Perinatal brain injury imaging characteristics - Multimodality pictorial review of perinatal encephalopathy in pre-term and term neonates with development of clinically relevant imaging pathway guideline.

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Learning Objectives

Learning Objectives:

1. Review of nomenclature and current guidelines in neonatal neuroimaging and neonatal encephalopathy.

2. MRI case-based review of hypoxic-ischemic neonatal brain injury patterns in term neonates.

3. Proposal of a clinically relevant neonatal neuroimaging pathway for term and preterm infants.

Background

Background of neonatal neuroimaging

- Neonatal encephalopathy (NE) neuroimaging has advanced in the last 10 years with more availability of higher field strength MRI and routine use of DWI and MRS.
- Despite advancements in NICU capabilities incidence of NE is largely unchanged (1-6 per 1000 live term births) and remains a significant cause of short-term morbidity and mortality in the NICU as well as long-term adverse neurodevelopmental disability.
- There are many logistical difficulties in neuroimaging of the sick neonate.

Neonatal neuroimaging plays 4 broad roles:

1. Screening of at risk premature neonates for brain injury.
2. Early diagnosis in suspected brain injury to aid in care strategy.
3. Short and long term prognostication and care planning including aiding decisions to withdraw care.
4. Valuable tool in determining the timing of suspected injury with significant medico legal implications

Current neonatal evidence based guideline by Ment et al:

Premature neonate:

- <30 weeks should have early (7-14days) cranial USS and follow up USS at 36-40 wks
- Insufficient evidence for routine MRI in all VLBW infants with abnormal screening USS.
Term neonate:

- NE with history of birth trauma should have CT to exclude intracranial hemorrhage. If CT cannot explain clinical status then MRI should be performed between days 2-8
- Encephalopathic term neonates with no history of birth trauma should have MRI between 2-8 days with MRS and DWI. CT only indicated if MRI not available.

Review of nomenclature

Easily confused between the neonatologist and radiologist.

- Accepted cutoff of neonates as preterm/term (premature/mature) is <36wks.
- Neonatal encephalopathy (NE) has multiple aetiologies that should be considered in the clinical, genetic, biochemical and radiological workup.

- Hypoxic-Ischemic Encephalopathy (HIE) is a clinical diagnosis that should be reserved for term infants who have a range of clinical findings and evidence of antepartum or perinatal asphyxia/hypoxic-ischemic injury with signs of fetal distress (including, but not limited to, pH<7.2, abnormal CTG, low Apgar scores).
- The reader is referred to the most commonly accepted staging system (HIE I-III) of early onset term encephalopathy developed by Sarnat and Sarnat which includes signs of altered tone, feeding difficulties, level of consciousness, primitive reflexes and neonatal seizures.
- HIE is the most common cause of neonatal encephalopathy in the term infant.
  - HIE should not be used synonymously with the generic term hypoxic-ischemic injury (HII) used by some authors.
  - HIE should not be used interchangeably with the term 'periventricular leukomalacia (PVL)' to describe white matter injury in the preterm infant. The term 'Preterm HIE' used by some authors should be avoided.
  - 'Birth asphyxia', 'perinatal asphyxia', 'hypoxic-ischemic injury (HII)', 'neonatal hypoxia/anoxia', 'neonatal hypoxic insult' and the like are non-specific terms that encompass all types/durations of hypoxic-ischemic insult.

Imaging Findings OR Procedure Details

MRI case-based review of common hypoxic-ischemic neonatal brain injury patterns in term neonates

Term (>36 weeks)
USS - In keeping with Ment et al, we have found the degree of hypoxic-ischemic injury is often underestimated compared to MRI - USS plays a limited role in cases of term NE.

CT - Limited role in cases of suspected intracranial haemorrhage with a significant history of birth trauma. We do not routinely undertake CT and substitute it with the addition of gradient echo susceptibility weighted sequence on MRI.

MRI (MRS not discussed) demonstrates 5 classical patterns of injury in HIE in the term infant:

1. **Basal-Ganglia-Thalamus (BGT) pattern** - affecting the ventrolateral thalami and posterior putamina, peri-rolandic (somatosensory) cortex and hippocampus often accompanied by internal capsule injury with loss of PLIC T1 hyperintensity. BGT pattern of injury is associated with severe long-term motor disability and cerebral palsy and is seen most commonly following a history of acute/profound asphyxia and a sentinel event. (Case 2i Fig. 1 on page 6 & 2ii Fig. 2 on page 6) with evidence of diffusion restriction on DWI and T1 hyperintensity.

2. **Watershed ischemia pattern** - ischemia to the ACA/MCA & MCA/PCA watershed zones with predilection for the parasagittal cortex and parieto-occipital lobes. This pattern is associated with a history of prolonged/partial hypoxic-ischemic insult and neonatal hypoglycemia. Long-term motor disability is less common than the BGT pattern but watershed injury is associated with visual, cognitive/behavioral sequelae and parieto-occipital epilepsy. (Case 3i Fig. 3 on page 7, 3ii & 4 Fig. 4 on page 8)

3. **'White cerebrum’ (global injury)** - diffuse supratentorial cortical and subcortical diffusion restriction with variable involvement of the deep grey nuclei and cerebellum. This pattern of injury is associated with poor short-term outcome often resulting in neonatal death. Difficulty in recognizing diffuse abnormality can be mitigated by using the cerebellum as a reference standard in conjunction with MRS. (Case 5 Fig. 5 on page 9, 6i & 6ii Fig. 6 on page 10)

4. **Scattered white matter injury** - periventricular distribution of punctate ischemic lesions on DWI usually associated with a more benign clinical course. Reported increased incidence of this pattern in newborns with underlying cardiac anomalies. (Case 7 Fig. 7 on page 12)

5. **Cerebral infarction** - also termed Perinatal Arterial Ischemic Stroke (PAIS) and not dissimilar in MRI appearance to adult territorial embolic stroke. Clinical history is often more complex than simple thromboembolic disease and thorough workup is required including thrombophilia screen, perinatal infectious screen and cardiac assessment. (Case 8 Fig. 8 on page 12)

Premature (<36 weeks)
USS - screening USS in all preterm neonates <30 weeks and selected cases 30-36 weeks. At our institution we undertake initial cranial USS within the first 7 days and repeat imaging at term equivalent dates or prior to discharge (>36wks). Interval USS is undertaken sooner if clinically indicated:

- **Periventricular leukomalacia (PVL)**
- **Germinal Matrix Haemorrhage (GMH)**
- **Assessment of gross architecture, posterior fossa structures, CSF spaces (including ventricular caliber) and venous sinuses.**

The gamut of sonographic appearances and grading of PVL and germinal matrix haemorrhage is beyond the scope of this educational poster and the reader is referred to the excellent online summary by Beek & Groenendaal (see references)

MRI - Paucity of cases demonstrating MR findings in the preterm neonate given the difficulty in transporting and scanning premature infants in conjunction with the fact that only a small number of premature infants develop severe hypoxic-ischemic lesions compared to term infants.

Classical injury patterns described in the literature include PVL in cases of mild hypotension with more diffuse ischemia of the metabolically active deep grey matter, brainstem and cerebellum in cases of severe hypoxic insult:

- **Periventricular Leukomalacia (PVL)** - the periventricular white matter is vulnerable in the premature infant due to the sensitivity of immature oligodendrocytes and foetal vascular supply from penetrating ventriculopetal arteries extending from the surface of the brain. Fig. 11 on page 13
- **Thalamus/Brainstem/Cerebellar vermis.** - profound/acute hypoxic-ischemic insult in the premature can result in a variant of the BGT pattern seen in term neonates with preferential injury to the thalamus and dorsal brainstem due to early myelination (25wks) and high metabolic demand of these structures.
- **Mixed pattern** - in the few premature infants we have imaged in our institution with history of profound hypoxic-ischemic insult we have encountered a number of cases with mixed patterns of watershed/global injury similar to those seen in term infants.
- **Intracranial haemorrhage** - Germinal matrix, intraventricular and cerebellar haemorrhage. Cerebellar haemorrhage is reported in up to 25% of preterm VLBW infants and is associated with long-term adverse neurodevelopmental outcome. Fig. 12 on page 14
- **DEHSI** - mention should be made of the term Diffuse Excessive High Signal Intensity (DEHSI) which was coined to describe diffuse high signal on T2W imaging in preterm infants when imaged at term equivalent age. The appearance of DEHSI was previously shown to correlate with a reduced developmental quotient at 18 months, however recent cohort
study from Kidokoro et al. found no relationship between DEHSI and 2 yr neurodevelopmental outcome (see references). Although DEHSI is reportedly seen in up to 80% of preterm infants, the clinical significance of such T2 high signal remains uncertain.

Images for this section:

*Case 2i. Basal Ganglia Thalamus Pattern*

**Clinical History 2i:** Term neonate (39+3) delivered by emergent LSCS for foetal distress (variable decelerations, scalp lactate 6.8). Apgar scores 2/4/8 (1min/5min/10min). Floppy and non-responsive at birth requiring resuscitation. D3 became lethargic, hypotonic with poor reflexes without overt seizure activity.

2i a-e MRI performed on day 6 post partum. DWI demonstrates restricted diffusion in the basal ganglia (2i a – yellow arrows) and peri-rolandic cortex (2i b – red arrow) with ADC correlate (2i c/d). On Ax T1 (2i e) there is loss of normal high signal within the PLIC. This case demonstrates BGT pattern consistent with acute/profound asphyxia without a clear history of sentinel hypoxic event.

**Fig. 1**
Case 2ii – Basal Ganglia Thalamus pattern with history of sentinel event.

Clinical History 2ii: Term (41+4). Non-reassuring CTG with fetal bradycardia. Born via emergent LSCS complicated by haemoperitoneum and uterine rupture. Apgar score 1/5/5 (1min/5min/10min) with cord pH6.8 with the infant requiring 2mins CPR and intubation. HIE with increased tone and seizures.

2ii a-c MRI performed on day 6 post partum. As in case 2i above there is evidence of bilateral diffusion restriction within the basal ganglia on DWI (2ii a) and ADC correlate (2ii b). Further peri-rolandic cortical diffusion restriction was also observed (not shown). Note is made of reduced bilateral PLIC hyperintensity on T1W imaing (2iiic) as well as subtle basal-ganglia hyperintensity (yellow arrow). In this case, the BG-T pattern is associated with a clear sentinel event of uterine rupture during complicated LSCS.

Fig. 2
Case 3i Watershed Pattern

Clinical History: Term neonate (38) delivered by emergent LSCS due to non-reassuring CTG and fetal distress. Apgar scores 1/7/9 (1min/5min/10min). Anemic at birth (Hb39) due to fetomaternal haemorrhage with multiorgan dysfunction. Developed HIE with seizures at 11 hours of age with abnormal EEG.

Case 3ii Watershed Pattern (MCA/PCA and ACA/MCA)

Clinical History: Term baby requiring neonatal ventilatory support with meconium aspiration syndrome and seizures. No other history provided.

3i a-c MRI performed D3 postpartum. Ax T2 (3i a) demonstrates T2 hyperintensity in the cortical and subcortical regions of the parieto-occipital regions with loss of grey-white differentiation with corresponding diffusion restriction on DWI (3i b). DWI (3i b) and ADC correlate (3i c) show involvement of the splenium of the corpus callosum (yellow arrow).

3i d-e MRI performed at 3 months of age. There is white matter volume loss with prominence of the lateral ventricles and surface CSF spaces. Cystic encephalomalacia is demonstrated bilaterally in the perieto-occipital lobes (white arrow).

3ii a MRI performed D8 post partum. Single image from DWI (3ii a) demonstrates multiple watershed areas of diffusion restriction with involvement of bilateral parieto-occipital regions (MCA/PCA watershed) and right frontal lobe (MCA/ACA watershed).

Fig. 3
Case 4: Watershed pattern with profound hypoglycemia

Clinical History: Term neonate (38) born via normal vaginal delivery. Obstetric history of gestational diabetes. Profound neonatal hypoglycemia with transient neonatal hyperinsulinism. Developed neonatal seizures day 0. No other history provided.

Fig. 4

4 a-c MRI performed on day 4 postpartum. Similar appearances to case 3i with bilateral symmetrical watershed ischemia in the parieto-occipital lobes with loss of grey-white differentiation on T2 weighted imaging (4a) and restricted diffusion involving the splenium of the corpus callosum (4b-c – white arrows).

4 d-e MRI performed at 2 months of age. Unlike case 3i, there is no evidence of cystic encephalomalacia or significant volume loss with only minor residual patchy T2 high signal in the parieto-occipital subcortical white matter (4d – yellow arrows). DWI at 2 months is unremarkable (4e).

Neonatal Hypoglycemia

- There is a complex relationship between neonatal hypoglycemia and HIE. These two conditions can often co-exist – animal models showing there is increased morbidity/mortality in cases where hypoxic injury and hypoglycemia are both present.
- Recent evidence from Wong et al. showed that the parieto-occipital watershed-predominant pattern of hypoxic ischemic injury was more commonly observed in cases of severe hypoglycemia. Furthermore MRI had high positive/negative predictive value for clinical hypoglycemia in cases without features of HIE.

Fig. 4
Case 5 'White Cerebrum' Global Injury with follow up MRI

Clinical History: Term neonate (38+1) born by elective caesarean with Apgar scores of 9/9 (1min/5min). Neonatal anemia of unknown cause developing seizures day 1 post partum with intermittent central apnoea. Abnormal EEG D4 post partum demonstrated burst suppression.

5 a-d MRI performed on day 3 post partum. Note is made of significant T2 hypointense intraventricular blood product within the occipital horns on T2 weighted imaging (5b) and isointense subdural blood overlying the occipital lobes of T1W imaging (5a – white arrows). There is bilateral loss of T1 hyperintensity in the PLIC (5a – yellow arrows) and reduced parieto-occipital grey/white differentiation on T2W (5b). There is diffuse cortical and subcortical diffusion restriction on DWI (5c) and ADC correlate (5d) with relative sparing of the periventricular white matter and deep grey nuclei.

5 e MRI follow up performed on day 9 post partum. There is diffuse T2 hyperintensity with loss of grey/white differentiation in keeping with severe supratentorial ischemic insult.

Fig. 5
Case 6i & 6ii ‘White Cerebrum’ Global injury with cerebellar reference

**Clinical History 6i:** Term neonate (40) with pregnancy complicated by abnormal CTG, proceeding to emergent LSCS. Apgar scores 4/4/6 (1min/5min/10min) and venous cord pH 6.97 requiring resuscitation and intubation. HIE stage III requiring ventilator support and complicated by multiorgan dysfunction with abnormal EEG. Infant died on day 13.

**Clinical History 6ii:** Term neonate (40) with spontaneous NVD. Apgar scores 5/7/7 (1min/5min/10min) with arterial cord pH 6.85 requiring ventilation. Abnormal EEG. HIE stage II with seizures developing at 7 hours of age and clinical course complicated by multiorgan dysfunction.

6i/6ii MRI both performed on Day 6 post partum

These two cases of severe global hypoxic-ischemic injury are included to highlight the value of using the relatively resistant cerebellum as a reference standard in cases of extensive supratentorial cortical hyperintensity on DWI (6i b, 6ii b/c) and ADC correlate (6i c, 6ii d/e). We have found anecdotally that it is easy to overlook these diffuse supratentorial insults and these cases highlight the need for a thorough clinical history.

T1 weighted imaging demonstrates variable loss of T1 hyperintensity in the PLIC with complete loss of normal high signal bilaterally in case 6i (6i a – yellow arrow), compared to inadequate, irregular asymmetric and nodular T1 hyperintensity in the right PLIC in case 6ii (6ii a – red arrow).
Case 7 Scattered White Matter Injury – Periventricular punctate

Clinical History: Term neonate (38+3) with non-reassuring CTG and decreased foetal movements resulting in emergent LSCS complicated by difficult extraction. Apgar scores 1/6 (1min/5min) with cord pH 6.9. Suspected perinatal asphyxia. HIE stage II with multiorgan dysfunction. EEG showed attenuation of basic rhythms but no electrical seizures. No seizures clinically.

7a-d MRI performed on day 11 post partum. Scattered foci (white arrows) of diffusion restriction on DWI (7a/7b) with ADC correlate (7c/7d). Sparing of the cortex, subcortical white matter, and deep grey nuclei. Normal T1 hyperintensity in PLIC (not shown)

Fig. 6

Fig. 7
Case 8 Cerebral Infarction

Clinical History: Term infant (41) with spontaneous NVD. Pregnancy complicated by GBS +ve swab. Apgar 9/10 (1min/5min) with no resuscitation required. Day 1 post partum noticed to have reduced tone, apnoea with desaturation and recurrent seizures. HIE stage II

8a-b  MRI performed on day 3 post partum. Right MCA territory infarction with lost of grey/white differentiation and increased T2 signal on T2W imaging (8a) with correlate right MCA territory diffusion restriction (8b) on DWI. No underlying cause identified following thrombophilia screen and work up for GBS meningitis.
Case 9 Severe PVL

Clinical History: Preterm (32) delivered via caesarean section with non-reassuring CTG and fetal distress. Twin pregnancy complicated by twin-twin transfusion. Apgar 6/8/9 (1min/5min/10min). Foetal anemia. Lethargy and apnoea on day 1 with abnormal electrical activity on neurophysiological monitoring.

9a-b MRI performed on day 5 post partum.

Fig. 11
Case 10 Cerebellar Haemorrhage

Clinical History: Premature (35) with PPROM delivered via NVD. Developed seizures at 6 hours. Cranial USS reported NAD. ?Hypoxic-ischemic injury.

10 a-b MRI performed day 5 post partum. T1 hyperintense focus (T2 hypointense not demonstrated) in the right cerebellar hemisphere (10a) in keeping with subacute haemorrhage with blooming on susceptibility weighted imaging (10b VENBOLD). No evidence of hypoxic-ischemic injury. Although cerebellar haemorrhage in the premature neonate usually arises from the ventricular germinal matrix it can be seen in the cerebellar hemispheres and correlation with history of birth trauma and MRV is recommended.

Fig. 12
Conclusion

Proposed neonatal neuroimaging pathway for term and preterm infants

Fig. 10 on page 17

Caveats to multimodality imaging in neonatal brain injury

Thorough obstetric and neonatal clinical history is essential.

Accurate history of duration and severity of suspected hypoxic/ischemic insult:

- Acute/profound/near-total asphyxia often associated with a 'sentinel event' e.g. placental abruption, cord prolapse, uterine rupture
- Prolonged/partial hypoxic-ischemic insult e.g. infection, hypoglycemia, hypotension, severe antepartum anemia

Knowledge of the normal appearance of neonatal brain is critical with particular attention to normal myelination patterns at term:

- Ordered sequence of myelination follows the basic pattern of caudal->rostral, medial->lateral, posterior->anterior.
- Posterior limb of the internal capsule (PLIC) should demonstrate myelination at 36 weeks and bilateral PLIC T1 hyperintensity should be observed in term neonates (Case 1 Fig. 9 on page 17). Absence of normal signal in the PLIC has been shown by Rutherford et al to be highly predictive of adverse long-term outcome.

Knowledge of image acquisition protocols - at our institution we undertake Axial/Sagittal T1 (FLAIR). Ax T2, DWI/ADC, SWI (VENBOLD - Philips) +/- MRS, MRA/MRV. Quantitative ADC measurements and DTI are not discussed in this introductory educational poster.

Optimal timing of MRI imaging in cases of NE/HIE.

- Changes of HIE may not be apparent on standard T1/T2 weighted sequences within the first 7 days.
  - Loss of PLIC T1 hyperintensity may not be apparent until 48-72 hours following the time of insult
• Routine use of diffusion imaging (DWI) and the addition of MRS allow early changes of HIE to be identified within the first few minutes after the hypoxic insult.
• Caution must be taken with DWI and ‘pseudonormalisation’ of signal abnormality at approximately 7-10 days.
• Our institution undertakes early MRI within 6 days from the onset of clinical signs of encephalopathy with initial emphasis on DWI/ADC and MRS.
• Follow up imaging after 12-14 days is often helpful to establish the full extent of injury on classical T1/T2 imaging and provide further information for prognostication, parental counselling and long term care planning.

Images for this section:

Case 1. Normal term neonate

Normal term (39 weeks) neonate.

Expected term myelination with T1 high signal in the PLIC (1a) on T1IR with correlate T2 low signal (1c). Also note normal appearance T1 high signal in the peri-rolandic cortex (1b) of a term neonate. In a term infant one third to one half of the PLIC should demonstrate T1 hyperintensity. PLIC high signal is not seen in a preterm infant (<36 weeks).

Fig. 9
Fig. 10

Neonatal Neuroimaging

This imaging pathway guideline serves as a basic introduction to neuroimaging in the neonatal period and is not a substitute for specialist radiology opinion.

Gestational Age at Birth

Preterm <36 weeks

Screening

Neonatal Encephalopathy (NE) of the premature (<36 weeks)

ULTRASOUND
- Cranial US in first 7-14 days
- <30 weeks - ALL neonates
- 36-36 weeks - sick neonates

- Periventricular Leukomalacia (PVL)
- Germinol Matrix Hemorrhage (GMH)

ULTRASOUND Serial Bedside Cranial USS

Inconclusive USS findings
- OR
- Unexplained Clinical Findings
- OR
- Severe PVL/White matter disease
- Large intracranial haemorrhage

ULTRASOUND Progress Cranial USS at term equivalent age (36-40 weeks)
- Interval follow up USS if clinically indicated

Term >36 weeks

Screening

Neonatal Encephalopathy (NE)

If there is concern of Hypoxic-ischemic Encephalopathy (HIE) then a thorough obstetric history is required:
- Acute/remote near term sentinel event?
- Prolonged/partial asphyxia?
- Biochemical correlation with pH, Hb etc.
- Clinical HIE staging features

History of Birth Trauma or Coagulopathy?

CT
- Intracranial haemorrhage
- Basal Ganglia Thalamic hypodensity

HIE Stage I/II?

MRI
- Ax/T1/2 Ax/T2
- MR spectroscopy
- DWI/ADC
- +/- MRA/MRV & SWI (BOLD)

Inconclusive CT findings
- OR
- Unexplained Clinical Findings

Early MRI 0-6 days
- Preferably performed within 6 days of clinical onset of neonatal encephalopathy

Late MRI >10-14 days
- Follow up MRI if clinically indicated

Early MRI
- +/− MRA/MRV
- +/- GRE susceptibility

T1/T2 weighted imaging

The Royal Australian and New Zealand College of Radiologists | www.ranzcr.edu.au
Personal Information

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