"Hypoxic-ischemic encephalopathy"

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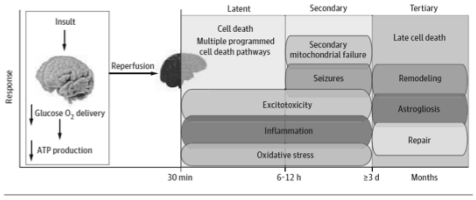
Hypoxic-Ischemic Encephalopathy: A Review for the Clinician

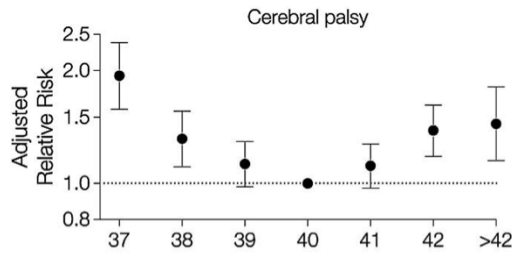
Martha Douglas-Escobar, Michael D.Weiss,
JAMA-Pediatr 2015

Figure 1. Schematic Overview of the Pathophysiological Features of Hypoxic-Ischemic Encephalopathy



Cerebral Palsy Among Term and Postterm Births.

Moster D et al; JAMA. 2010;304(9):976-982



Prenatal Factors in Singletons with Cerebral Palsy Born at or near Term

Nelson and Blair, NEJM 2015

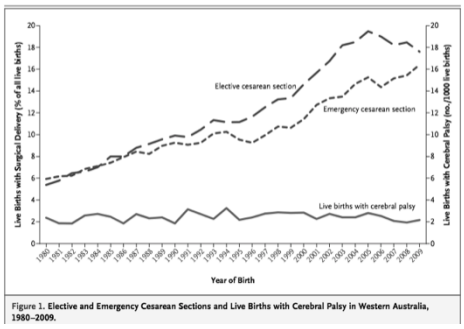


Figure 1. Elective and Emergency Cesarean Sections and Live Births with Cerebral Palsy in Western Australia, 1980–2009.

Sellier E et al; 2015; Prevalence in NBW children showed a non-significant trend from 1.17 to 0.89 per 1000 live births (p=0.22).

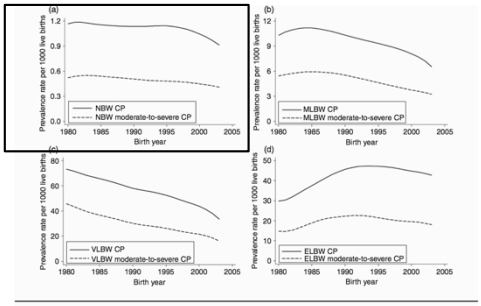


Figure 3. (a) Prevalence rate of cerebral palsy (CP) for children born with a birthweight ≥2500g, per 1000 live births. (b) Prevalence rate of CP for children born with a birthweight between 1500g and 2499g, per 1000 live births. (c) Prevalence rate of CP for children born with a birthweight between 1000g and 1499g, per 1000 live births. (d) Prevalence rate of CP for children born with a birthweight below 1000g, per 1000 live births. NBW, normal birthweight; MLBW, moderately low birthweight; VLBW, very low birthweight. ELBW, extremely low birthweight.

Introduction

- Hypoxic-ischemic encephalopathy (HIE) due to presumed perinatal asphyxia is still of major concern,
- Incidence:
  1-2/1000 for the severely affected infant
- With the introduction of hypothermia, outcome has improved significantly, as reported in infancy and early childhood

Underlying causal pathways

Antenatal	Intrapartum	Postpartum
Associated problem Reduced fetal movements Placental insufficiency	**Sentinel event** Placental abruption Uterus rupture Tight nuchal cord	Postnatal collapse Postnatal infection ECMO +complic
WS injury	**BGT injury**	**BGT-WS-stroke**

Or a combination of two or three

Assessment of HIE

- Neurological assessment
  - Sarnat classification
  - Thompson score
  - UCSF clinical score
- Neurophysiological assessment
  - aEEG/ EEG
  - evoked potentials
- Neuro-imaging
  - cranial ultrasound
  - MRI

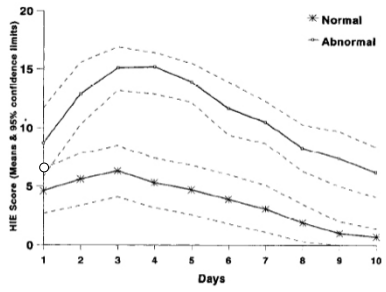
Sarnat score (1976)

	Sarnat and Sarnat (1976)	Levene et al (1985)
Grade I	Hyperalert	Resolves < 24-48 h
Grade II	Lethargic Tube feeding Seizures	Improvement < 7 days
Grade III	Stupor Severe hypotonia Tube feeding Prolonged seizures	Improvement up to 6 wks

The "Thompson score";
Thompson CM; Acta Paediatr. 1997;86(7):757-61.

Sign	Score 0	1	2	3
Tone	Normal	Hypertonia	Hypotonia	Flaccid
LOC	Normal	Hyperalert stare	Lethargic	Comatose
Fits	None	Infreq < 3/day	Frequent > 2/day	Decerebrate
Posture	Normal	Fisting, cycling	Strong distal flexion	IPPV (apnea)
Moro	Normal	Partial	Absent	
Grasp	Normal	Poor	Absent	
Suck	Normal	Poor	Absent ± bites	
Resp	Normal	Hyperventilation	Brief apnea	
Fontanel	Normal	Full, not tense	Tense	

The value of a scoring system for HIE in predicting neurodevelopmental outcome.
Thompson CM, Acta Paediatr. 1997;86:757-61.

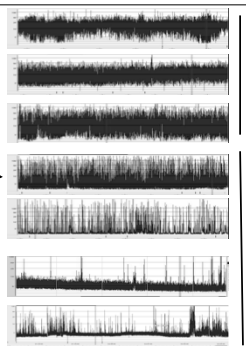


aEEG/CFM	EEG
Immediately available Long registration **No detail** **Pattern recognition**	**On appointment** **Short registration** A lot of detail Interpretation difficult
Seizure detection algorithm available	Video-EEG more widely available

aEEG classification

Hellström-Westas, Rosén, de Vries, Greisen. Neoreviews 2006

- Discontinuous (DC)
- Burst-suppression (BS)
  - *Burst density >100/h (BS+)*
  - *Burst density <100/h (BS-)*
- Low Voltage (LV)
- Flat (FT isoelectric)



Neuroimaging in the Evaluation of Neonatal Encephalopathy

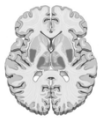
Barnette, et al, Pediatrics 2014;133;e1508

TABLE 2 Neuroimaging Results

	Ultrasound	CT	MRI
Number of infants	2006/4111 (48.8)	933/4107 (22.7)	2690/4109 (65.5)
Day of life at first scan, median (interquartile range)	2 (1–3); *N* = 2001	2 (2–3); *N* = 928	6 (4–8); *N* = 2682
Any reported abnormality	642/1985 (32.3)	552/930 (59.4)	1798/2676 (67.2)
Intraventricular hemorrhage	171/2001 (8.5)	110/930 (11.8)	220/2686 (8.2)
Extraaxial hemorrhage	59/2003 (2.9)	321/927 (34.6)	487/2686 (18.1)
Parenchymal hemorrhage	90/2001 (4.5)	125/929 (13.5)	292/2687 (10.9)
Deep nuclear gray matter abnormality	140/1994 (7.0)	65/926 (7.0)	603/2671 (22.6)
Cystic white matter injury	43/1997 (2.2)	24/928 (2.6)	151/2677 (4.9)
Diffuse white matter injury	—	—	628/2674 (23.5)
Venous or arterial occlusion	22/1980 (1.1)	54/925 (5.8)	183/2657 (6.9)
Ventriculomegaly	84/2004 (4.2)	39/929 (4.2)	92/2687 (3.4)
Cerebellar injury	21/1986 (1.1)	29/929 (3.1)	137/2677 (5.1)
Brainstem injury	—	7/927 (0.8)	126/2677 (4.7)
Diffuse cortical signal abnormality	—	—	572/2673 (21.4)
Parasagittal watershed injury	—	—	285/2665 (10.7)
Absent posterior limb of the internal capsule	—	—	114/2659 (4.3)
Other abnormality	329/2000 (16.5)	190/931 (20.4)	588/2686 (21.9)

Data presented as *n*/*N* (%) unless noted otherwise.

Importance of cranial ultrasound on admission



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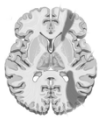
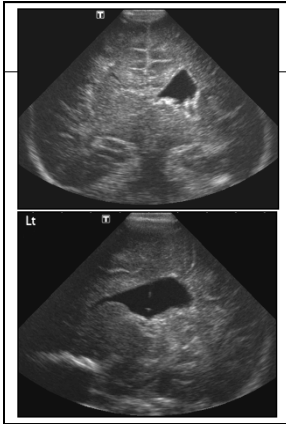
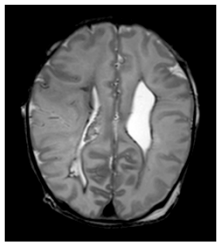


HIE?

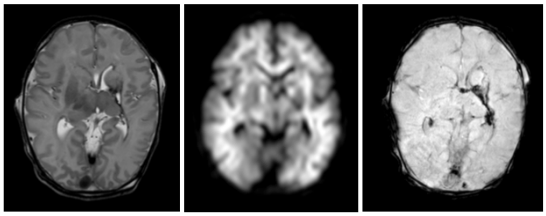


Reduced fetal movements for 2 days; Preterminal CTG
Born by emergency caesarean section for fetal distress.
Apgarscores 2, 4 and 6
Arterial lactate 21.9 mmol/l.

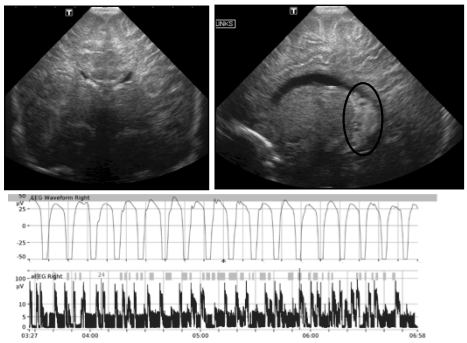


Hypothermia was started, but… *COL4A1* mutation

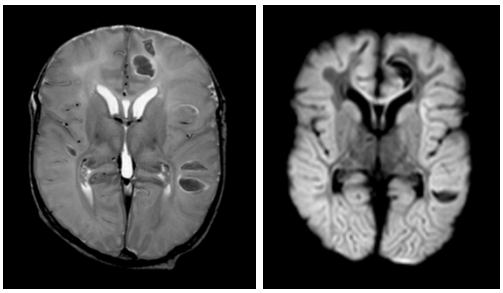
MRI (T2SE, DWI, SWI) day 4



Ultrasound on admission, no history of HIE

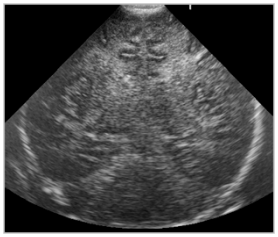


Molybdenum cofactor deficiency (HIE-mimick)



Referred for hypothermia

cUS useful on admission for **timing of injury**

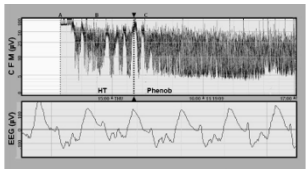


GA 40 4/7; EmCS; thick meconium; Apgar 4/6
PVE on first cUS

Epelman
Imaging Clin N Am

EmCS; thick meconium; Apgar 4/6 PVE on first cUS and seizures < 6 hrs

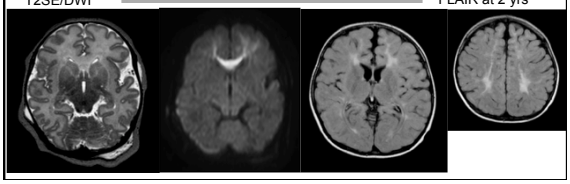
MRI day 6 (T2/DWI) and at 2 yrs (FLAIR)



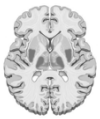
BSID-III at 2 y
90/110
ASD at 5y

Neonatal T2SE/DWI

FLAIR at 2 yrs



Two main patterns of injury



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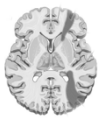
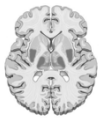
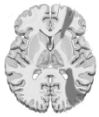


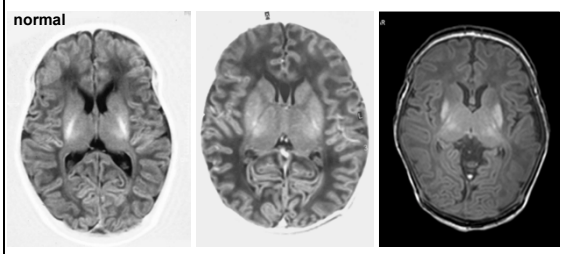




Acute near total asphyxia	Partial subacute asphyxia
• Sentinel event common	• Often normal or mildly complicated labor
• Delivery room resuscitation common	• No delivery room resuscitation
• Criteria for hypothermia present	• Often not meeting criteria for hypothermia
• Hypothermia given	• No hypothermia
• **Outcome clear <18m**	• **Outcome clear at school**

Importance of the PLIC

normal



Abnormal PLIC in relation to outcome;
Rutherford MA et al; Pediatrics 1998

	Normal outcome	Abnormal outcome
Normal PLIC	28	4*
Abnormal PLIC	0	41

Best seen in 2nd week after birth!

* these infants had extensive white matter damage; sensitivity 0.90; specificity 1; PPV 1; NPV 0.87

Predicting motor outcome and death in term HIE.
Martinez-Biarge M et al; Neurology 2011

An abnormal predicted the inability to walk independently by 2 years with a sensitivity of 0.92, a specificity of 0.77

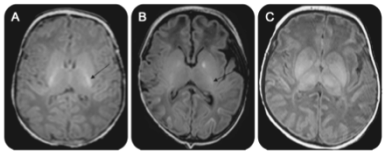


Table 2 Relation between the signal intensity in the posterior limb of the internal capsule (PLIC) and the ability to walk at 2 years

Total cohort (n = 175)	Normal PLIC (24, 14%) (all these infants had mild BGT lesions)	Equivocal PLIC (18, 10%) (4 infants had mild BGT, 13 had moderate, and one severe BGT lesions)	Abnormal PLIC (133, 76%) (24 of these infants had moderate and 109 severe BGT lesions)
Died	0	0	37% (n = 49)
Survivors (n = 126)	Normal PLIC (n = 24)	Equivocal PLIC (n = 18)	Abnormal PLIC (n = 84)
Survivors walking by 2 y	100% (n = 24)	67% (n = 12)	12% (n = 10)

Outcomes after central grey matter injury in term perinatal HIE.
Martinez-Biarge M et al. EHD 2010; 86:675–682

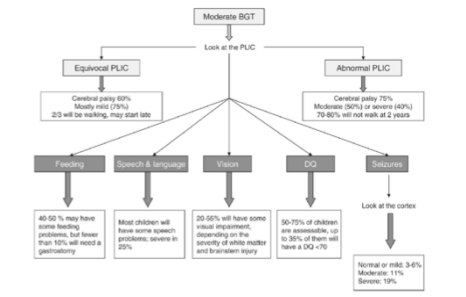
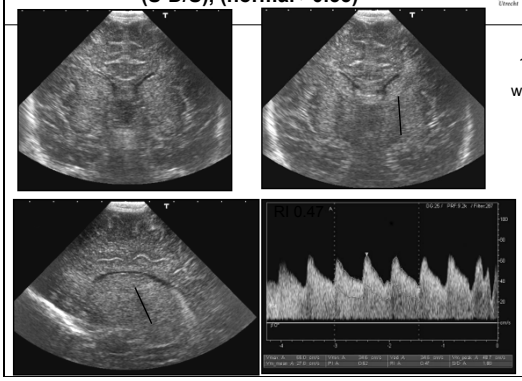


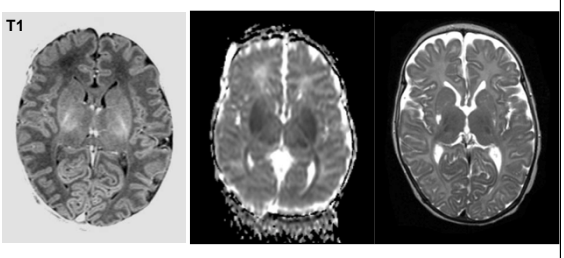
Fig. 5. Flow chart showing patterns of outcome with moderate basal ganglia/thalamic (BGT) injury. DQ, developmental quotient; PLIC, posterior limb of the internal capsule.

Ultrasound Doppler, measuring RI (S-D/S), (normal >0.55)

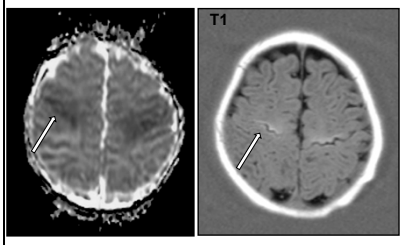


1st week

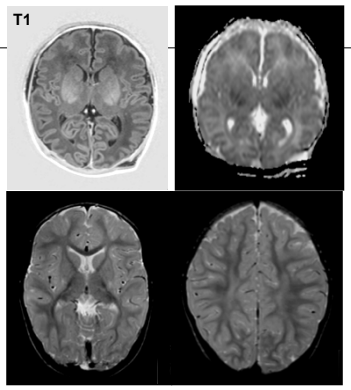
severe BGT involvement MRI day 6 and at 3mo



Also note involvement perirolandic cortex neonatal ADC and T1 at 3 months; outcome: severe dyskinetic CP



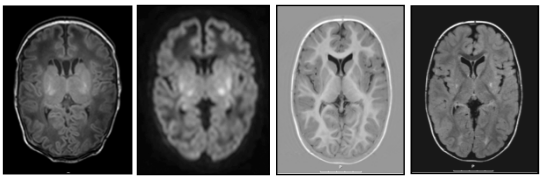
Krageloh-Mann I, DMCN 2002



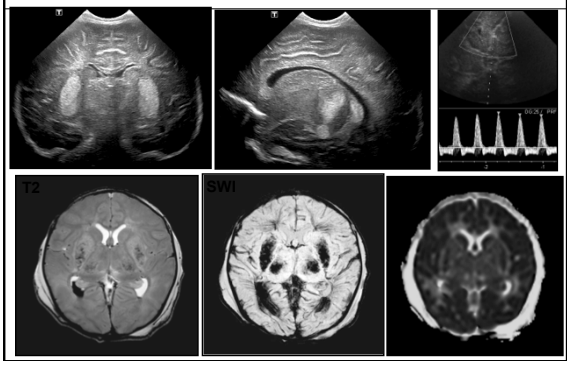
Abnormal PLIC-T1
ADC abn BGT
Suble T2 abn 2 yrs
Dyskinetic CP
Walks unaided
TIQ 100 at 5 yrs

- Full-term male, GA 40 1/7 wks, BW 4200 gram.
- Uterus rupture, born by Emergency CS
- mmol/l.
- Apgar scores: 2, 4 and 6 at 1, 5 and 10 minutes.

First MRI day 5

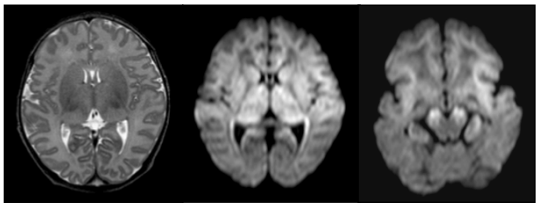


Shoulder dystocia; Apgar 0/1/1; cap.pH 6.4
Homozygous for MTHFR (C677T)



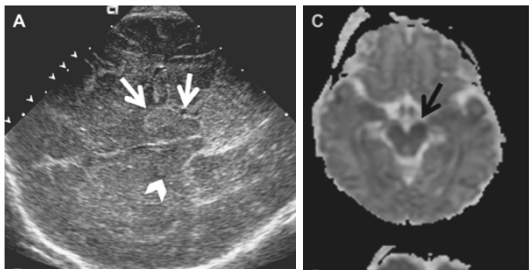
Severe BGT and severe white matter involvement
Near Total Brain Injury
MRI day 3

Also note involvement of CST



The white cerebrum; Vermeulen RJ et al; Neuroped 2003

Head Ultrasound and MR Imaging in the Evaluation of Neonatal Encephalopathy: Competitive or Complementary Imaging Studies?
Epelman et al. Magn Reson Imaging Clin N Am 20 (2012) 93–115



MRI Findings in Infants With Infantile Spasms After Neonatal HIE.
Gano D et al; Pediatr Neurol 2013; 49:401-405

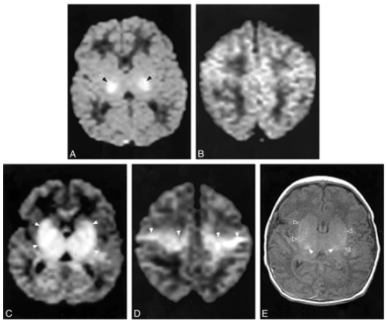
TABLE 2.
Brain injury in newborns with HIE that develop infantile spasms

Patient	Pattern	Cortical Extent	Midbrain	Pons	Medulla	Hypothalamus
1	BG/T	+	+	–	–	–
2	Total	++++	++	++	–	+
3	Total	+++	–	–	–	–
4	BG/T	+	+	–	–	–
5	Total	++++	+	++	+	–
6	BG/T	+++	+	–	–	+
7	Total	++++	++	–	++	–
8	BG/T	+	–	+	–	–

Abbreviations:
BG/T = Basal ganglia/thalamus
HIE = Hypoxic-ischemic encephalopathy
Extent of cortical injury: + indicates 1-25%, ++ 26-50%, +++ 51-75%, ++++ 76-100% of cortex involved; levels of brainstem: – indicates absence of injury, + mild, ++ moderate to severe; hypothalamus: – indicates absence of injury, + presence.

Infantile spasms after HIE is associated with BGT injury particularly when extensive cortical injury and/or injury to the midbrain is present.

Proton Spectroscopy and Diffusion Imaging on the First Day of Life after Perinatal Asphyxia: Preliminary Report.
Barkovich AJ et al 2001, AJNR, 22:1786-94



Day 1

Day 7

Early MRI in term infants with perinatal hypoxic ischaemic brain injury: Interobserver agreement and MRI predictors of outcome at 2 years.
Goergen SK et al. Clin Radiol 2014; 69(1):72-81

Table 6
Kappa statistic values for agreement[a] between the three radiologists regarding scores for different regions of the brain for diffusion-weighted imaging (DWI) and non-DWI MRI images.

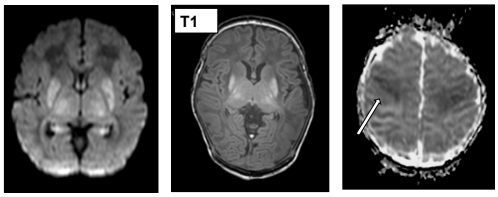
Region	ADC/DWI	T1/T2 WI
Cortex	0.64	0.44
Paracentral white matter	0.27	0.35
Lentiform nucleus	0.66	−0.11
Thalamus	0.48	0.09
Posterior limb internal capsule	0.62	−0.05
Brainstem	0.66	0.34
Vermis	—	−0.056

ADC, apparent diffusion coefficient; WI, weighted imaging.
[a] Agreement was defined as all three radiologists scoring the region as "0" or at least two of the three scoring the region as 1, 2, or 3. A kappa value of 0.6–0.8 is considered to be good agreement, 0.4–0.6 as moderate, 0.2–0.4 as fair, and <0.2 as poor agreement. Negative kappa values indicate that the level of agreement is below that expected by chance, i.e., potential systematic disagreement between the observers.

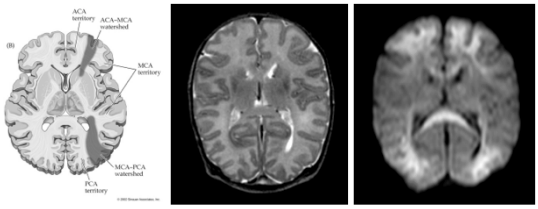
Make use of DWI !
Perform MRI day 4-6 whenever possible!!

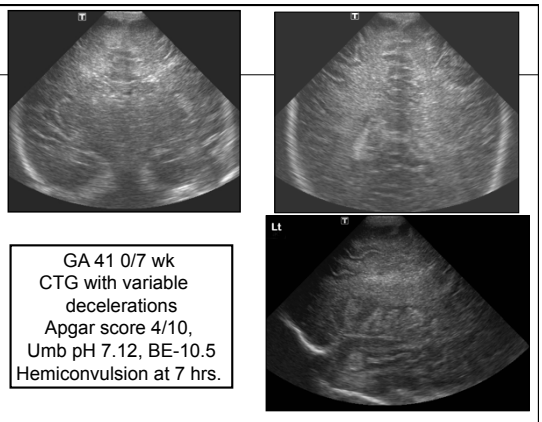
Conclusions BGT injury due to "acute near total asphyxia"

- extend over the first 3-5 days
- PLIC can be useful, but best appreciated in the second week after brith
- Involvement of perirolandic cortex important



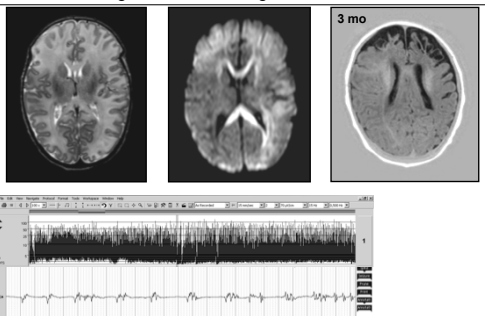
II: "Subacute Partial Asphyxia"





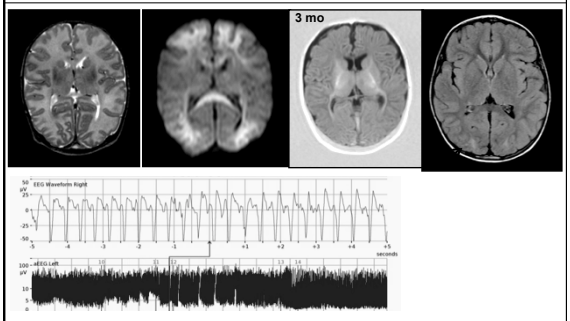
GA 41 0/7 wk
CTG with variable decelerations
Apgar score 4/10,
Umb pH 7.12, BE-10.5
Hemiconvulsion at 7 hrs.

Asymmetrical and extensive T2 and DWI changes,
MRI day 7. Cystic evolution at 3 months.
Ictal discharges on a BS background on the aEEG



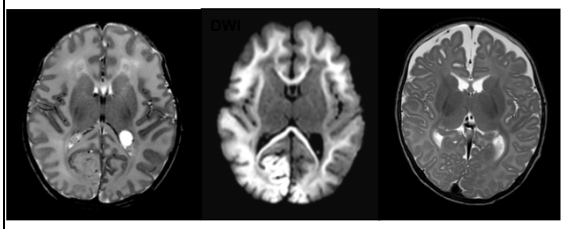
Griffiths test at 48 months: DQ 88/ TIQ 69 at 5 years

Bilateral symmetrical WS abnormalities.
MRI day 3
Ictal discharges on DNV background



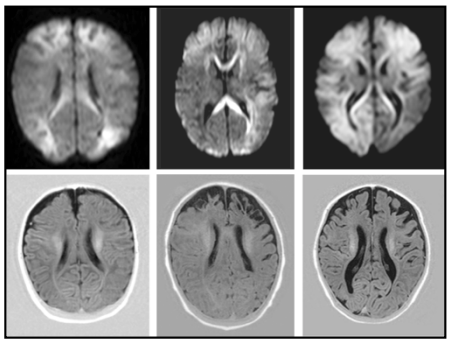
Normal WPPSI test at 5 years (TIQ 97); Mov –ABC p25

Even extensive DWI abnormalities may not show cystic evolution



MRI at 3 m often of limited value
Developed epilepsy at 9 months

DWI changes in cerebral watershed distribution following NE are not invariably associated with an adverse outcome
Harteman JC et al, DMCN 2013;55(7):642-53



DWI changes in cerebral watershed distribution following NE are not invariably associated with an adverse outcome
Harteman JC et al, DMCN 2013;55(7):642-53

	WS only n=7	WS and BGT involvement n=11
Died	**0**	**6**
DQ > 85 at 18 -24 months	**6**	**0**
Postneonatal Epilepsy	**1**	**3**
Cerebral palsy	**0**	**2**
Behavioral problems/autism	**2**	**0**
Cerebral Visual impairment	**2**	**1**

Importance of long term follow-up

White Matter and Cortical Injury in HIE: Antecedent Factors and 2-Year Outcome.
Martinez-Biarge M, J Pediatr 2012; 61(5):799-807

Table I. Neurodevelopmental outcomes

	Normal and mild WM n = 28	Moderate WM n = 34	Severe WM n = 22	P
Motor outcome				
CP, n (%)	0	1 (3)	4 (18)	.018
Delayed walking (>18 mo), n (%)	0	1 (3)	5 (23)	.005
Other outcomes				
Feeding impairment, n (%)	0	3 (9)	5 (23)	.026
Communication impairment, n (%)	1 (4)	9 (28)	14 (64)	<.001
Visual impairment, n (%)	0	1 (3)	7/20 (35)	<.001
Hearing loss, n (%)	0	1 (3)	1 (4.5)	.72
Behavioral problems, n (%)	1 (3.5)	10 (30)	13/19 (68)	<.001
Seizures (follow-up), n (%)	0	3 (9)	8 (36)	<.001
	Normal and mild WM n = 22	**Moderate WM n = 28**	**Severe WM n = 21**	**P***
DQ				
DQ, mean ± SD				
Total DQ	112 ± 14.1	104.3 ± 11.1	88.5 ± 20.5	<.0001
Motor	108.4 ± 10.5	107.3 ± 15.9	92.8 ± 24.6	.12
Social	114.3 ± 13.3	108.5 ± 12.9	96.1 ± 23.7	.02
Hearing & language	111.7 ± 18.4	106 ± 21.2	83.2 ± 23.6	<.001
Eye & hand coordination	109.4 ± 11.6	99.3 ± 11.5	83.4 ± 17.6	<.001
Performance	115.6 ± 17.4	103.5 ± 12.4	83.6 ± 18.3	<.001

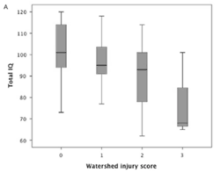
Long-Term Neurodevelopmental Outcome with HIE.
Perez A et al. J Pediatr 2013; 163(2):454-9.

Assessed at about 11 years

Table IV. Neurodevelopmental outcome for children without major disability (n = 57)

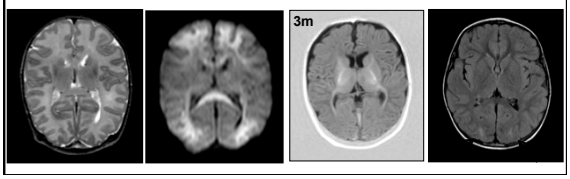
	n	Value	P value*
Intellectual outcome			
Full-scale IQ score, mean (range)	57	95.3 (62-120)	.02
Verbal IQ score, mean (range)	57	98.2 (63-123)	.33
Performance IQ score, mean (range)	57	94.9 (66-118)	.01
Full-scale IQ score <85, n (%)	57	14 (24.6)	.04
Full-scale IQ score <70, n (%)	57	3 (5.3)	.09
ZNA score <10th percentile, n (%)			
Pure motor	53	26 (49.1)	<.001
Adaptive fine motor	53	17 (32.1)	<.001
Adaptive gross motor	53	21 (39.6)	<.001
Static balance	52	2 (3.8)	.14
Associated movements	49	29 (59.2)	<.001

*Wilcoxon paired rank-sum test, compared with normative values of 100 for IQ and 10% for ZNA.

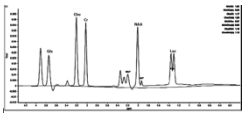


Conclusions watershed/WM injury "Subacute Partial Asphyxia"

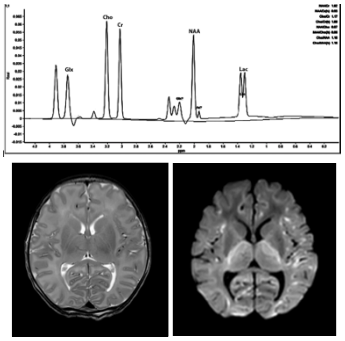
- DWI extremely useful and abnormalities may be missed with conventional T1/T2
- MRI at 3 months may underestimate degree of injury in the absence of cystic evolution
- Long-term outcome required, children grow into their deficit



Additional value of MRS

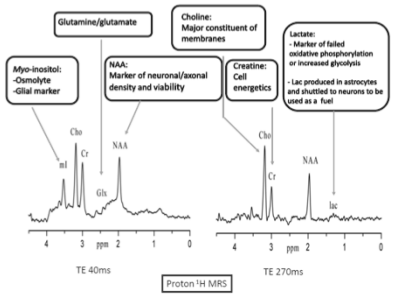


Additional value of ^{1}H-MRS



MRI at 36 hrs of age

Magnetic Resonance Spectroscopy Biomarkers in Term Perinatal Asphyxial Encephalopathy: From Neuropathological Correlates to Future Clinical Applications. *Robertson NJ. Current Pediatric Reviews, 2014*



Magnetic Resonance Spectroscopy Biomarkers in Term Perinatal Asphyxial Encephalopathy: From Neuropathological Correlates to Future Clinical Applications. *Robertson NJ. Current Pediatric Reviews, 2014*

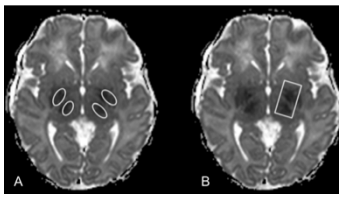
		Sensitivity	Specificity
Lac/NAA	10 studies	82%	95%
NAA/Cr	9 studies	61%	94%
cMRI	19 studies	91%	51%
PLIC	6 studies	71%	86%
ADC	5 studies	66%	64%

0.6 0.8 1.0
AUC (SE) from sROC

NB: Lac=Lactate, NAA=N-acetyl aspartate, Cr= creatine, cMRI=conventional MR imaging, PLIC=loss of normal high signal intensity in posterior limb of internal capsule;ADC=apparent diffusion coefficient

MR Imaging and Outcome of Term Neonates with Perinatal Asphyxia : Value of Diffusion weighted MR Imaging and 1 H MR Spectroscopy.

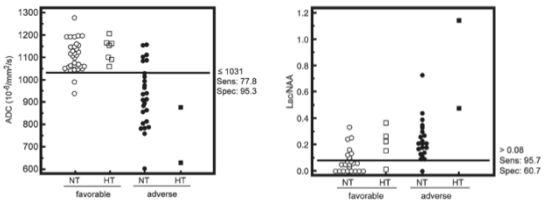
Alderliesten T et al, Radiology 2011;261(1):235-42.



n= 81 (51+MRS) MRI (median 4 days);

MRI combined with Lac/NAA ratios or ADCs in the BGT < 7 days of life had a better association with outcome than did MRI alone (P = .006)

MR Imaging and Outcome of Term Neonates with Perinatal Asphyxia : Value of Diffusionweighted MR Imaging and 1 H MR Spectroscopy.
Alderliesten T et al, Radiology 2011;261(1):235-42



ADC in BGT
< 7 days

Lac/NAA in BGT
< 7 days

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

When to do the MRI in cooled infants?

Neonatal Encephalopathy and Neurologic Outcome, Second Edition

Report of the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy

Executive Summary

Obstet Gynecol
2014;123(4):896-901

Early MRI obtained between 24-96 hrs may be more sensitive for the delineation of the timing of perinatal cerebral injury, whereas an MRI at 10 days (7-21 d) will best delineate the full extent of cerebral injury.

Westin et al *Acta Paed Scand* 1962; **51:** 1–80.

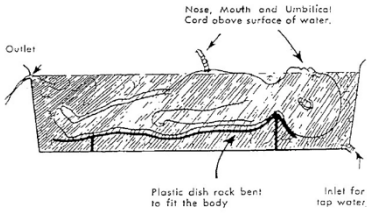
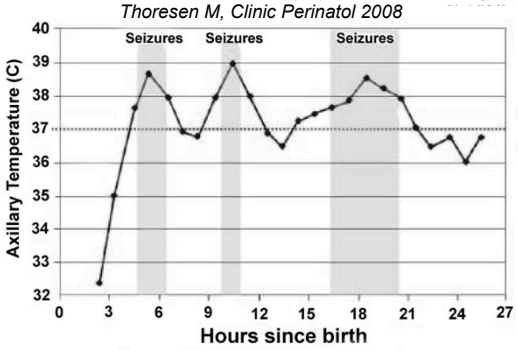


Figure 1. The immersion bath used by Westin *et al.* [33] to resuscitate and cool newborn infants who were unresponsive (Apgar 0–3) after 5 min.

Supportive care during hypothermia;
Thoresen M, Clinic Perinatol 2008



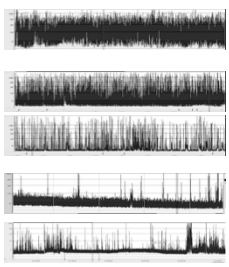
Apgar 0 (1 min), 0 (5 min), 2 (10 min). Intubated by 53 minutes when arrived in hospital. Rapid rewarming in incubator from 2 hours of age

Criteria for hypothermia

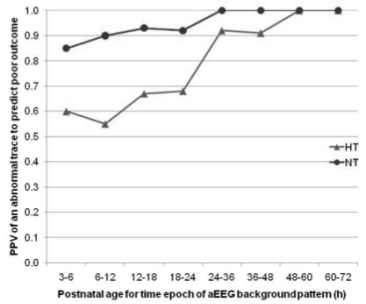
- Perinatal asphyxia
  -
  - *mmol/L*

AND

- Encephalopathy
  - *Thompson*
  - *aEEG (DNV or worse)*



Effect of HT Treatment on the Predictive Value of aEEG
Thoresen M, Hellström-Westas L, Liu X, de Vries LS, Pediatrics; 2010; 125:e358-66



Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic–ischemic encephalopathy: a nested substudy of a RCT

Rutherford et al .

The accuracy of prediction by MRI of death or disability to 18 months of age was similar in both groups

Assessment of brain tissue injury after moderate hypothermia in neonates with HIE with and without HT

Rutherford et al Lancet Neurol. 2010;9:39-45
and Cheong JLY et al, Arch Pediatr Adolesc Med 2012; 166:634

Therapeutic hypothermia was associated with a reduction in lesions in (OR and 95% CI)

	Rutherford	Cheong
WM	0.30 (0.12-0.77)	0.28 (0.09-0.82)
BGT	0.36 (0.15-0.84)	0.41(0.17-1.00)
PLIC	0.38 (0.17-0.85)	

See also, Shankaran S et al; Arch Dis Child 2012 and Bonifacio S et al, J Pediatr 2011

The effect of whole-body cooling on brain metabolism following perinatal hypoxic–ischemic injury.

Corbo ET et al; Pediatr Res 2012; 71(1):85-92

Retrospective comparison of HT and NT patients

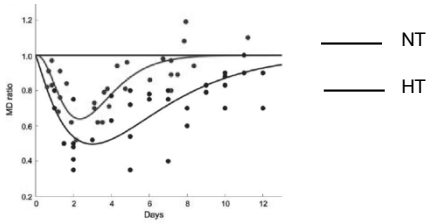
Table 4. Metabolite ratios in the basal ganglia and thalami of healthy neonates and neonates with HII who did (HII/HT⁺) and did not (HII/HT⁻) receive hypothermia treatment

	Control ($n = 9$)	HII/HT⁺ ($n = 19$)	HII/HT⁻ ($n = 19$)	*P* value: C vs. HII/HT⁺	*P* value: C vs. HII/HT⁻	*P* value: HII/HT⁺ vs. HII/HT⁻	Correlation coefficient to encephalopathy score
Basal ganglia							
NAA/Cr	1.07 ± 0.07	0.80 ± 0.12	0.83 ± 0.15	<0.01	<0.01	1.00	−0.12 ($P = 0.51$)
NAA/Cho	0.74 ± 0.10	0.57 ± 0.09	0.53 ± 0.13	<0.01	<0.01	0.74	−0.39 ($P = 0.02$)
Cho/Cr	1.48 ± 0.27	1.44 ± 0.07	1.74 ± 0.59	1.00	0.50	0.11	0.46 ($P < 0.01$)
% Neonates with Lac	0	15.8	35.3			0.14*	
Thalami							
NAA/Cr	1.11 ± 0.18	0.97 ± 0.17	0.83 ± 0.24	0.39	0.02	0.17	−0.42 ($P = 0.02$)
NAA/Cho	0.78 ± 0.10	0.62 ± 0.13	0.51 ± 0.18	0.05	<0.01	0.12	−0.57 ($P < 0.01$)
Cho/Cr	1.46 ± 0.31	1.58 ± 0.29	1.59 ± 0.40	1.00	0.86	1.00	0.09 ($P = 0.62$)
% Neonates with Lac	0	10.5	29.4			0.01*	

Values are expressed as the group means ± SD. Statistical differences were measured by one-way ANOVA with Bonferroni post hoc or χ^2 analysis (*). Correlation coefficients were determined using Spearman's ρ analysis.
C, control; Cho, choline; Cr, creatine; HII/HT, hypoxic–ischemic injury with hypothermia therapy; Lac, lactate; NAA, *N*-acetyl-aspartate; NS, not significant.

Impact of therapeutic hypothermia on MRI diffusion changes in neonatal encephalopathy.

Bednarek N et al; Neurology 2012; 78(18):1420-7



TH slows the evolution of diffusion abnormalities on MRI following HIE in term infants

MRI and spectroscopy in (near) term neonates with perinatal asphyxia and therapeutic hypothermia.

Alderliesten T et al, ADCFN 2016

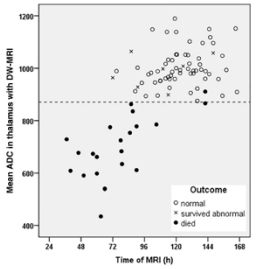


Figure 2 Apparent diffusion coefficient (ADC) values ($\times 10^{-6}$ mm^2/s) of the thalamus versus time after birth in infants with a good outcome (open circles) or adverse outcome (survived: crosses; died: closed circles). The horizontal dotted line indicates the cut-off value of 871×10^{-6} mm^2/s. DWI, diffusion-weighted MRI.

What this study adds?

- Low apparent diffusion coefficient values and high lactate/N-acetylaspartate (LAC/NAA) ratios in the basal ganglia and thalamus in infants with perinatal asphyxia are associated with an adverse outcome, also during and after therapeutic hypothermia.
- Results of DW-MRI (apparent diffusion coefficient values) and proton MRS (Lac/NAA ratios) can be used as biomarkers of outcome in infants with perinatal asphyxia and therapeutic hypothermia; cut-off levels of these biomarkers differed slightly from those in normothermic infants.
- Apparent diffusion coefficient values were dependent on the MRI sequences.
- Findings of proton MRS in 1.5 T and 3.0 T magnetic fields were comparable.

Comparison early and later MRI in infants treated with hpothermia

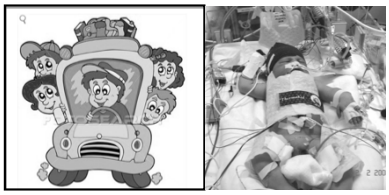
	number	Day of MRI	Agreement
Wintermark et al, 2011	12	1, and 2-3 and 8-13	Day 2-3 showed good agreement with 8-13
Gano et al, 2013	24	1 and 3	Good agreement DTI/ MRS values
Skranes et al, 2015	41	4 and 11	Good agreement in 37/41 infants
Chakkarapani et al, 2016	89 (43 HT)	3-6 and 10-14	Good agreement; worsened in 1 of 43

Perform MRI after rewarming unless redirection of care is considered

Neuro-imaging changes during the first week

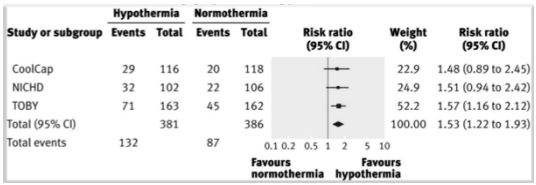
- Cranial ultrasound abnormalities, especially in the basal ganglia and thalami become clear (48-72 hrs)
- PLIC will change and may become clearly abnormal in second part of the first week
- DWI will increase and change from thalami only to thalami and basal ganglia and corpus callosum
- ^{1}H-MRS will show increased lactate from day 1 onward, but NAA will decrease later in the first week

Outcome in infancy and at school age following hypothermia



Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data.

Edwards AD et al; BMJ 2010; 340:c363. doi: 10.1136/bmj.c363.



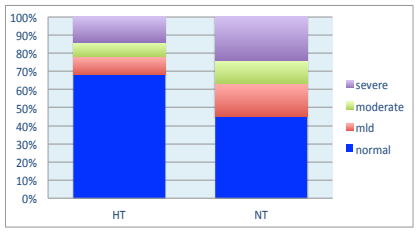
Study or subgroup	Hypothermia Events	Hypothermia Total	Normothermia Events	Normothermia Total	Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
CoolCap	29	116	20	118		22.9	1.48 (0.89 to 2.45)
NICHD	32	102	22	106		24.9	1.51 (0.94 to 2.42)
TOBY	71	163	45	162		52.2	1.57 (1.16 to 2.12)
Total (95% CI)		381		386		100.00	1.53 (1.22 to 1.93)
Total events	132		87				

effect of therapeutic hypothermia compared with standard care (normothermia) on survival with normal neurological function (“events”).

Effects of Hypothermia for Perinatal Asphyxia on Childhood Outcomes.

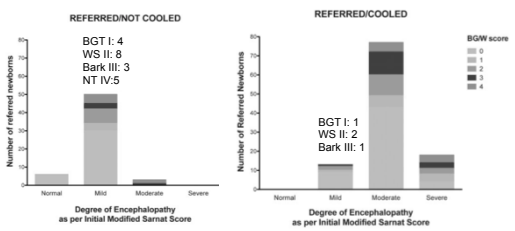
Azzopardi D et al, TOBY trial; NEJM 2014

Percentage of children with a disability



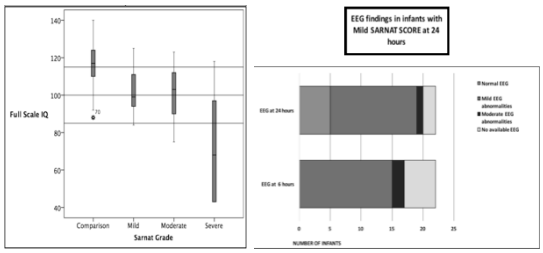
Newborns Referred for Therapeutic Hypothermia: Association between Initial Degree of NE and Severity of Brain Injury (What About the Newborns with Mild NE on Admission?)

Maude Gagne-Loranger; Am J Perinatol 2016;33:195–202.



Early EEG and outcome at 5 years following mild neonatal hypoxic ischemic encephalopathy.

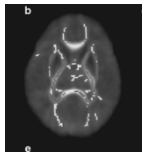
Murray D et al; Pediatrics 2016



Do we need aEEG after birth asphyxia in level 2 hospitals as well for early assessment?

“Use of advanced neuro-imaging in infants treated with hypothermia

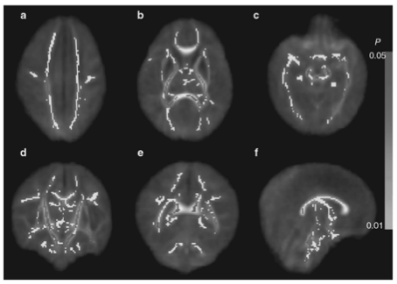
University Medical Center Utrecht



Prediction of neurodevelopmental outcome after HIE treated with HT by DTI analyzed using tract-based spatial statistics.
Tusor N et al, Pediatr Res 2012; 72(1):63-9.

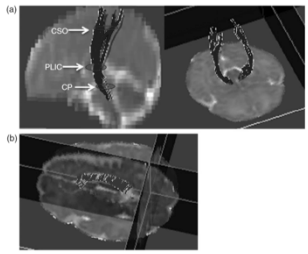
- were carried out at a median (range) age of 24 (12–28) mo
- Significantly lower FA values (*P < 0.05)* were found in *the centrum semiovale, corpus callosum (CC), anterior and posterior limbs of the internal capsule, external capsules, fornix, cingulum, cerebral peduncles, optic radiations, and inferior longitudinal fasciculus.*
- DTI analyzed by TBSS provides a qualified biomarker that can be used to assess the efficacy of additional neuroprotective therapies after HIE.

Prediction of neurodevelopmental outcome after HIE treated with HT by DTI analyzed using tract-based spatial statistics.
Tusor N et al, Pediatr Res 2012; 72(1):63-9.



Mean FA skeleton (yellow) overlaid on mean FA image. Voxels wherein infants with unfavorable outcome had significantly lower FA are shown in blue.

White matter tract integrity and developmental outcome in newborn infants with HIE treated with hypothermia.
Massaro A et al, DMCN 2015; 57(5):441-8

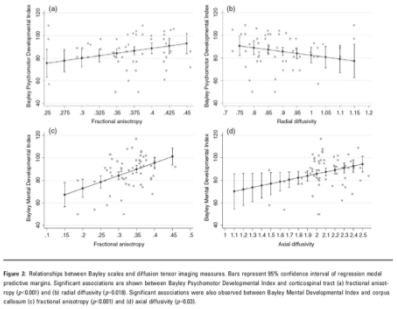


Fifty-two infants DTI at median age of 8 days.

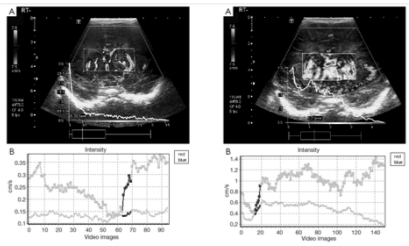
Outcomes were assessed in 42/50 (84%) children at 15 months and 35/50 (70%) at 21 months.

Lower FA values in CC and CST were associated with lower MDI and PDI

White matter tract integrity and developmental outcome in newborn infants with HIE treated with hypothermia.
Massaro A et al, DMCN 2015; 57(5):441-8



Basal ganglia perfusion using dynamic color Doppler sonography in infants with HIE receiving therapeutic HT: a pilot study.
Faingold R et al, Quant Imaging Med Surg 2016;6:510



n=28 who had cUS <48 hours of HT treatment.
CPI values were higher in the 7 non-survivors when compared to survivors (0.226±0.221 *vs*. 0.111±0.082 cm/sec; P=0.02).

Arterial spin-labelling perfusion MRI and outcome in neonates with HIE.
De Vis JB et al; Eur Radiol 2015; 25:113-21.

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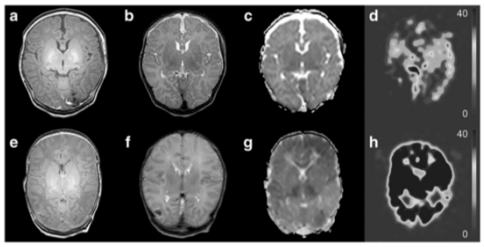

Normal outcome (top); abnormal outcome (bottom) with hyperperfusion

Arterial spin-labelling perfusion MRI and outcome in neonates with HIE.
De Vis JB et al; Eur Radiol 2015;25:113-21.

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Table 4 Predictive values of the MRI parameters for hypoxic-ischemic encephalopathy

Parameter	N*	AUC (95 % CI)	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
MRI score	28 (8/20)	0.97 (0.82–0.99)	> 1	100	95	89	100
ASL (ml/100 g/min)	24 (7/17)	0.92 (0.74–0.99)	> 51	85.7	100	100	96
Lac/NAA	25 (7/18)	0.96 (0.80–0.99)	> 0.28	100	89	78	100
ADC (10^{-6}/mm^2/s)	28 (8/20)	0.92 (0.75–0.99)	≤ 910	75	100	100	92

PPV, positive predictive value; NPV, negative predictive value; HIE-stage, hypoxic-ischemic encephalopathy grade; aEEG, amplitude-integrated electroencephalography

* Numbers in parentheses are number of patients with adverse/favourable outcome

ASL perfusion was a mean value obtained from region-of-interest analysis in the basal ganglia and thalami. Lac/NAA was measured in the left basal ganglia, and ADC was a mean value obtained from region-of-interest analysis in the basal ganglia and the thalami

Multiple regression analysis demonstrated that the combination of Lac/NAA and ASL was the best predictor of outcome (r2=0.86, p<0.001).