, (D) biparietal diameter.

- in the postnatal course using linear ultrasound biometric measures correlate with 2-year outcome in very preterm infants.
- Larger lateral ventricles in the parietal region at 1 month of age are associated with poorer motor outcome at 2 years.

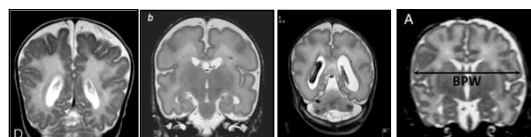
Single TEA-MRI identifies severe as well as subtle lesions

- The right neonatal sequences are used
- Slice thickness is 1-2 mm rather than 5mm
- There is no or minimal movement artefact
- The MRI is performed at TEA, allowing assessment of myelination of the PLIC

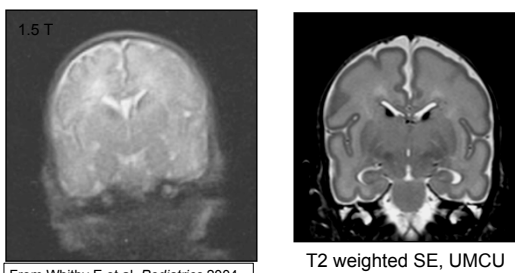


Single MRI at TEA

- conventional T1 and T2 for identification of
 - * White matter abnormalities
 - * Punctate white matter lesions
 - * Cerebellar abnormalities
 - * Performing 2D- measurements



The right neonatal sequences are used and 3T rather than 1.5 Tesla

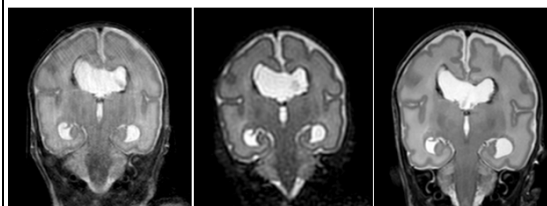


From Whitby E et al, *Pediatrics* 2004

Fig 4. Germinal matrix bleed on the right. T2 fast spin-echo sequence (TR = 20 000 milliseconds, TE = 75 milliseconds, SLT = 5 mm, ETL = 132, and NEX = 1).

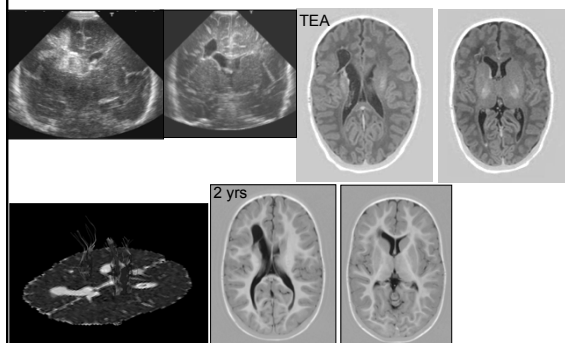
Use of fast sequences for movement artefact (BLADE/PROPELLAR/ T1-FLAIR-BLADE)

A good cUS tells you more than a poor MRI !!

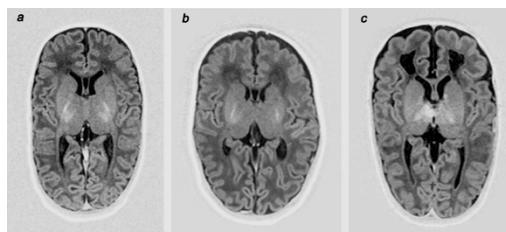


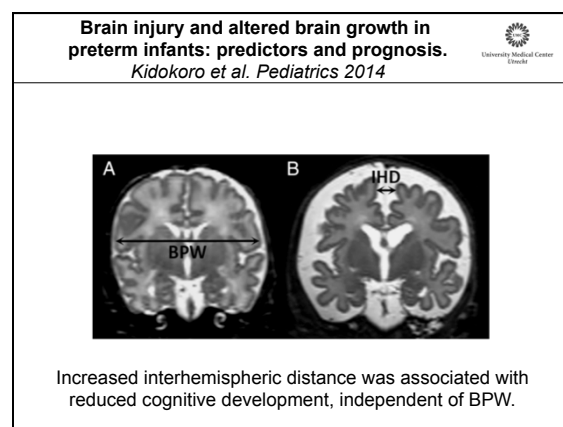
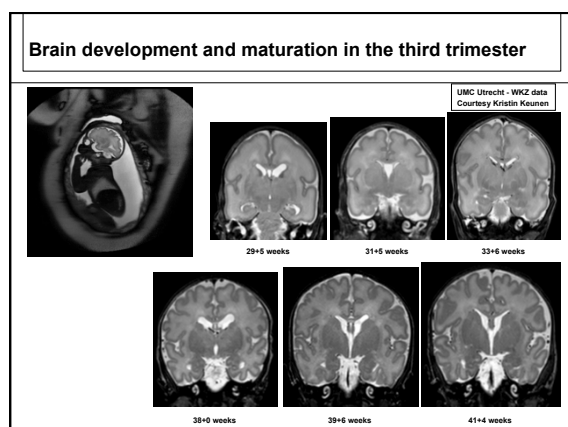
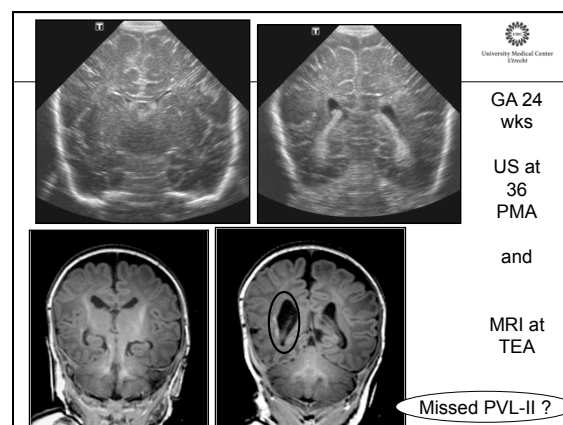
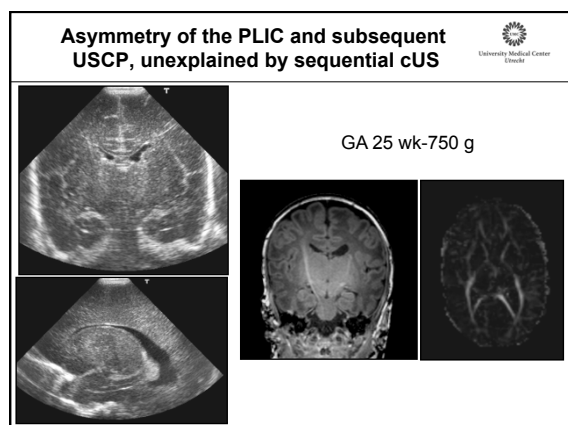
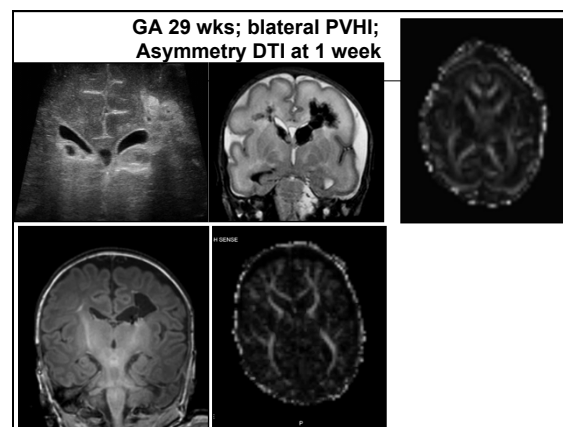
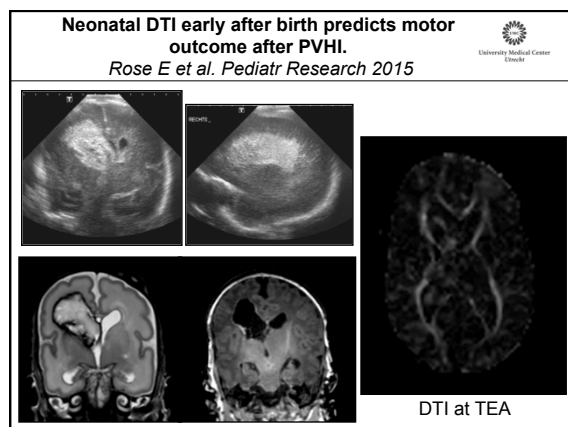
Moved fast sequence high resolution

TEA- MRI will show (asymmetrical) myelination of the posterior limb of the internal capsule (PLIC)



Myelination of the PLIC at TEA predictive of CP, not yet present at 36 wks!





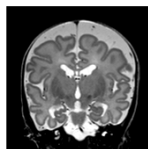
Brain injury and altered brain growth in preterm infants: predictors and prognosis.

Kidokoro et al. *Pediatrics* 2014



TABLE 5 Clinical Risk Factors for Small BPW or IHD Brain Patterns

Characteristics	Increased IHD (n = 106)	
	OR (95% CI)	P
Gestational age <27 weeks	0.94 (0.59–1.5)	.81
SGA	0.65 (0.25–1.7)	.37
Male gender	2.0 (1.3–3.2)	.003
Multiple birth*	0.83 (0.51–1.3)	.44
Antenatal corticosteroids	0.61 (0.32–1.2)	.14
Chorioamnionitis*	1.0 (0.57–1.8)	.97
Cesarean delivery	0.84 (0.51–1.4)	.49
Five-minute Apgar score of <7	0.92 (0.49–1.7)	.78
Inotropic support*	1.3 (0.82–2.1)	.26
Treated PDA	0.91 (0.57–1.5)	.71
Postnatal sepsis*	0.96 (0.59–1.6)	.86
Neonatal enterocolitis	0.57 (0.18–1.8)	.34
Dexamethasone	2.3 (1.1–4.9)	.034
Oxygen at 36 weeks	1.1 (0.69–1.8)	.64
Postnatal nutrition >14 days	1.9 (0.73–2.9)	.46
High-grade injury (grade 3 or 4)	2.1 (1.0–4.4)	.048



Both the BPW z score and IHD were predictors of MDI scores (P = <.001 in BPW, P < .001 in IHD) in the multivariable analyses



TABLE 6 Outcomes in Infants With Small BPW and/or Increased IHD Brain Patterns

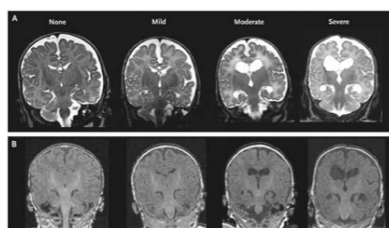
Infants and Brain Patterns	n	Mean (SD) MDI Score	MDI <70, n (%)
Overall infants	232		
Small BPW and increased IHD	15	72.8 (23.0)**	7 (47)*
Small BPW only	54	81.8 (16.2)**	9 (17)
Increased IHD only	54	79.9 (22.6)**	17 (32)*
Remainder	109	91.6 (15.4)	7 (6)
Infants with high-grade injury	19		
Small BPW and increased IHD	1	40	1 (100)
Small BPW only	5	62.6 (19.3)	2 (40)
Increased IHD only	7	56.7 (24.0)	4 (57)
Remainder	6	79.7 (22.8)	2 (33)
Infants without high-grade injury	213		
Small BPW and increased IHD	14	74.1 (22.1)**	6 (43)*
Small BPW only	49	83.7 (14.7)*	6 (12)
Increased IHD only	47	83.4 (20.5)*	12 (26)*
Remainder	103	92.3 (14.7)	5 (5)

n = 232. *P < .05, **P < .01 versus the remainder group in each row by Bonferroni post hoc tests.

Predictive value of specific type of lesions

Moderate-severe WMI

Woodward et al; *NEJM* 2006



WM signal abn.
WM volume loss
WM cysts
Degree of VM
Corpus callosum
thinning.

Neonatal white matter abnormalities an important predictor of neurocognitive outcome for very preterm children.

Woodward LJ, *PlosOne* 2012

Table 4. Unadjusted and Adjusted Odds of Neurocognitive Delay for Very Preterm Children with None, Mild, and Moderate-to-Severe White Matter Abnormalities (WMA) on Neonatal MRI Relative to Children in the Full-Term Group.

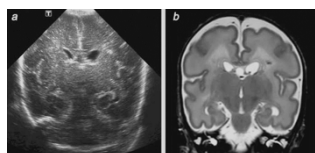
Measure	Age 4 Years		Age 6 years	
	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Any Intellectual Delay				
None WMA	1.3 (0.4–4.2)	1.1 (0.3–3.9)	1.5 (0.5–4.5)	1.1 (0.4–3.4)
Mild WMA	2.8 (1.3–6.3)	2.7 (1.0–7.3)	5.3 (2.6–10.9)	4.0 (1.6–9.8)
Moderate-to-Severe WMA	16.6 (3.8–74.7)	<.0001 15.3 (3.6–66.6)	202 (14.0 (4.3–43.8)	<.0001 8.1 (2.1–31.7)
Any Language Delay				
None WMA	1.2 (0.4–4.1)	1.1 (0.3–3.9)	0.6 (0.1–2.7)	0.5 (0.1–2.2)
Mild WMA	1.9 (0.9–4.2)	1.8 (0.7–4.9)	2.5 (1.2–5.4)	2.4 (0.9–6.1)
Moderate-to-Severe WMA	9.4 (3.2–27.6)	<.0001 7.8 (1.9–31.4)	202 (14.0 (4.3–43.8)	<.0001 4.3 (1.2–17.7)
Any Executive Functioning Delay				
No WMA	0.7 (0.2–2.4)	0.6 (0.2–2.5)	2.0 (0.7–5.9)	1.6 (0.5–5.0)
Mild WMA	2.2 (1.1–4.7)	2.2 (0.9–5.6)	3.6 (1.7–7.8)	2.8 (1.1–7.3)
Moderate-to-Severe WMA	16.6 (3.8–74.7)	<.0001 15.3 (3.6–66.6)	202 (14.0 (4.3–43.8)	<.0001 8.1 (2.1–31.7)

*Adjusted for child sex, neonatal medical risk, and family social risk.
doi:10.1371/journal.pone.0018799.t004

At 4 and 6 years, very preterm children without cerebral white matter abnormalities showed no apparent neurocognitive impairments relative to their full-term peers

Predictive value of specific type of lesions

Punctate white matter lesions (PWML)



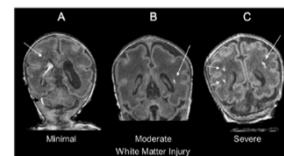
University Medical Center
Utrecht

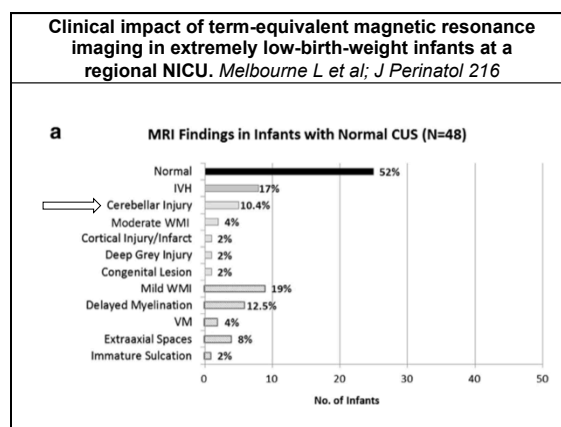
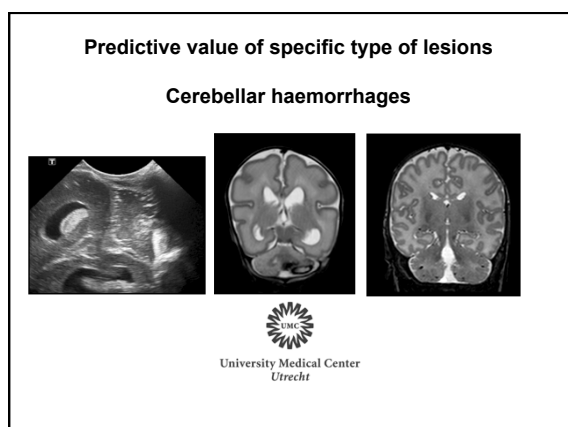
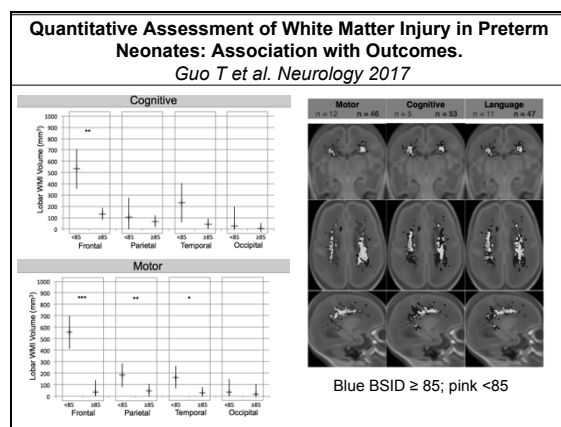
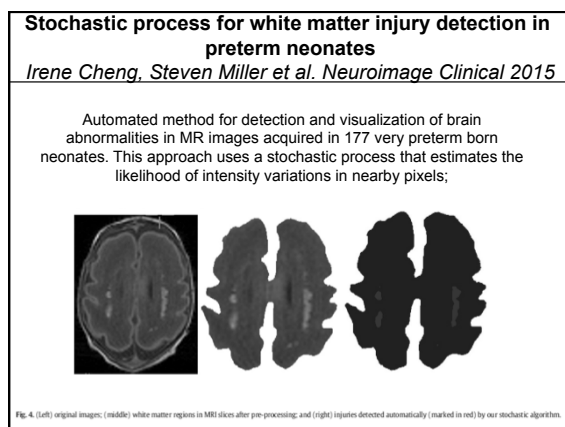
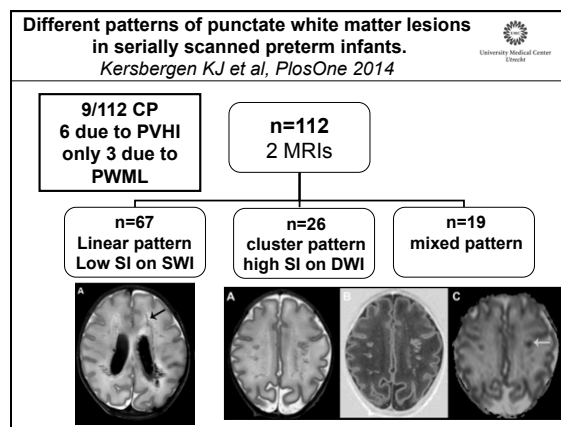
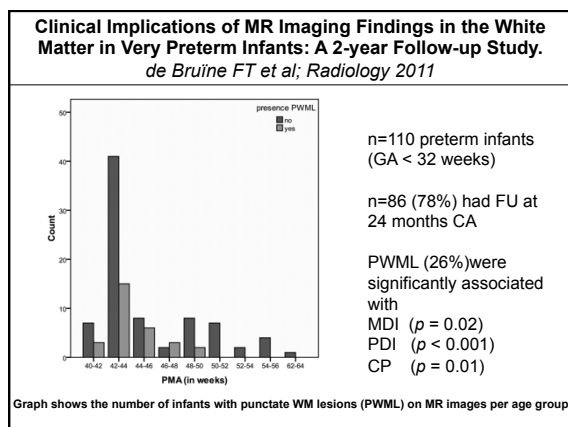
Early Brain Injury in Premature Newborns Detected with MRI is Associated with Adverse Early Neurodevelopmental Outcome. Miller SP et al, *J Pediatr* 2005

Table II. MRI findings at each MRI by neurodevelopmental outcome in survivors

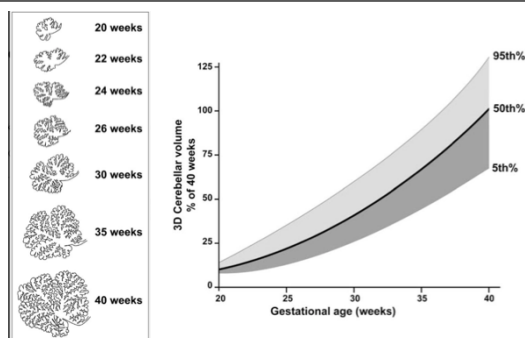
Neurodevelopmental outcome	Normal	Borderline	Abnormal	P
First MRI				
White matter injury				.03
None	26 (37%)	9 (41%)	4 (33%)	
Minimal	9 (20%)	7 (32%)	1 (8%)	
Moderate	11 (24%)	5 (23%)	5 (42%)	
Severe	0	1 (5%)	2 (17%)	
Ventriculomegaly				<.0001
None	48 (64%)	18 (22%)	4 (6%)	
Mild	3 (4%)	2 (9%)	2 (15%)	
Moderate/severe	0	2 (9%)	5 (38%)	
Intraventricular hemorrhage				.006
None	36 (71%)	15 (68%)	5 (38%)	
Grade 1–2	15 (29%)	4 (18%)	5 (38%)	
Grade 3–4	0	3 (14%)	3 (23%)	
Cerebellar hemorrhage	5 (10%)	4 (18%)	0	.3

N=83;
outcome at 12–18 months
Early and TEA-MRI

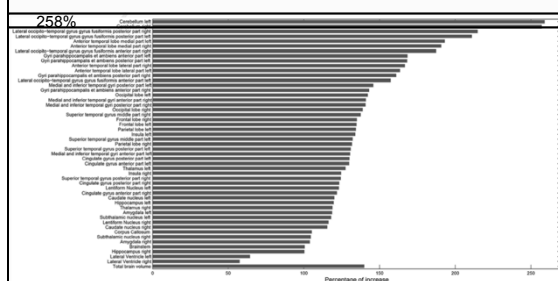




Cerebellum of the Premature Infant: Rapidly Developing, Vulnerable, Clinically Important. Volpe JJ; J Child Neurol 2009



Longitudinal Regional Brain Development and Clinical Risk Factors in Extremely Preterm Infants. Kersbergen KJ et al J Pediatr 2016



Seeking a unified framework for cerebellar function and dysfunction: from circuit to cognition. D'Angelo E, Casali S. Front Neural Circuits 2013; 6:116

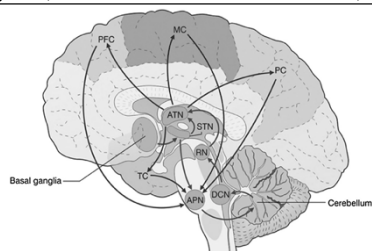
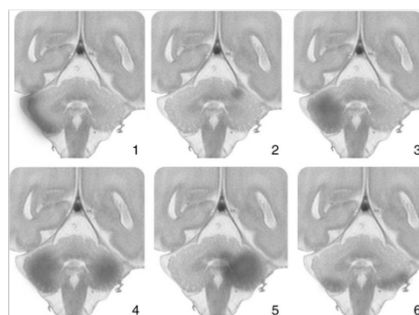
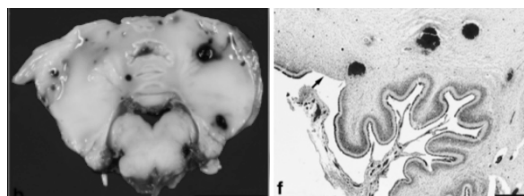


Fig. 2. Schematic of the bidirectional connectivity between the cerebellum and other brain regions including the cerebral cortex. Most cerebro-cerebellar afferent projections pass through the basal (anterior or ventral) pontine nuclei and intermediate cerebellar peduncle, whereas most cerebello-cerebral efferent projections pass through the dentate and ventrolateral thalamic nuclei. DCN, deep cerebellar nuclei; RN, red nucleus; ATN,

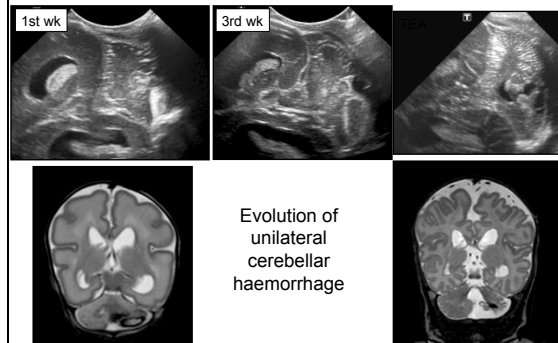
The clinical presentation of preterm cerebellar haemorrhage. Ecury-Goossen GM et al; Eur J Pediatr (2010) 169:1249–1253

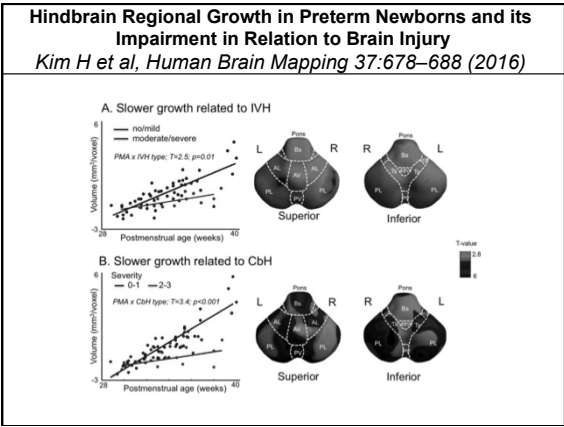
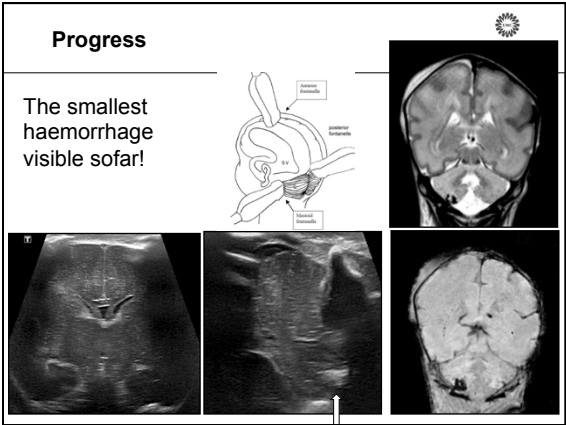
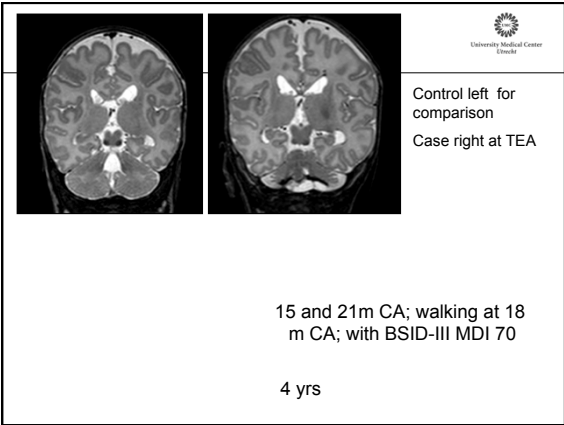
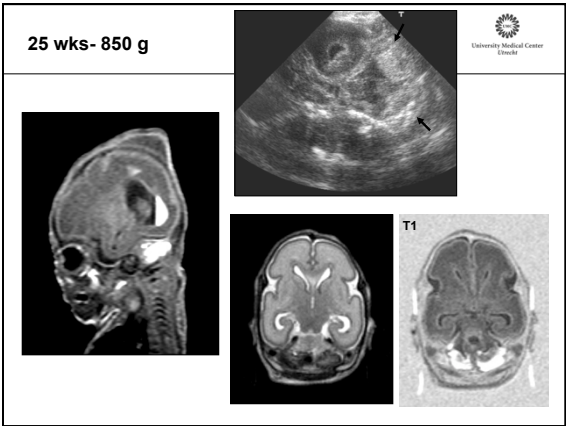
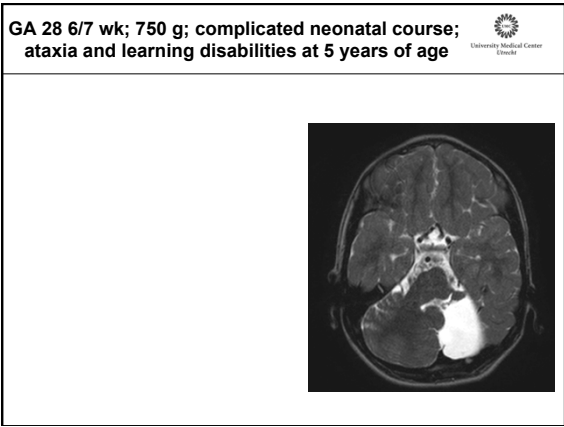


Cerebellar hemorrhagic injury in premature infants occurs during a vulnerable developmental period and is associated with wider neuropathology. Haines KM et al, Acta Neuropathologica Communications 2013



27 weeks-515 g; cUS and simultaneous MRI





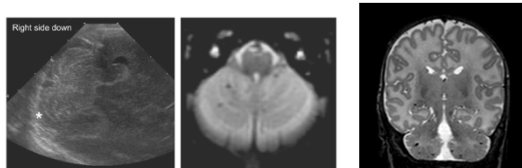
**Does Cerebellar Injury in Premature Infants Contribute to the
High Prevalence of Long-term Cognitive, Learning, and
Behavioral Disability in Survivors?**
Limperopoulos C. et al, Pediatrics 2007

TABLE 2 Comparison of Mean \pm SD Scores of the MSEL, PDMS, and
VABS Between Infants With CHI and Controls

Outcome Measure	Isolated CHI (n = 35)	Preterm Controls (n = 35)	P
MSEL			
Gross motor	29.2 \pm 7.2	37.6 \pm 3.3	<.001
Fine motor	29.9 \pm 10.1	42.1 \pm 6.1	<.001
Visual reception	32.7 \pm 10.2	45.1 \pm 7.3	<.001
Receptive language	33.9 \pm 11.2	42.8 \pm 5.9	<.001
Expressive language	30.3 \pm 9.1	45.0 \pm 7.1	<.001
Early learning composite	69.3 \pm 16.3	90.1 \pm 7.8	<.001
PDMS			
Gross motor	74.1 \pm 7.4	84.7 \pm 6.3	<.001
Fine motor	73.0 \pm 8.6	87.5 \pm 6.4	<.001
VABS			
Communication	76.5 \pm 10.2	91.1 \pm 7.4	<.001
Daily living	72.7 \pm 11.2	86.7 \pm 5.5	<.001
Socialization	75.2 \pm 11.1	89.6 \pm 6.9	<.001
Motor	74.6 \pm 11.4	86.9 \pm 5.3	<.001

Cerebellar Hemorrhage on Magnetic Resonance Imaging in Preterm Newborns Associated with Abnormal Neurologic Outcome. *Tam E et al, J Ped 2011;158:245-50*

- Cerebellar hemorrhage was detected on both cUS and MRI in 3/131 preterm newborns, whereas smaller hemorrhages were seen in 10 newborns (total incidence, 10%).
- No association with the Wechsler -III but five fold increase in abnormalities of neurologic examination



MRI and cUS at term equivalent age; prognostic value Selected papers



MRI and US at term equivalent age; prognostic value



- et al: Neuroimaging and Neurodevelopmental Outcome in Extremely Preterm Infants
- n = 480 infants <28 weeks' gestation surviving to near term in the Neonatal Research Network.
- Outcomes included NDI or death and significant gross motor impairment or death, with NDI defined as cognitive composite score <70, significant gross motor impairment, and severe hearing or visual impairment

Neuroimaging and Neurodevelopmental Outcome in Extremely Preterm Infants. *Hintz S et al; Pediatrics 2015*



n=480; GA <28 wks

TABLE 7 Classification Statistics for ROC Curve Analyses Based on Stepwise Models

Outcome	Model Variables	AUC	95% CI
NDI or death	Perinatal/neonatal	0.743	0.67–0.82
	Perinatal/neonatal + Early CUS	0.773	0.70–0.84
	Perinatal/neonatal + Early + Late CUS	0.800	0.73–0.87
	Perinatal/neonatal + Early CUS + MRI	0.800	0.75–0.87
	Perinatal/neonatal + Early + Late CUS + MRI	0.825	0.76–0.88
Significant gross motor impairment or death	Perinatal/neonatal	0.833	0.75–0.92
	Perinatal/neonatal + Early CUS	0.859	0.79–0.93
	Perinatal/neonatal + Early + Late CUS	0.885	0.82–0.95
	Perinatal/neonatal + Early CUS + MRI	0.892	0.83–0.96
	Perinatal/neonatal + Early + Late CUS + MRI	0.908	0.85–0.97

Conclusions



- Sequential cUS will identify
 - major lesions, often resulting in cerebral palsy –
 - TEA-cUS will show VM and increased eCSF space associated with motor and cognitive outcome
- TEA-MRI allows
 - assessment of myelination of the PLIC
 - will allow 2D measurements (transcerebellar)
 - will allow quantitative MRI measurements (DTI)
 - will find chance findings (PMG)

MRI should be performed in every ELBW infant

Yes: because

- cUS misses migrational disorders
- cUS misses infants who develop mild CP
- cUS unable to assess subtle WMI and small cerebellar lesions
- MRI is a wonderful research tool

No: because

- cUS should detect all lesions that result in CP
- MRI only of additional value when done well using adjusted neonatal sequences in a baby who is not moving
- MRI is expensive
- Worry for the parents (Pierce R, Acta Paediatr 2012)