IMAGING OF HYPOXIC ISCHEMIC INJURY IN A NEONATE

FN3 STATE MEETING

NEMOURS CHILDREN'S HOSPITAL ORLANDO,FL

08/04/18

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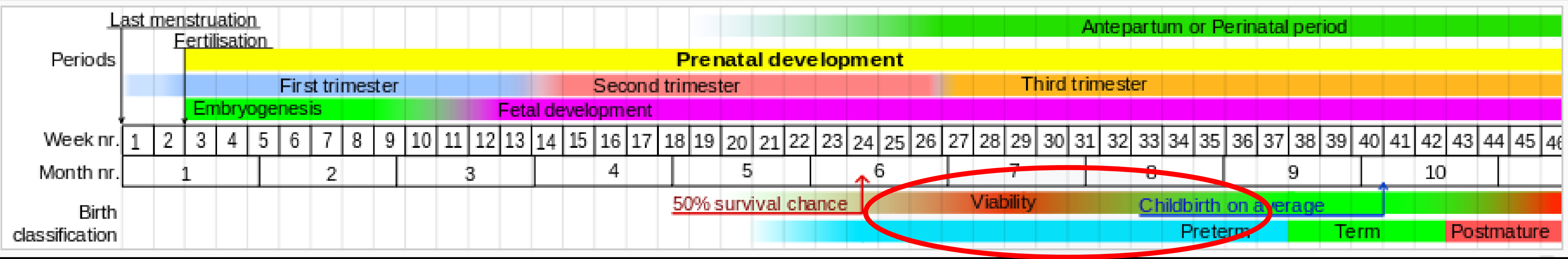
OBJECTIVES:

- To discuss the role of Imaging in the neonates suspected top have Hypoxic Ischemic injury
- To assess imaging patterns in neonates with hypoxic-ischemic injury in term versus premature infants
- To discuss the technical aspects of obtaining the ideal imaging in the patients with suspected HIE



Last menstruation
Fertilisation
Periods
Antepartum or Perinatal period
Prenatal development
First trimester
Second trimester
Third trimester
Embryogenesis
Fetal development
Week nr.
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45
Month nr.
1 2 3 4 5 6 7 8 9 10
Birth classification
50% survival chance
Viability
Childbirth on average
Preterm
Term
Postmature

HEAD US: INDICATIONS-PREMATURE INFANTS

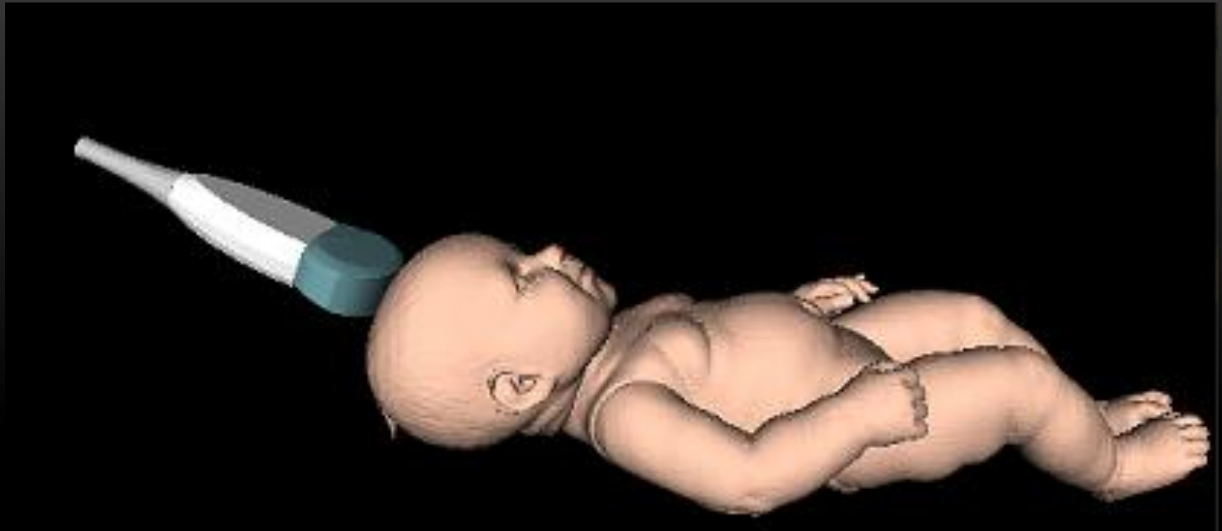
- To detect
  - Intracranial hemorrhage
  - Periventricular leukomalacia/ischemia
  - Hydrocephalus
  - Extra-axial fluid collections

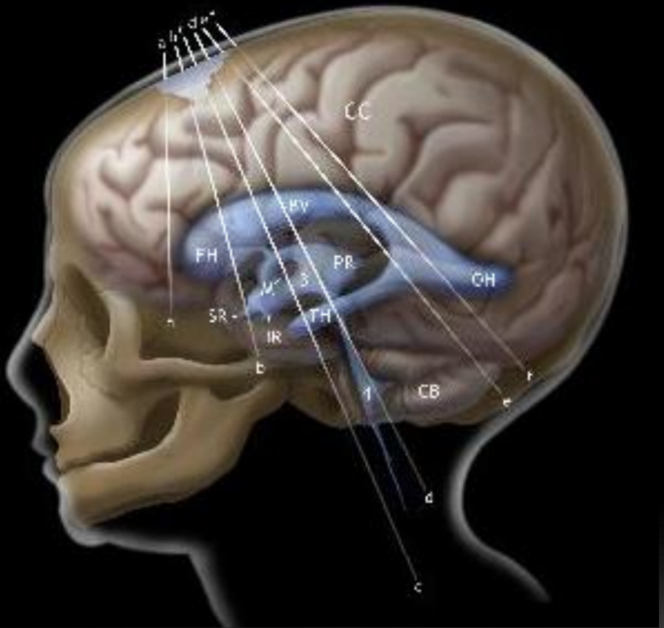
HEAD US: INDICATIONS-PREMATURE INFANTS

- **To follow**
  - Intracranial hemorrhage, hydrocephalus, extra-axial fluid collections
- Usually at day 7 ….
- Day 1-PENUT, Seizures, decreased hematocrit, changes in neurologic status, bradycardia
- < 32 weeks or < 1500 g

HEAD US:TECHNIQUE

- Transducers - 7-13 MHz for extraaxial fluid, dura,
  meninges, convexities
  - 3.5-6MHz for posterior fossa, entire
  brain
- Anterior fontanelle - large enough up to 6 months(closes 9-15 mths)
- Posterior fontanelle - posterior fossa
- Mastoid fontanelle - posterior lateral(open until 2 yrs)

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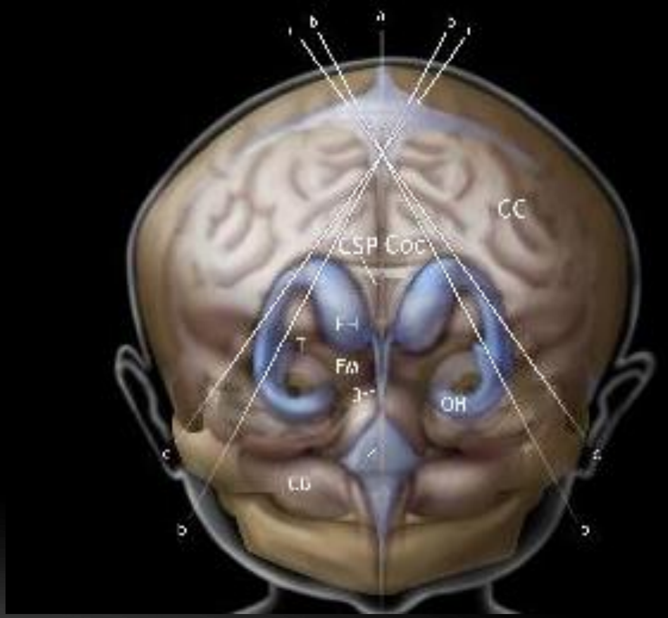
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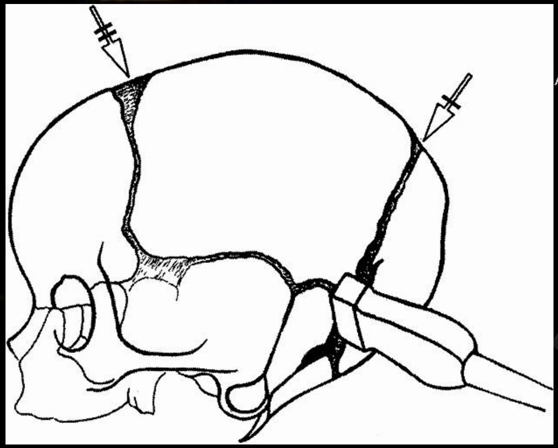



PATIENT IMAGING-MRI

- Right preparation
- Imaging parameters
- Safety- Team, Suction pump,O2 supply,Laryngoscope, devices
- Examination on the day of the study
- Swaddling-Feed and wrap technique
- Scan on side
- Adult knee coil

MRI

- Neonates’ vital signs are prone to fluctuate, and several parameters must be closely monitored
- STABLE- sugar, temperature, artificial breathing, blood pressure, and laboratory test results
- ***High-quality coronal diffusion-weighted images also can be obtained- neonates lack pneumatized paranasal sinuses***

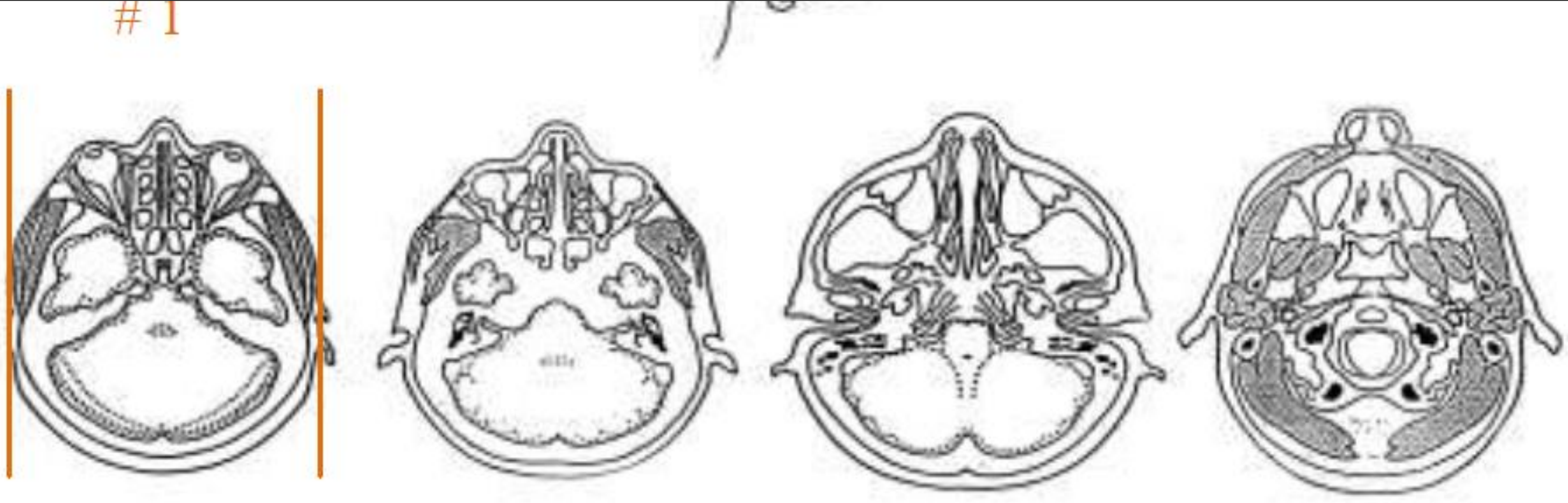
19 MIN PROTOCOL

Protocol for MR Evaluation of Neonatal Encephalopathy

Priority of Sequence	Type of Sequence	Acquisition Time
1	Diffusion-weighted imaging	45 sec
2	T1-weighted imaging	4 min 35 sec
3	T2-weighted imaging	3 min 17 sec
4	T2*-weighted imaging	3 min 47 sec
5	MR spectroscopy	5 min 38 sec

RadioGraphics 2010; 30:763–780

1



Indications

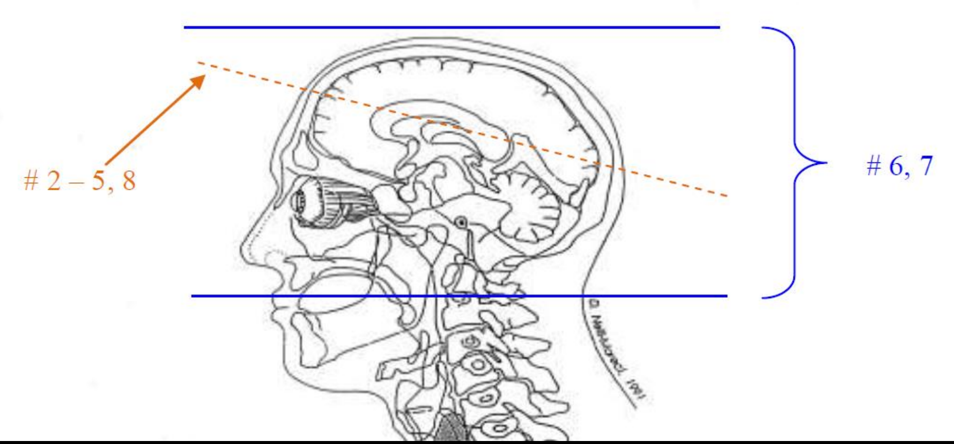
Periventricular leukomalacia (PVL)
Intraventricular hemorrhage (IVH)
Prematurity
Neonatal hypoxic ischemic encephalopathy (HEI)

MR Brain Neonatal Screen without IV Contrast

Acquisition	1	2	3	4	5	6*	7*	8
Plane	Sagittal	Axial	Axial	Axial	Axial	Axial	Axial	Axial
Sequence	T1	FLAIR FS	T1	T2	SWI/GRE	MDDW	3D MPRAGE	DWI
Contrast								
SLT / SP	4 / 1 mm	4 / 1 mm	4 / 1 mm	4 / 1 mm	4 / 1 mm	2 mm	1.5 mm	4 / 1 mm
FOV	16 cm	16 cm	16 cm	16 cm	16 cm	240 mm	256 mm	16 cm

SPECIAL INSTRUCTIONS:

*Do Not Angle / whole head



MR Brain Neonatal HIE without IV Contrast

Acquisition	1	2	3	4	5*	6*	7**
Plane	Axial	Axial	Axial	Axial	Axial	Axial	Loc
Sequence	T1	T2	SWI/GRE	DWI / ADC	3D MP RAGE	MDDW	mMRS
Contrast							
SLT / SP	4 / 1 mm	4 / 1 mm	4 / 1 mm	4 / 1 mm	1.5 mm	2 mm	N/A
FOV	16 cm	16 cm	16 cm	16 cm	256 mm	24 cm	N/A

SPECIAL INSTRUCTIONS:
For neonatal brains, post warming protocol
*** Do NOT angle volume slab.**
** Place slab for multi-voxel MRS in right or left basal ganglia region. Voxel volume has to be > 2.5 cc.

Indications
Suspected neonatal HIE
Neuro protective cooling

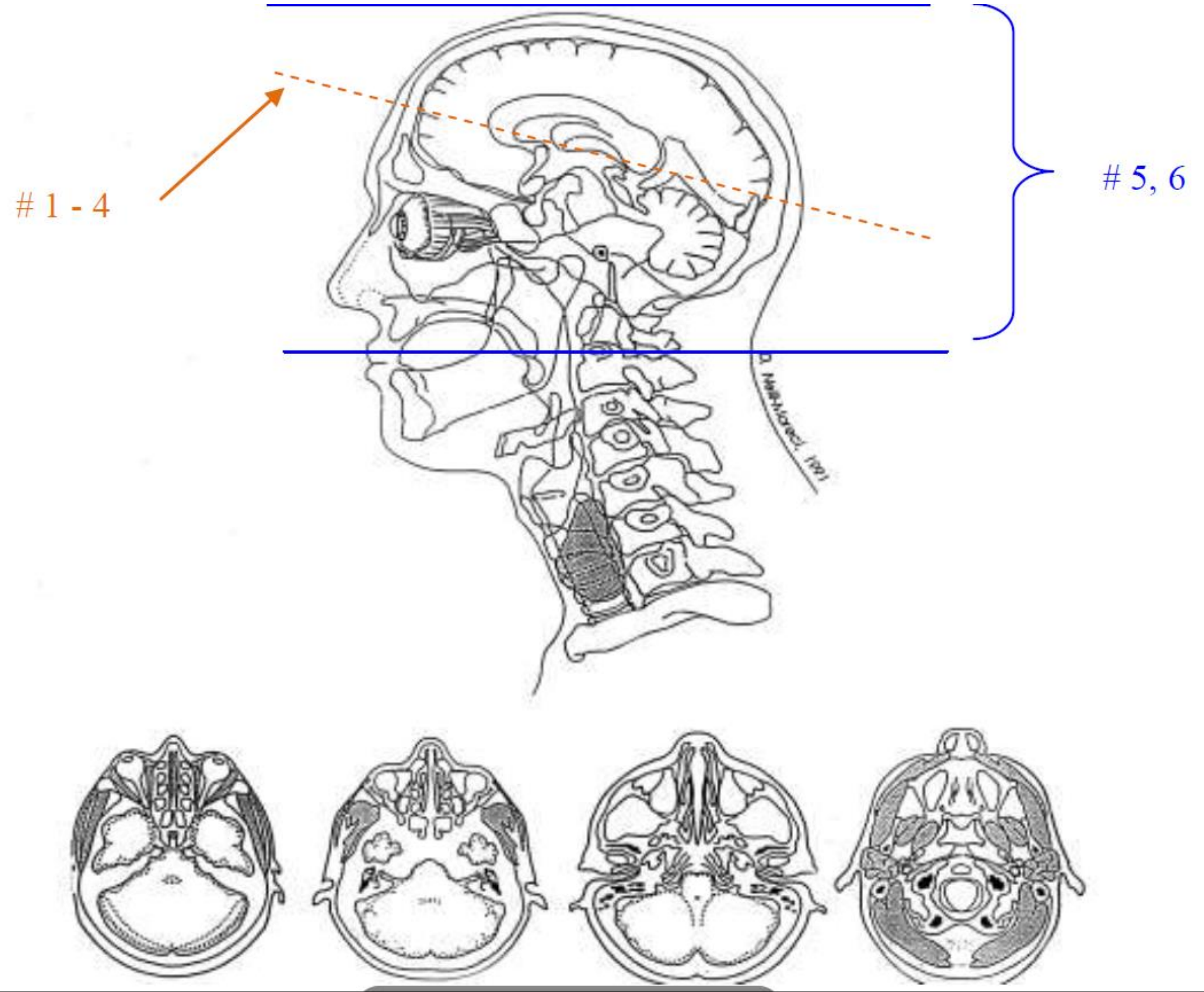
FLAIR-Poor due to high water content
Imaging best -1-2 week
Diffusion-False negative < 24 hrs
Pseudonormalize- 6 day

SPECIAL INSTRUCTIONS:

For neonatal brains, post warming protocol

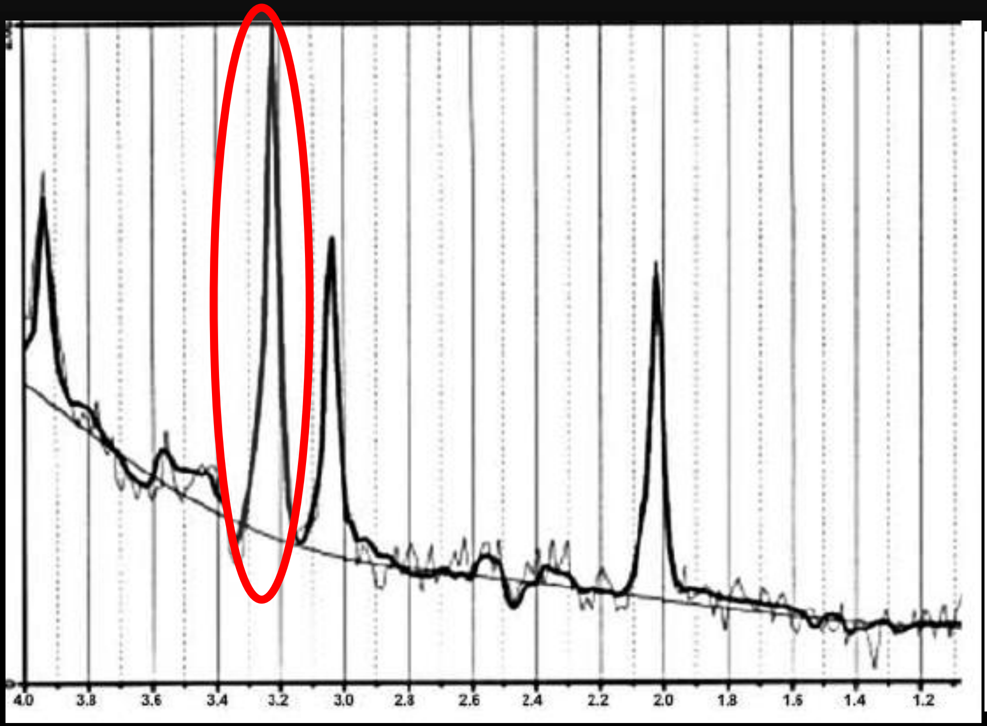
*** Do NOT angle volume slab.**

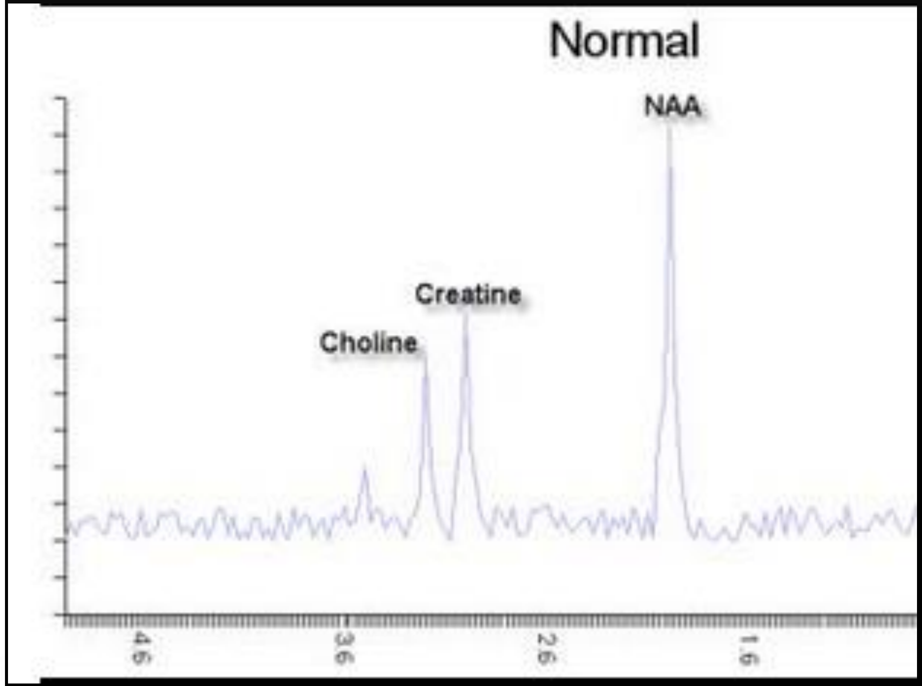
** Place slab for multi-voxel MRS in right or left basal ganglia region. Voxel volume has to be > 2.5 cc.



NORMAL MRS IN A TERM INFANT

NORMAL MRS IN AN ADULT

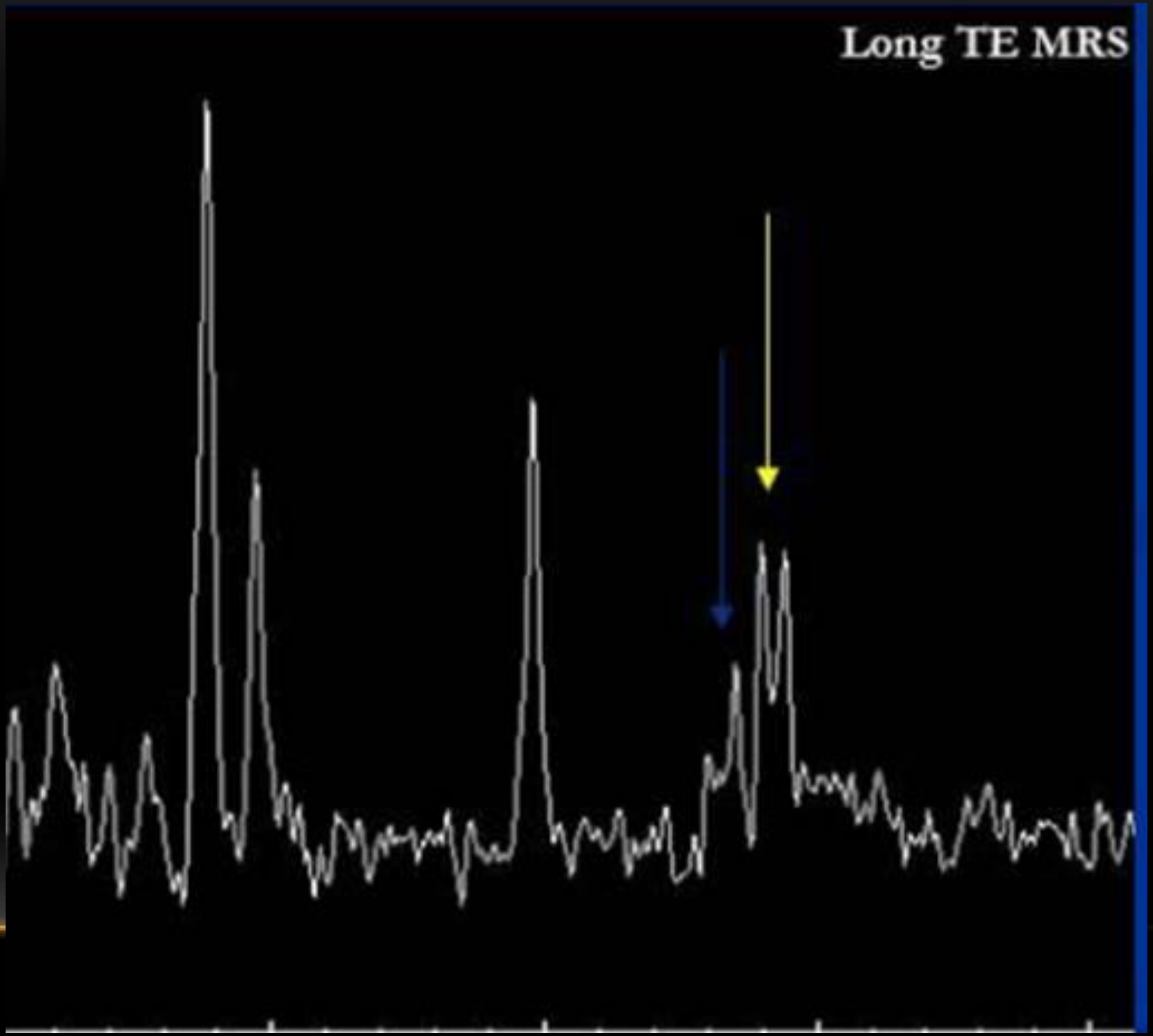




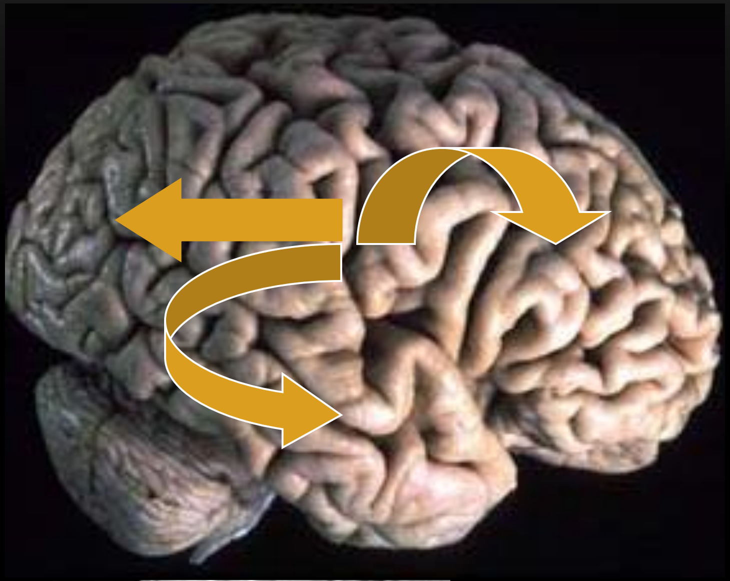
RadioGraphics 2010; 30:763–780

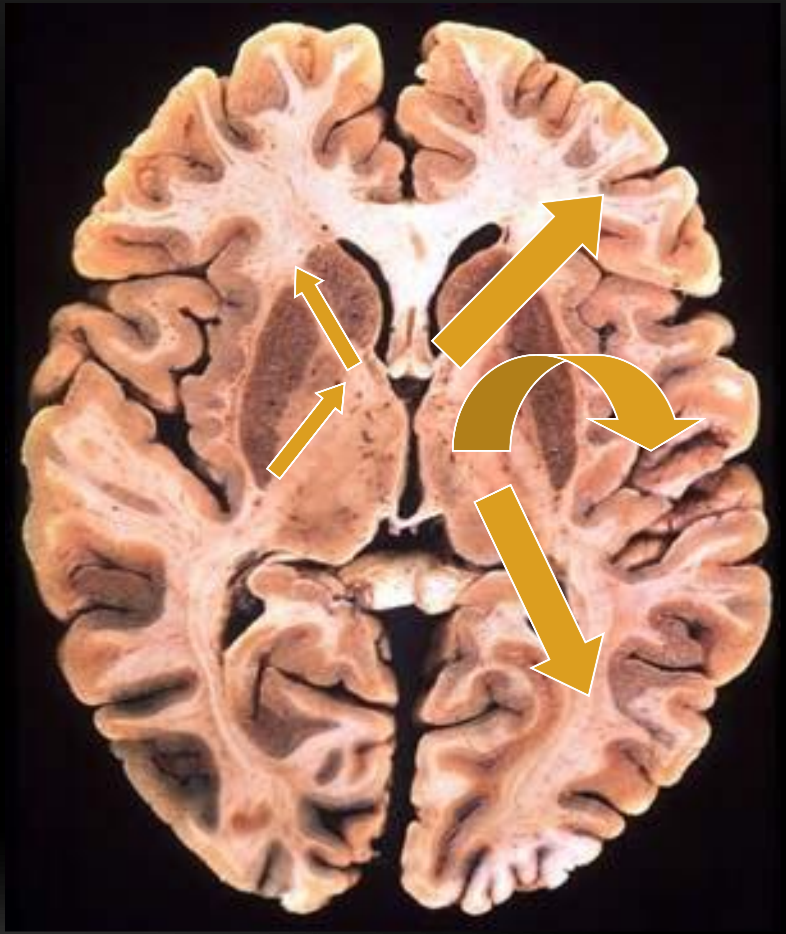
Premie MRSpectroscopy

Varies
Preterm may contain lactate



PROGRESSION OF MYELINATION

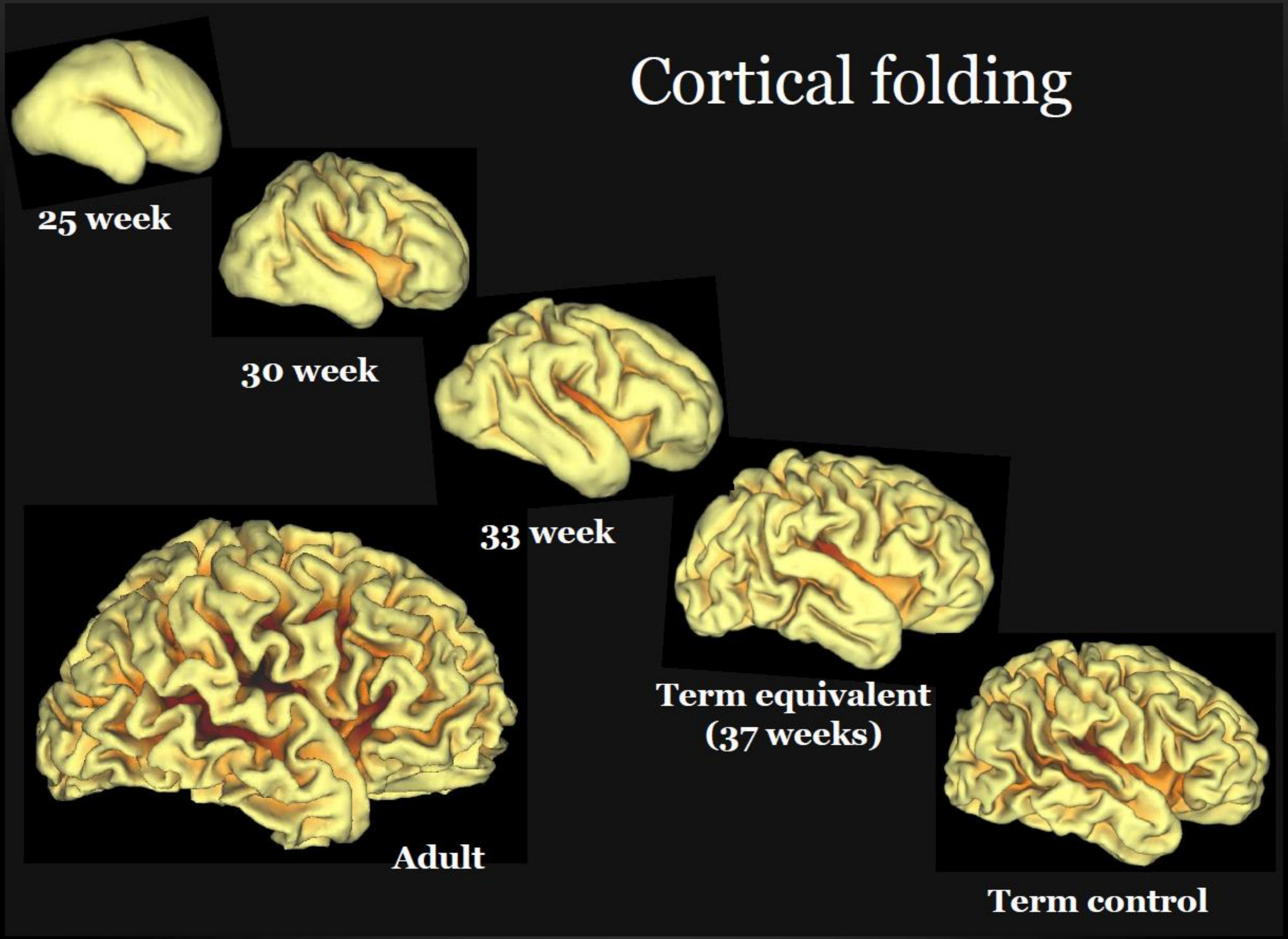




Rostral to caudal; Posterior to anterior; Central to peripheral

Myelination

- 20 weeks-Pons,Post medulla
- 29 weeks-Sup and Inf cerebellar peduncles
- 32 weeks-Midbrain
- 33 weeks-Inferior colliculi, lateral putamen,ventrolateral thalami
- 35 weeks-Post limb of Internal capsule
- 35 weeks-2 mths- Optic tracts,medial temporal lobes,perirolandic fissures,calcarine,central white matter,rest of the basal ganglia

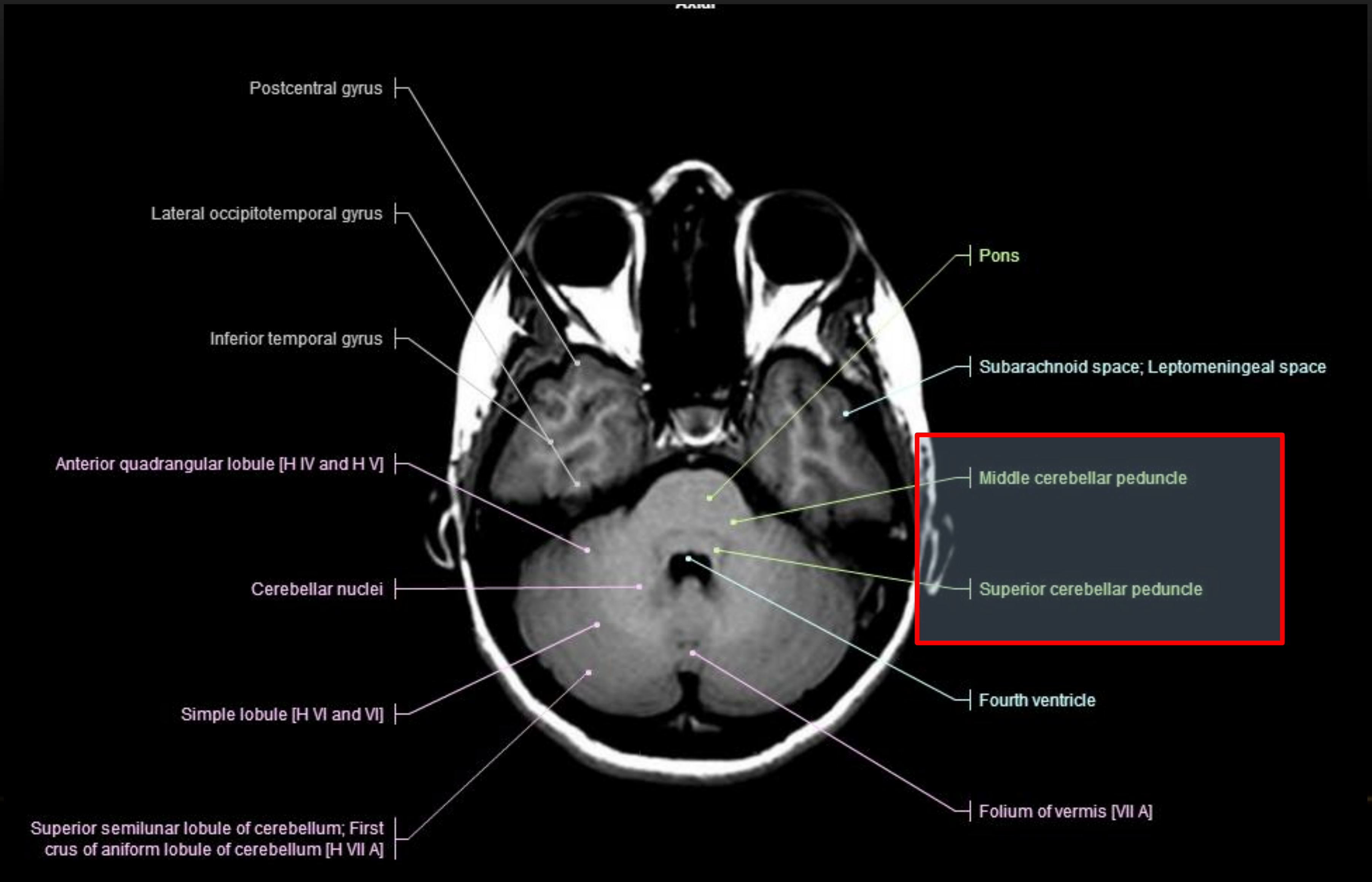


Courtesy: Dr. Robert McKinstry

Sulcation

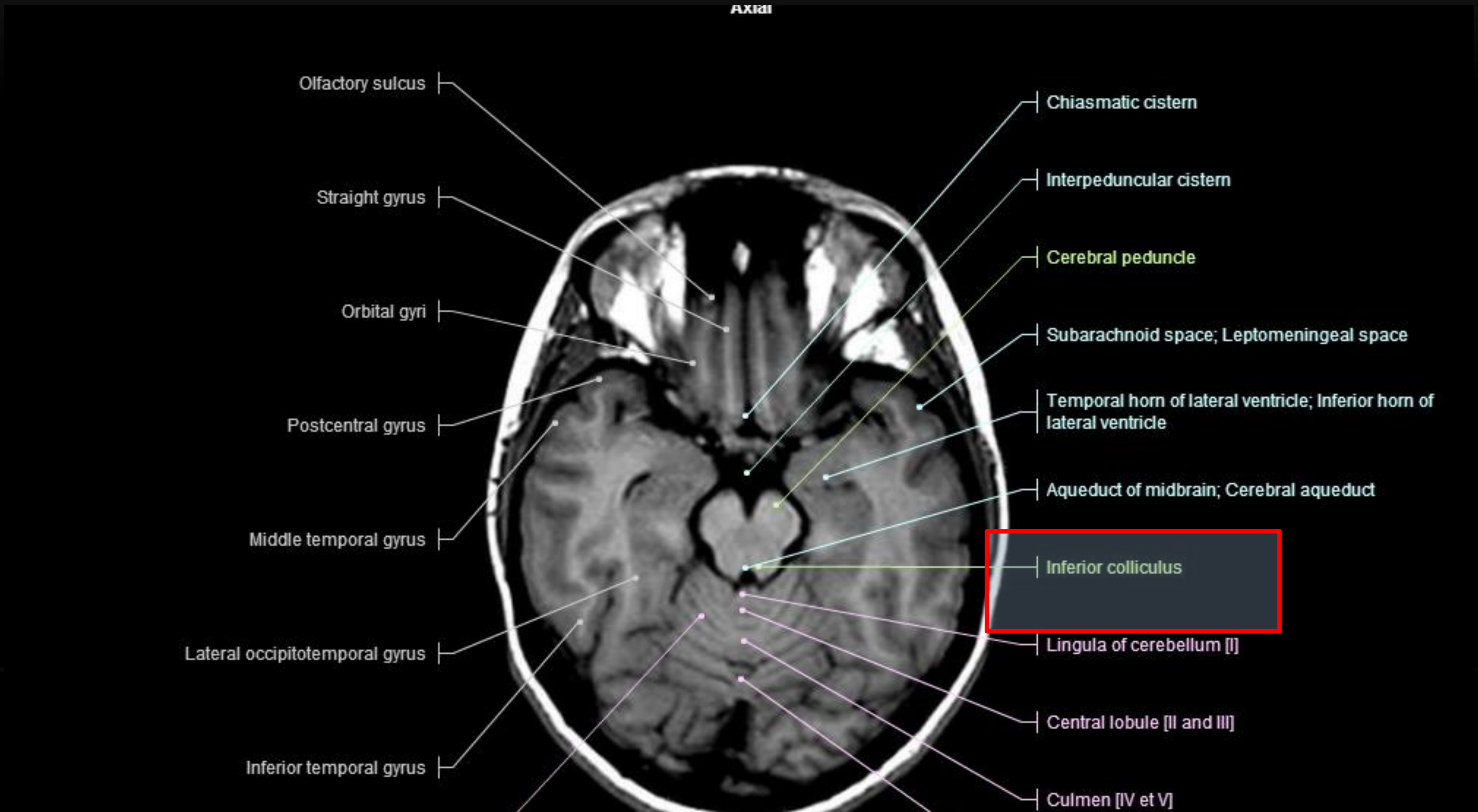
- 16 weeks-Interhemispheric and sylvian
- 22 weeks-Parietooccipital, Hippocampal,Callosal
- 23-24 weeks- Calcarine
- 24 weeks-Cingulate
- 26 weeks-Central
- 27-Precentral,Superior temporal,marginal
- 28 weeks-Post central
- 29 weeks-Superior frontal,Inferior frontal
- 33 weeks-Inferior temporal

29 WEEKS



Postcentral gyrus
Lateral occipitotemporal gyrus
Inferior temporal gyrus
Anterior quadrangular lobule [H IV and H V]
Cerebellar nuclei
Simple lobule [H VI and VI]
Superior semilunar lobule of cerebellum; First crus of aniform lobule of cerebellum [H VII A]
Pons
Subarachnoid space; Leptomeningeal space
Middle cerebellar peduncle
Superior cerebellar peduncle
Fourth ventricle
Folium of vermis [VII A]

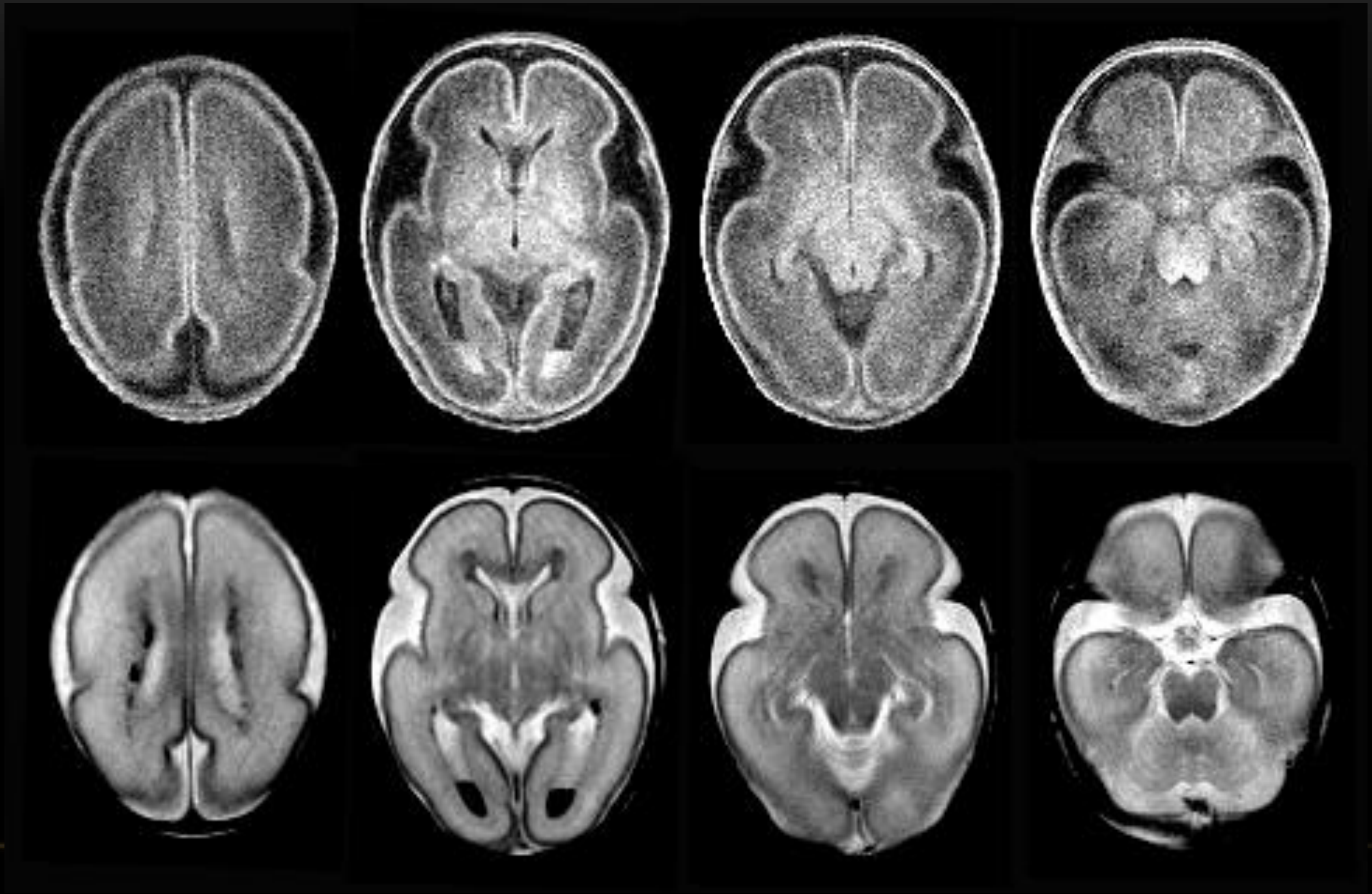
33 WEEKS


Axial
Olfactory sulcus
Straight gyrus
Orbital gyri
Postcentral gyrus
Middle temporal gyrus
Lateral occipitotemporal gyrus
Inferior temporal gyrus
Chiasmatic cistern
Interpeduncular cistern
Cerebral peduncle
Subarachnoid space; Leptomeningeal space
Temporal horn of lateral ventricle; Inferior horn of lateral ventricle
Aqueduct of midbrain; Cerebral aqueduct
Inferior colliculus
Lingula of cerebellum [I]
Central lobule [II and III]
Culmen [IV et V]

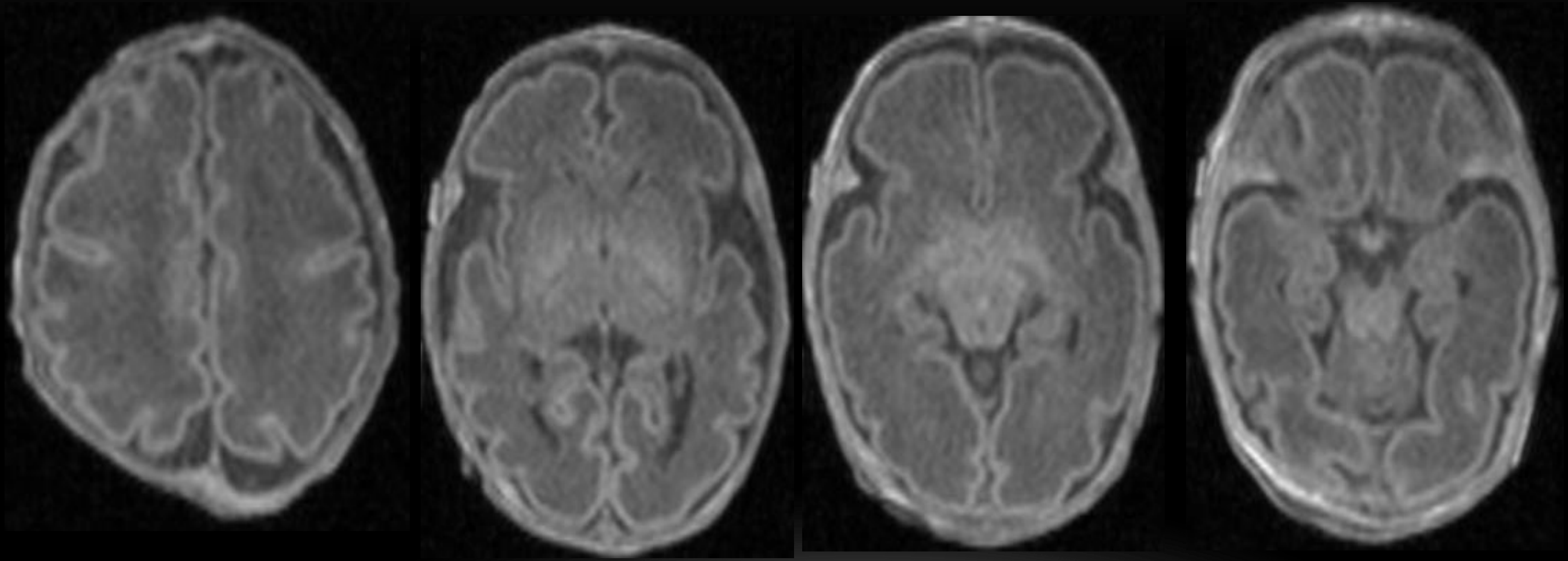
PRE-TERM (26 WKS)

T1

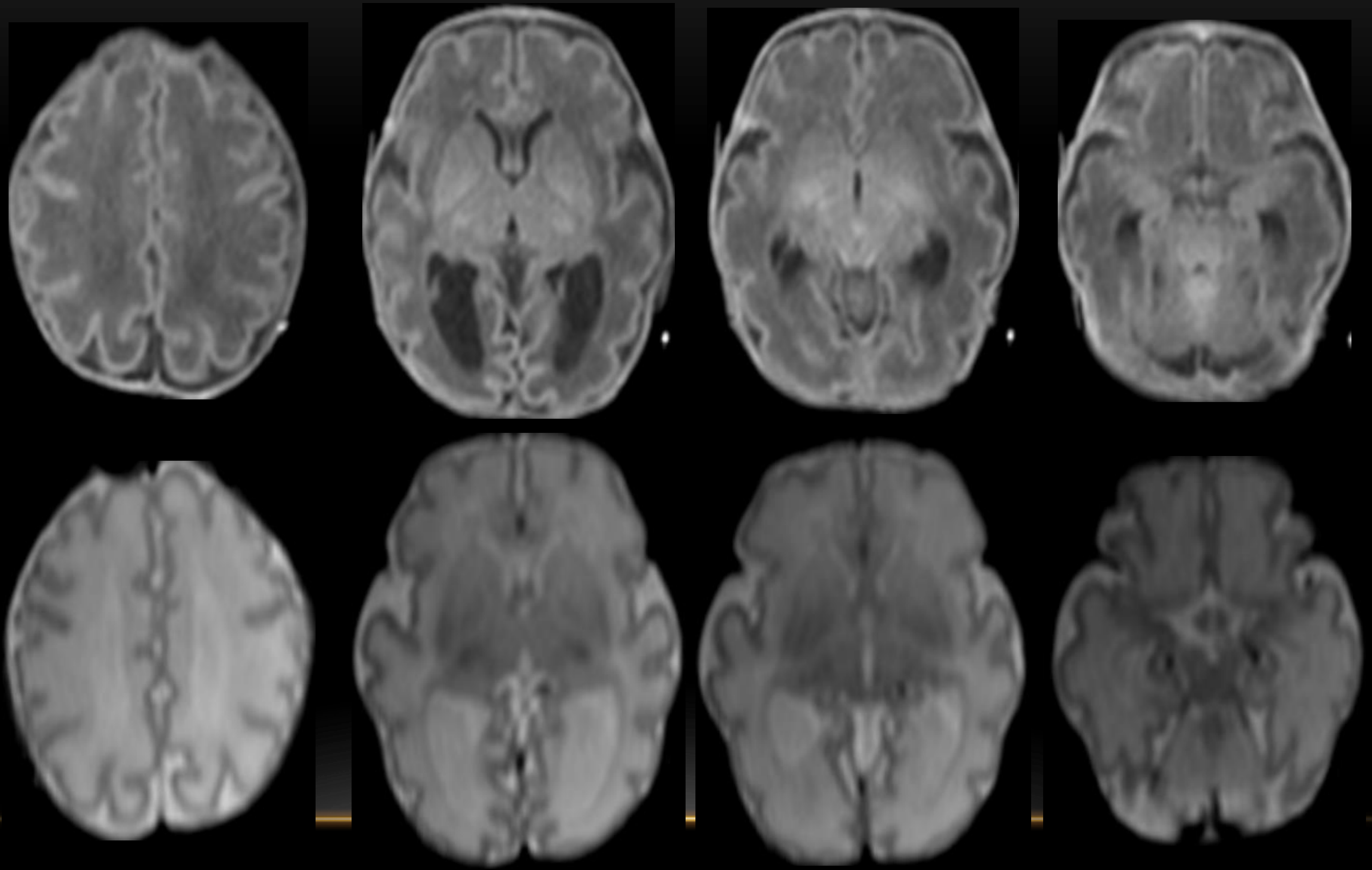
T2



PRE-TERM (30-WEEK)



34-WEEK PRETERM INFANT



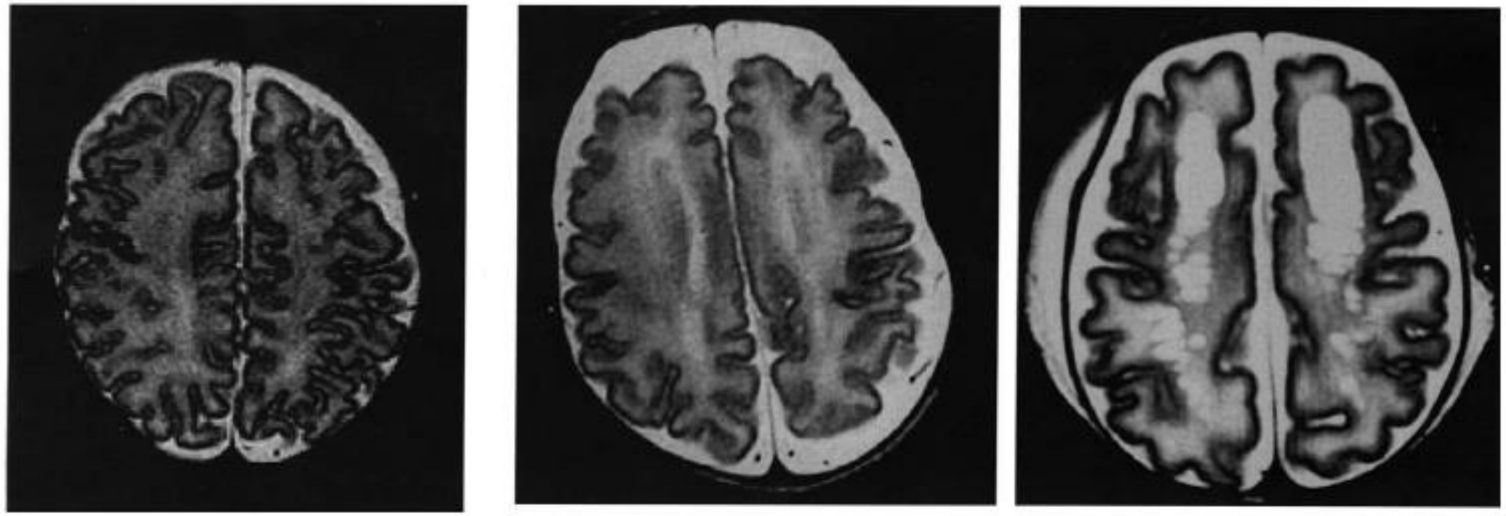
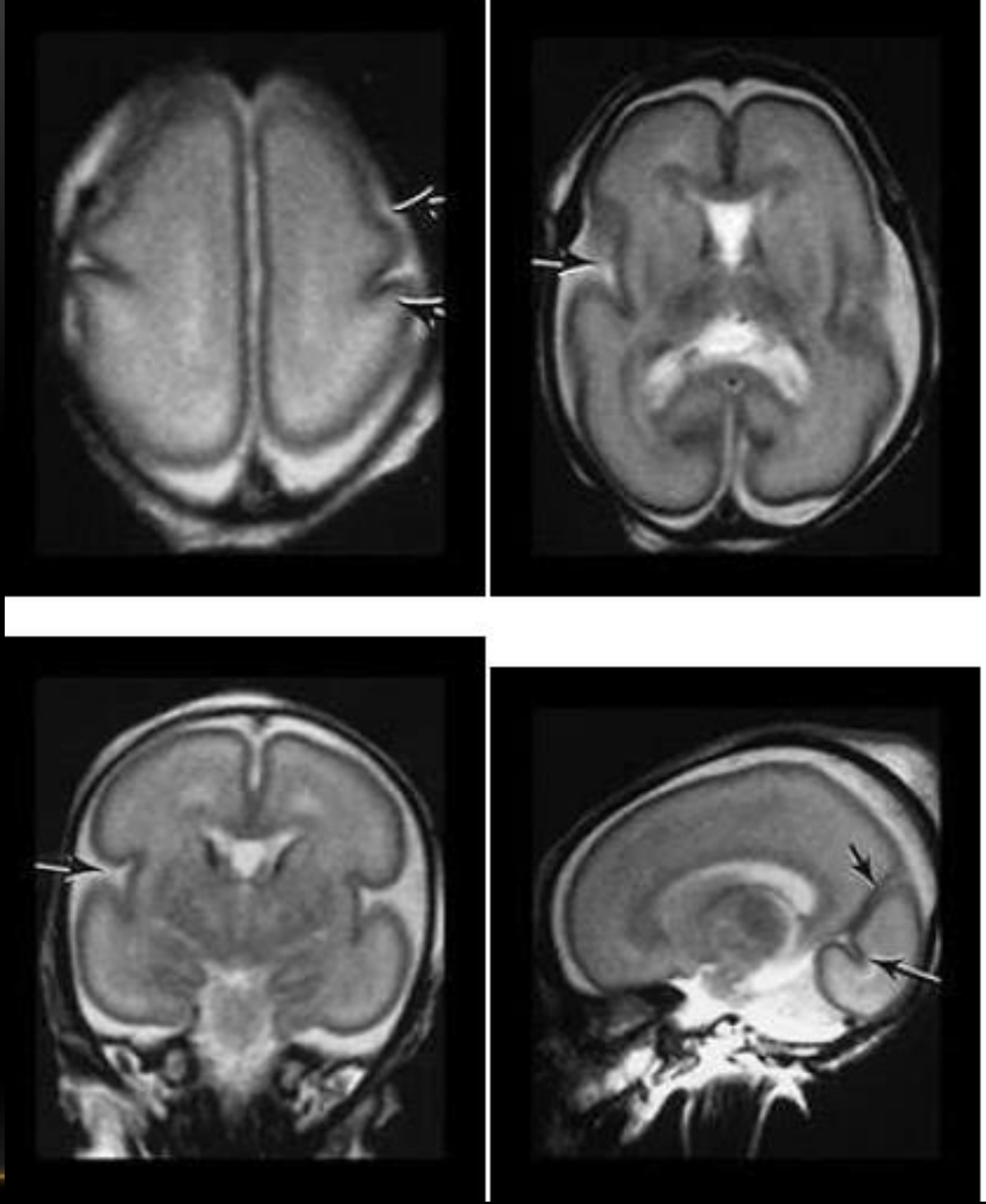


Fig 2. Representative MRI of the three grades of abnormality in gray matter gyral maturation in the premature infants on MRI at term: **A**, grade 1 with normal gyral maturation at term; **B**, grade 2 demonstrating a reduction in complex gyral folding but secondary gyri in the transverse sulci and gyri consistent with 36 to 37 weeks' gestational age; and **C**, grade 3 demonstrating severe impairment in gyral development in all regions consistent with 34 weeks' gestational age.

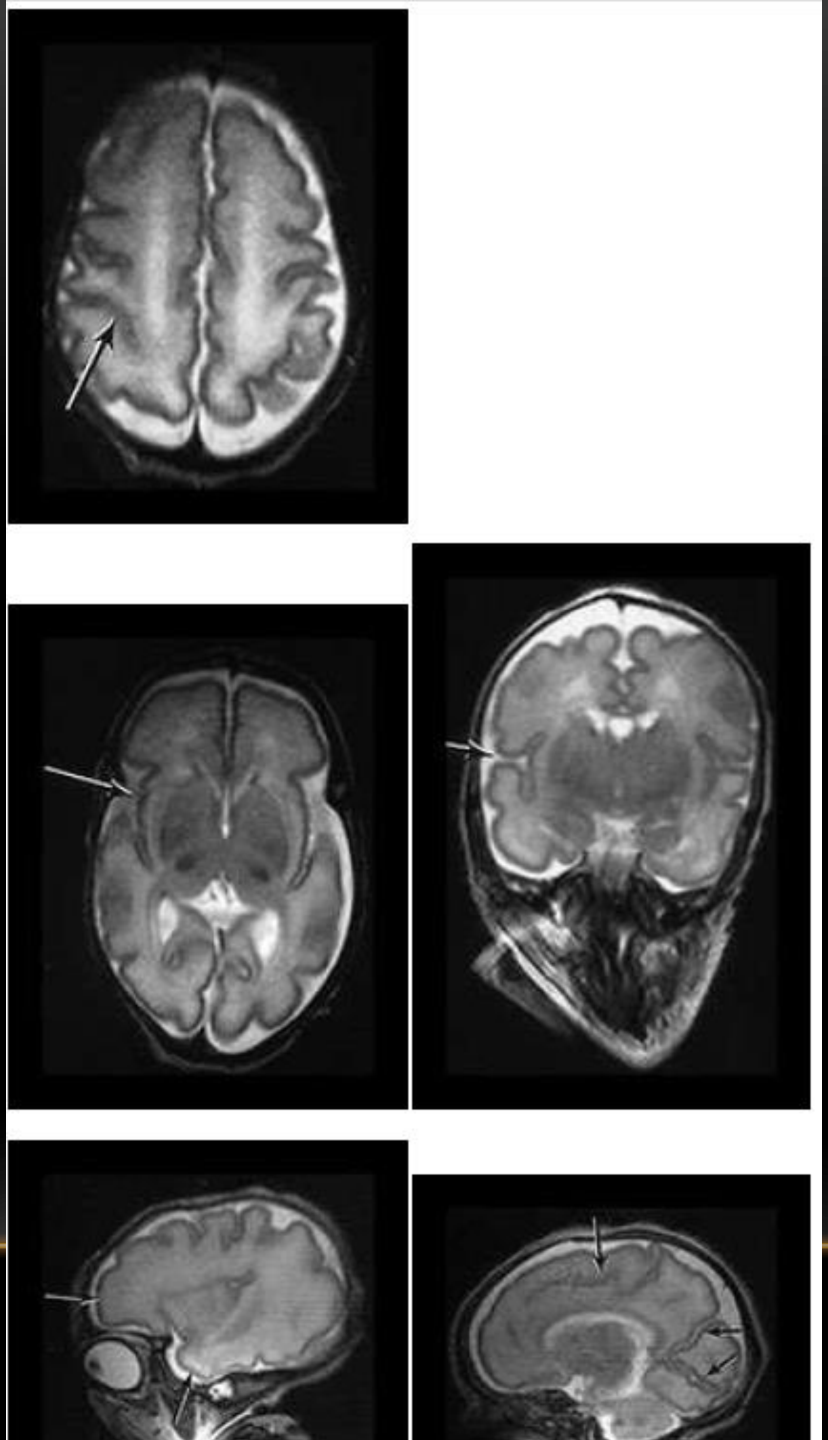
(J Pediatr 2003;143:171-9)

26 WK



MRI of the Neonatal Brain - Mary A Rutherford

32 WK



Sulcation

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Sulcation

- 16 weeks-Interhemispheric and sylvian
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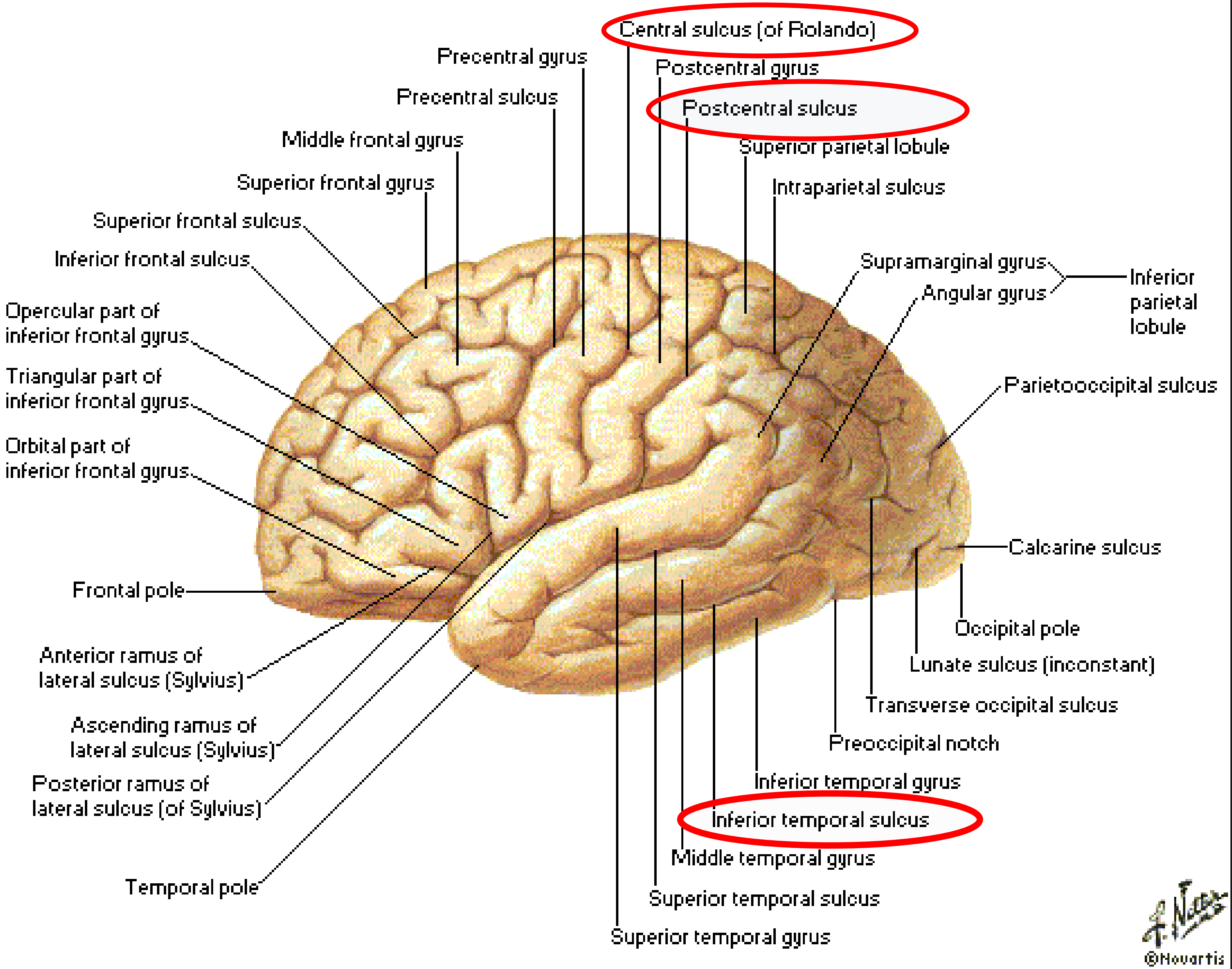
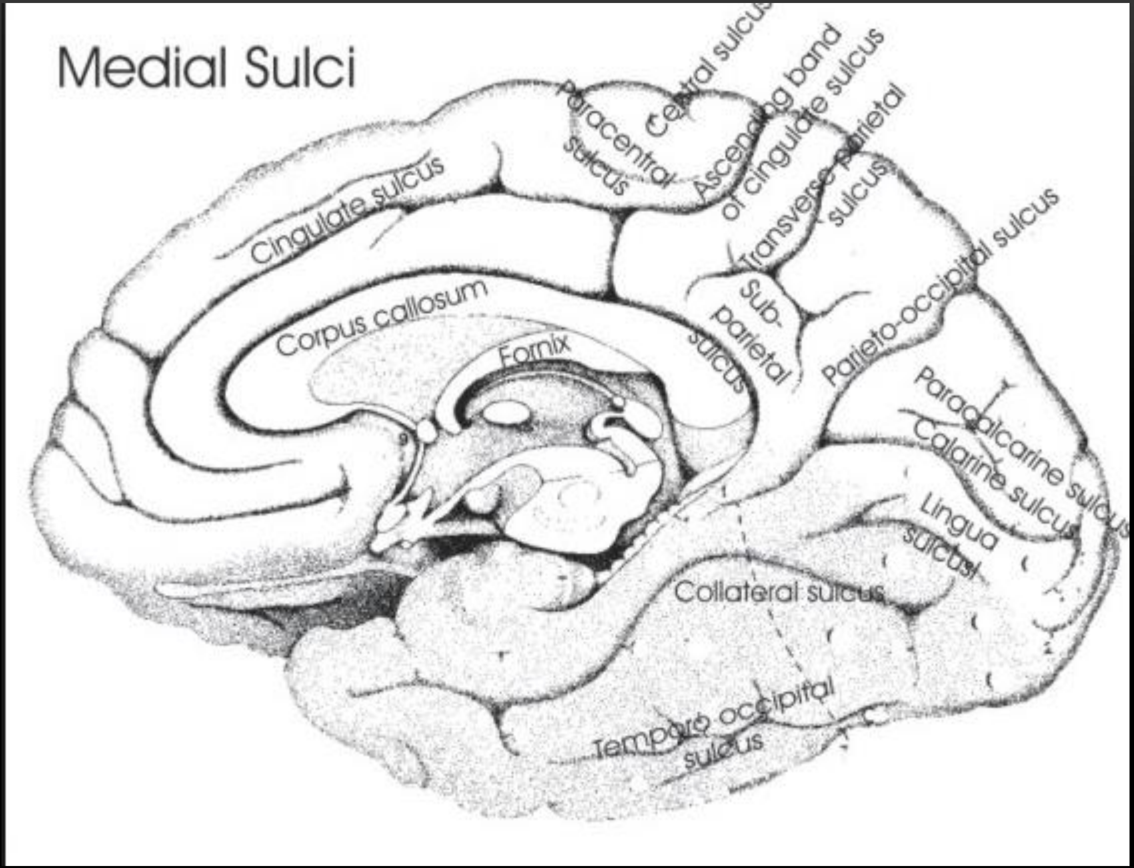
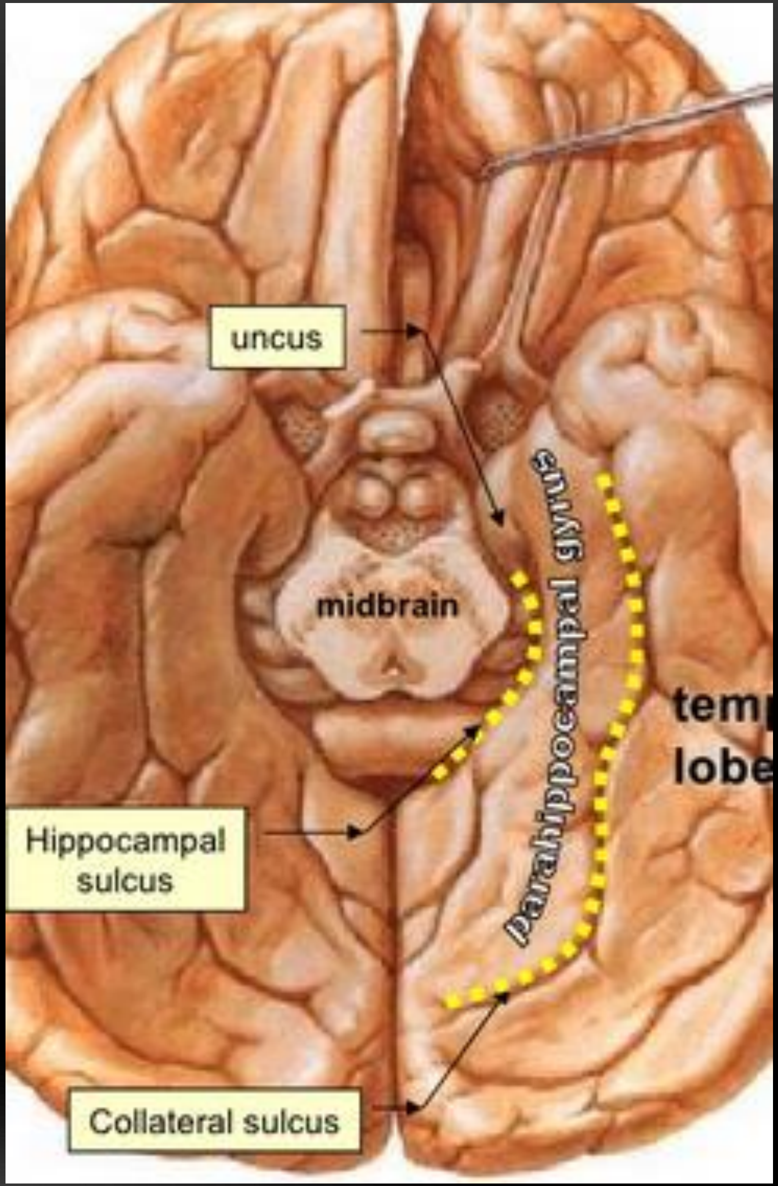
Cerebrum

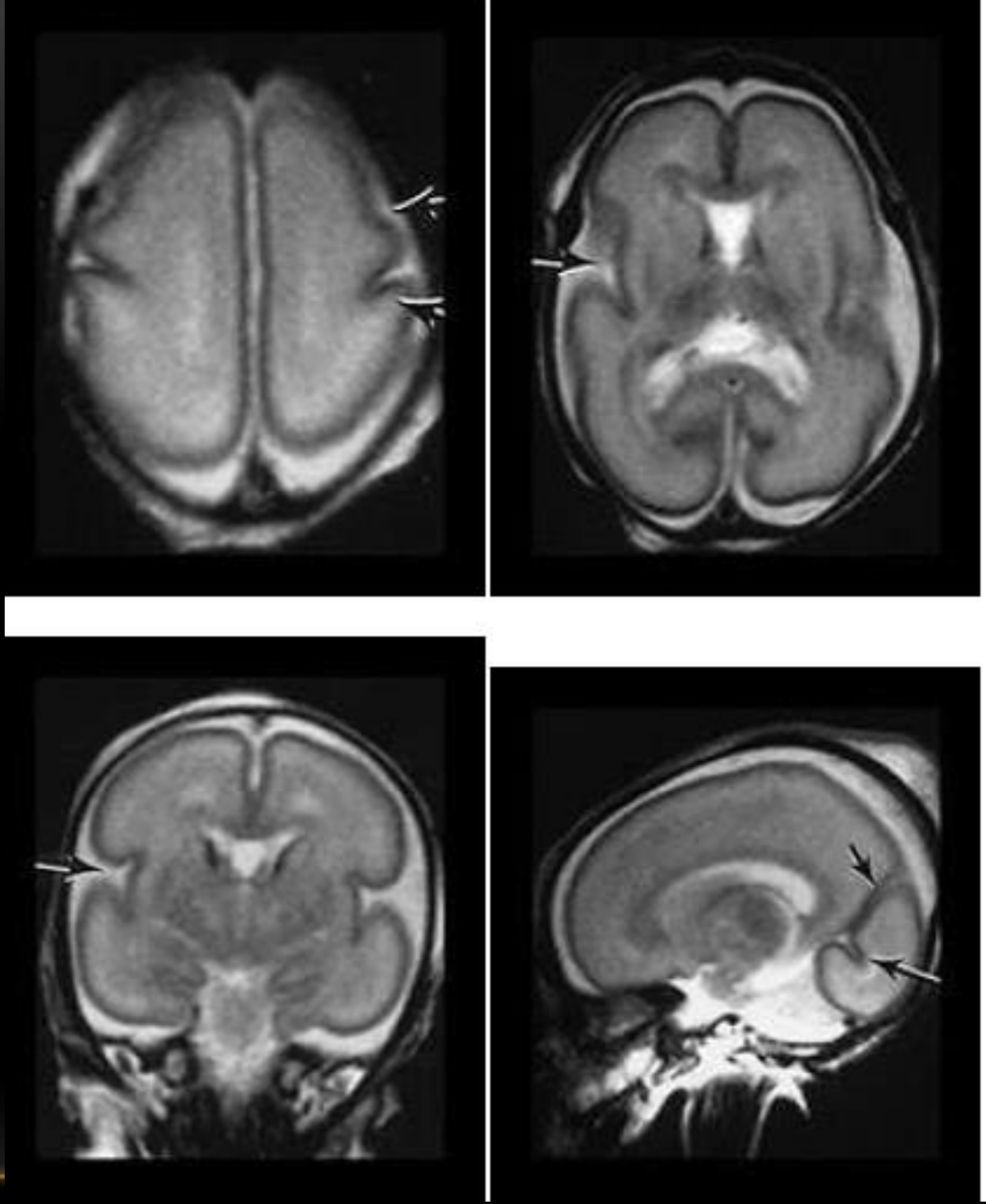
Lateral View




Medial Sulci
Central sulcus
Paracentral sulcus
Ascending band of cingulate sulcus
Transverse parietal sulcus
Cingulate sulcus
Corpus callosum
Fornix
Sub-parietal sulcus
Parieto-occipital sulcus
Paracalcarine sulcus
Calcarine sulcus
Lingua sulcus
Collateral sulcus
Temporo occipital sulcus

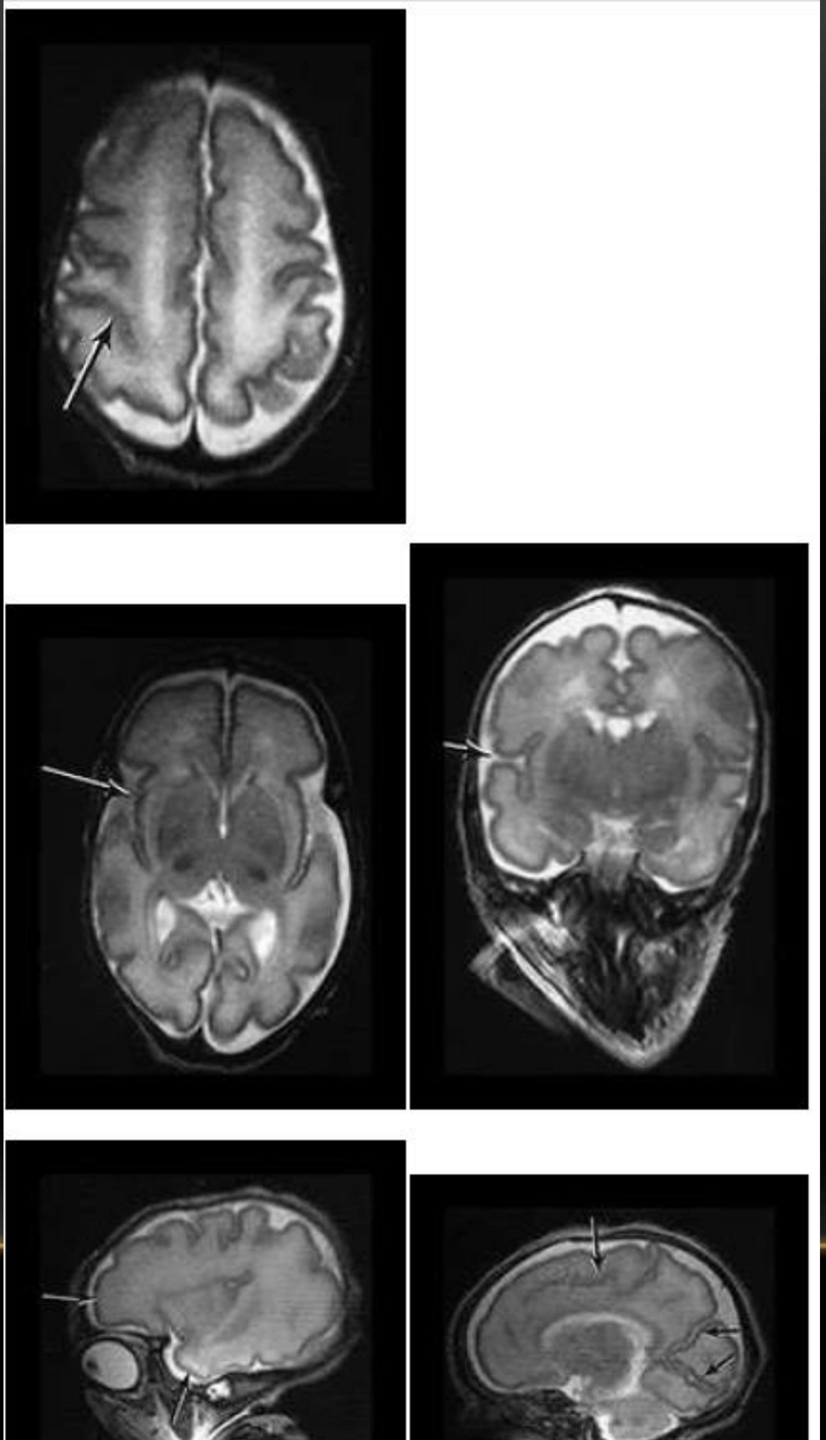

uncus
midbrain
parahippocampal gyrus
Hippocampal sulcus
Collateral sulcus

26 WK



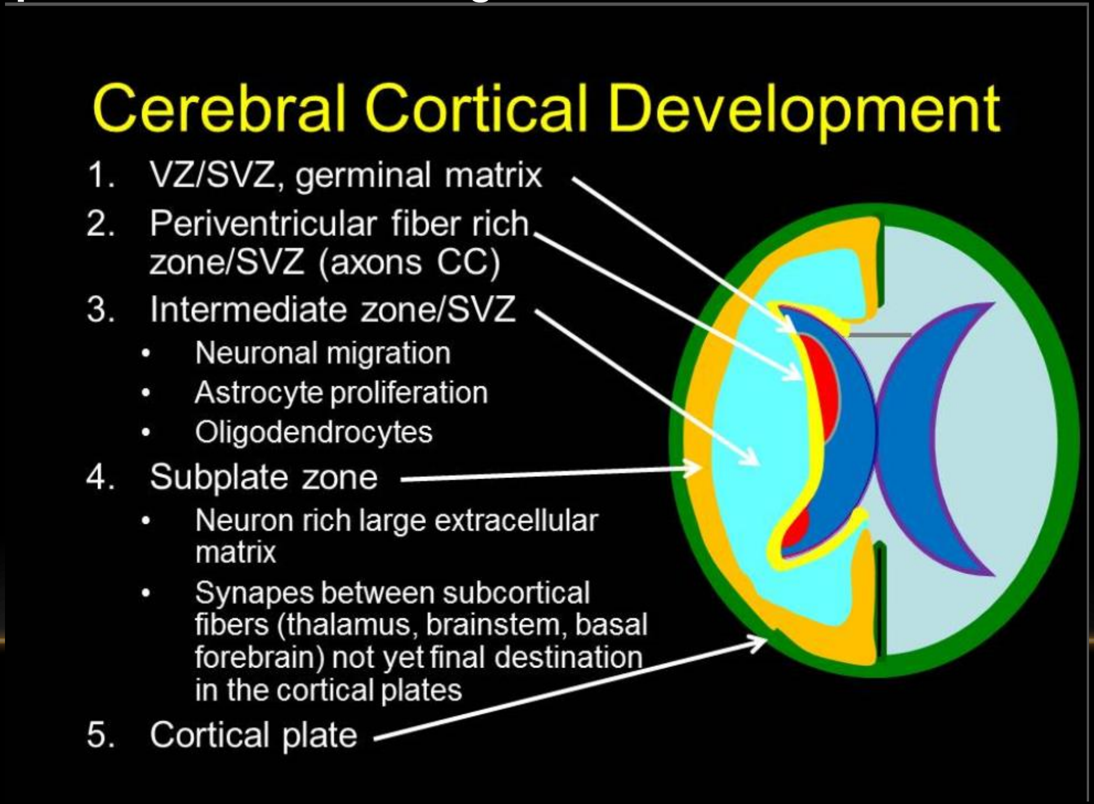
MRI of the Neonatal Brain - Mary A Rutherford

32 WK



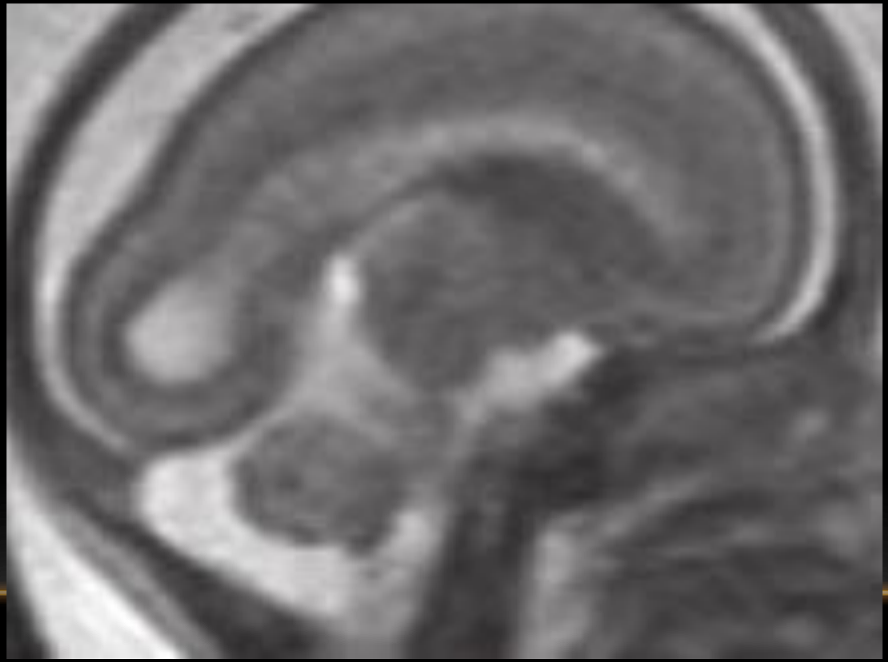
Germinal matrix

- **5-14 wk-Ventricular zone-Ependymal**
- **15-36 wk**
  - **Subependymal, deep WM,Gangilionic eminences-20% cortical,BG,amygdala,hippocampus**
  - **Lateral sparse/dense cellular-glial cells**



Normal preterm MRI

- Germinal matrix-Low on T2,high on T1
- WM-Low TI,high T2
- 20-30 Weeks-Band of low T2 and high T1-Migrating cells
- Crossroads by frontal horns-36 weeks



GMH/IVH

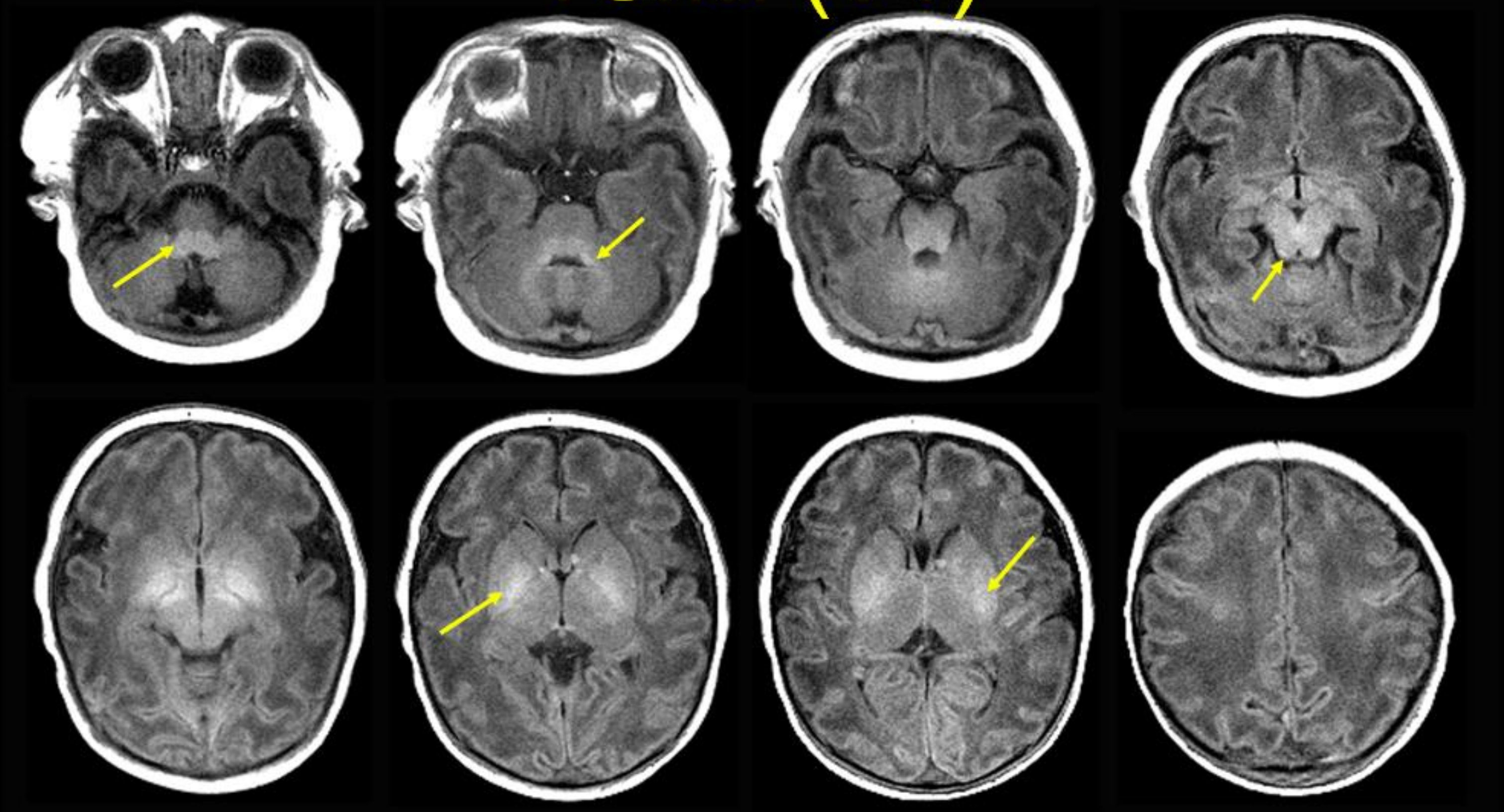
- < 3 days Hypo T1,Marked hypo T2
- 3-7 days-Hyper T1,Hypo T2
- 7 days-months-Hypo to CSF T1,hyper to CSF on T2

Table 1 Evolution of signal intensity in parenchymal haemorrhage[41]

Age of haemorrhage	T1 weighted imaging	T2 weighted imaging
2 days	Not seen/high signal intensity rim	Low signal intensity
3–10 days	Not seen/high signal intensity	Low signal intensity (with high signal intensity periphery)
10–21 days	High signal intensity	High signal intensity
3–6 weeks	High signal intensity	High signal intensity (with low signal intensity periphery)
6 weeks – 10 months	Not seen/minimal high signal intensity	Not seen/low signal intensity
10–22 months	Not seen	Minimal low signal intensity/not seen

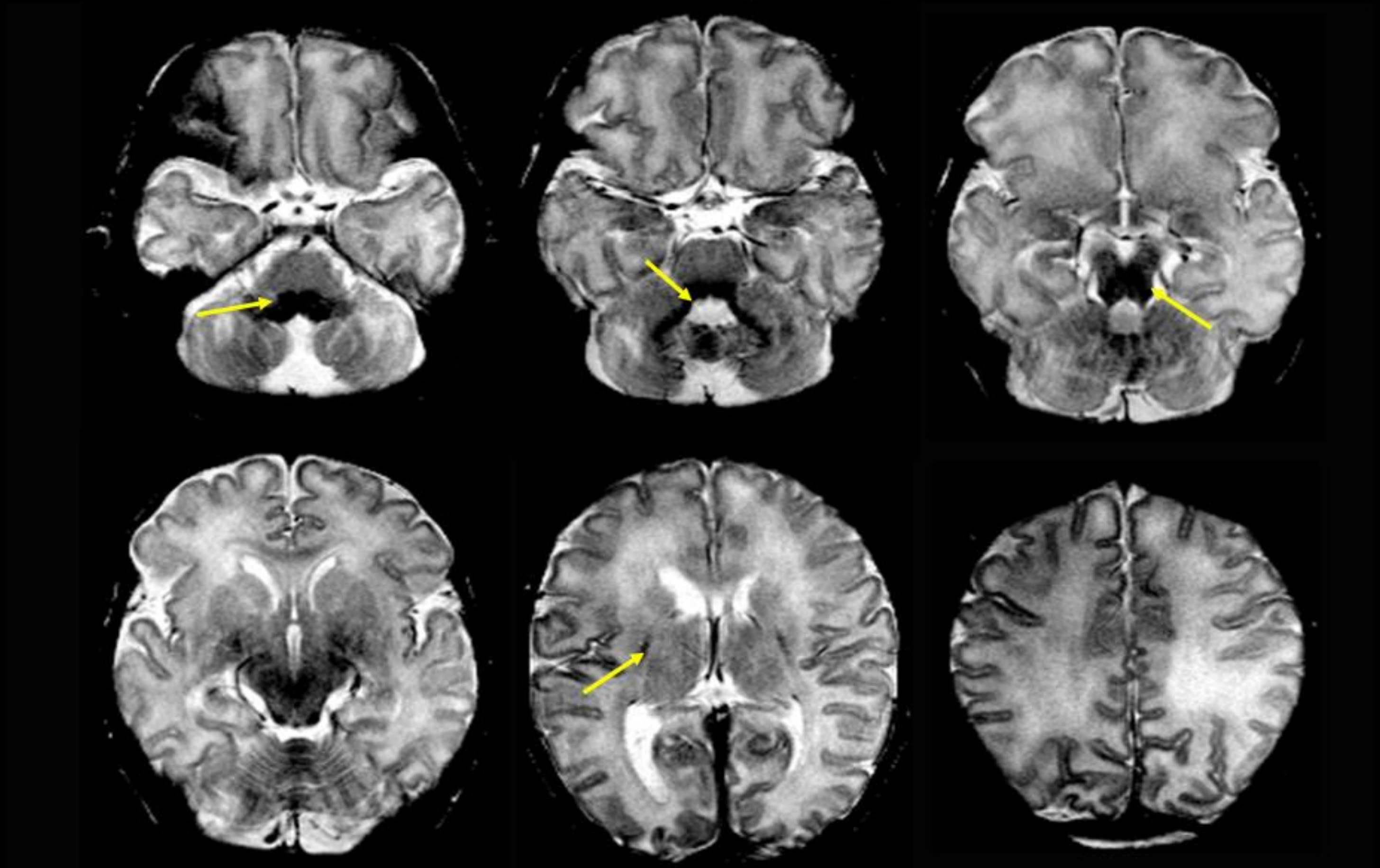
Arch Dis Child Fetal Neonatal Ed 2003;**88**:F269-F274 doi:10.1136/fn.88.4.F269

Term (T1)



Dorsal Medulla   Cerebellar Peduncles   Dorsal Midbrain
Ventrolateral Thalamus   Posterior Limb of Internal Capsule

Term (T2)



Dorsal Medulla Cerebellar Peduncles Dorsal Midbrain
Posterior Limb of Internal Capsule

TABLE 2: Scoring systems

Score	Finding
Basal ganglia (BG)	
0 =	Normal or isolated focal cortical infarct
1 =	Abnormal signal in thalamus
2 =	Abnormal signal in thalamus and lentiform nucleus
3 =	Abnormal signal in thalamus, lentiform nucleus, and perirolandic cortex
4 =	More extensive involvement
Watershed (W)	
0 =	Normal
1 =	Single focal infarction
2 =	Abnormal signal in anterior or posterior watershed white matter
3 =	Abnormal signal in anterior or posterior watershed cortex and white matter
4 =	Abnormal signal in both anterior and posterior watershed zones
5 =	More extensive cortical involvement
Basal ganglia/watershed (BG/W)	
0 =	Normal
1 =	Abnormal signal in basal ganglia or thalamus
2 =	Abnormal signal in cortex
3 =	Abnormal signal in cortex and basal nuclei (basal ganglia or thalami)
4 =	Abnormal signal in entire cortex and basal nuclei
Summation (S)	
Arithmetic sum of BG and W	
Enhancement (E)	
0 =	No enhancement
1 =	Enhancement in white matter only
2 =	Enhancement in deep gray matter nuclei
3 =	Enhancement in cerebral cortex
4 =	Enhancement in cortex and deep gray matter or white matter

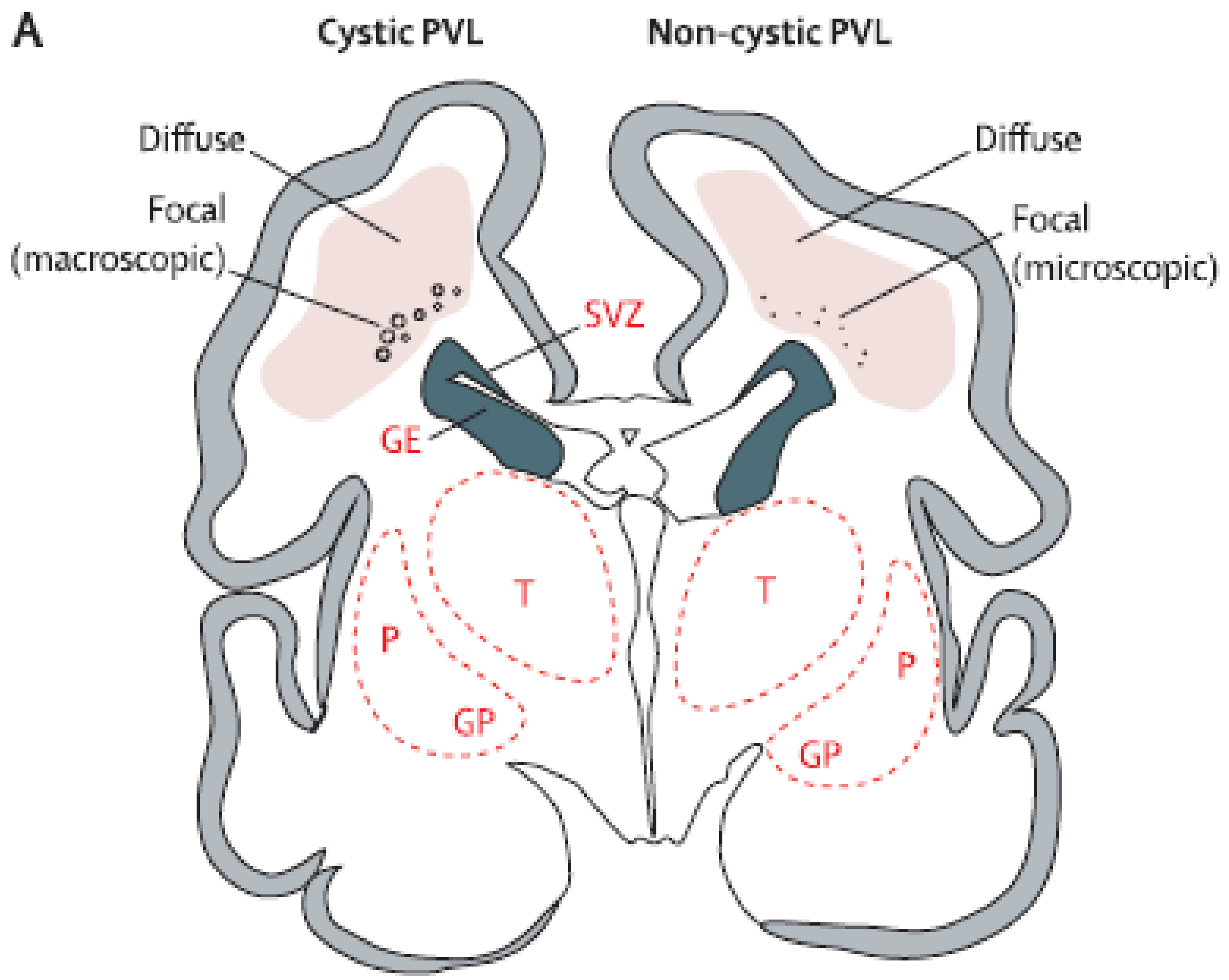
Report gestational age

Age at time of scan

Scoring System from A. James Barkovich, MD

HIE IN PRETERM

- 50% of cases of cerebral palsy –Premature infants
- Up to 19% of infants born before 28 weeks of gestation develop cerebral palsy
- Hypoperfusion –Watershed Ischemia-Premyelinating neurons
- Lack of autoregulation

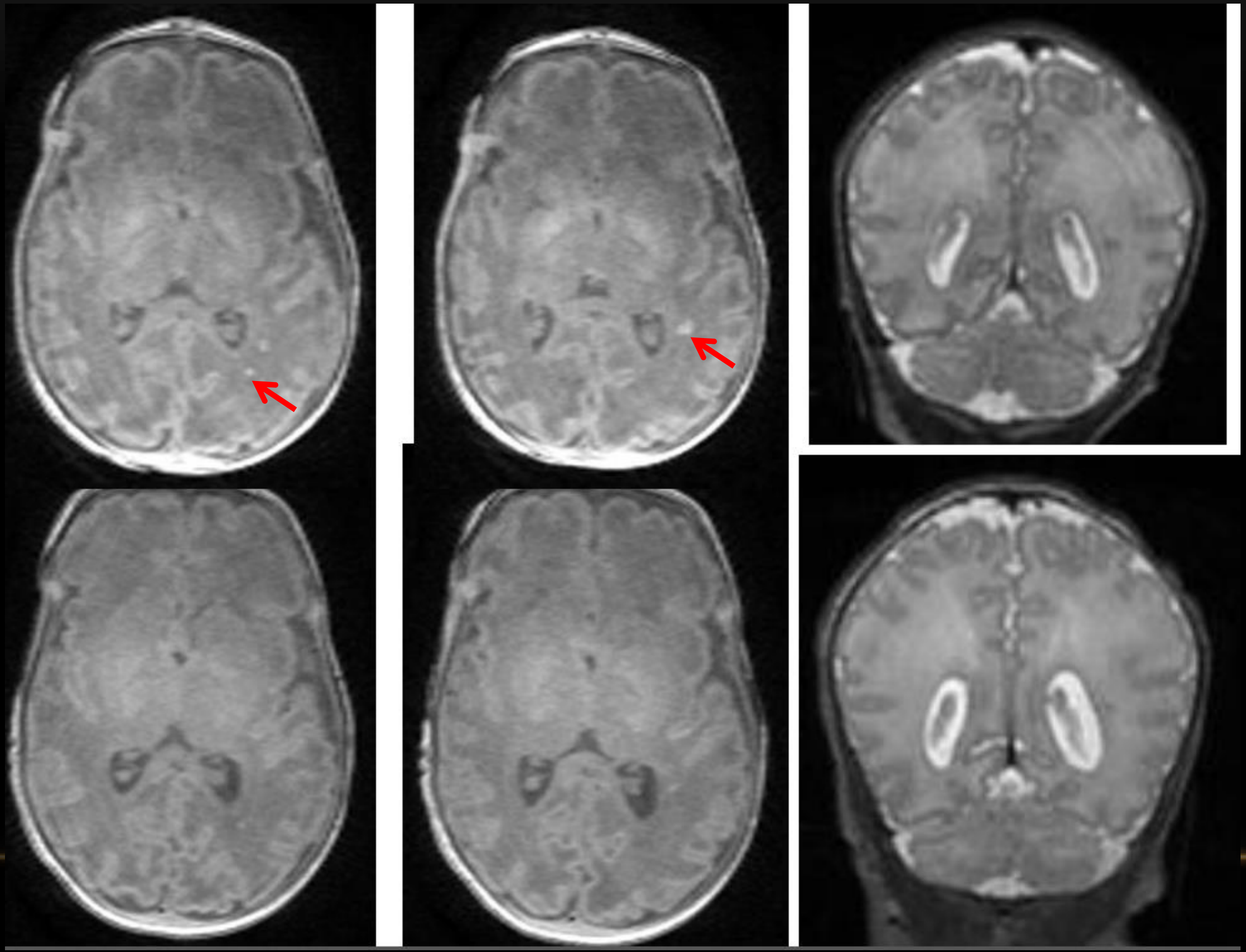


Volpe, Lancet Neurol 2009

PREMATURE INFANTS

- White Matter Injury (WMI) of Prematurity
  - Focal (cystic/noncystic)
  - Diffuse
- Encephalopathy of prematurity
- Cerebellar Injury
- Hemorrhagic HIE of premature-WM Injury
- Chronic WM injury-mixed pattern
- Chronic WM injury

FOCAL NON CYSTIC EX 30 WEEK EGA



MRI at term

Follow up MRI

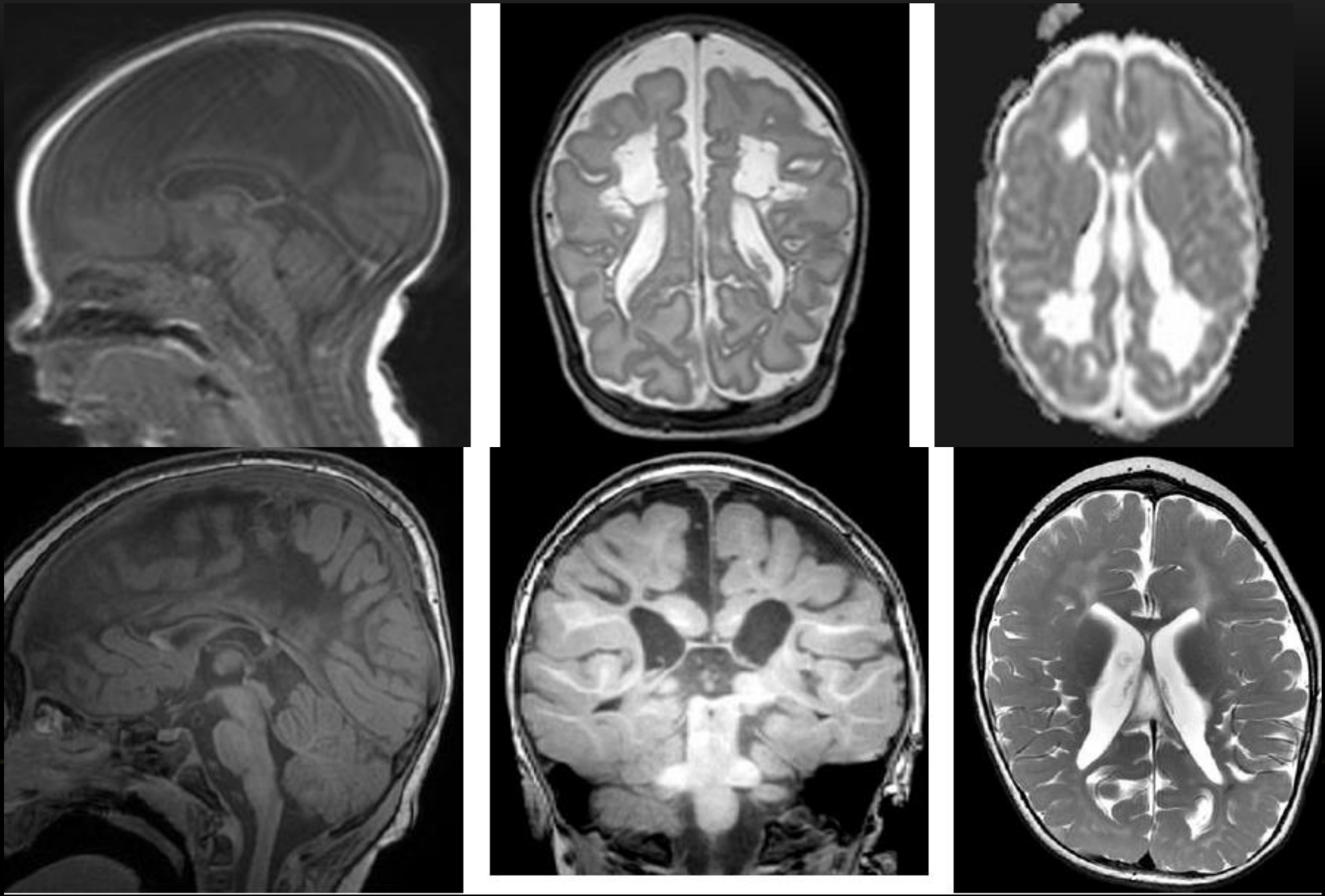
WHITE MATTER INJURY (WMI) OF PREMATURITY
• FOCAL, NONCYSTIC

Common- 20-50%

- Difficult to detect with US
- Microscopic focal necroses-glial scar
- Foci of increased T1, decreased T2
- Foci disappear on follow-up MR scans
- Decreased ADC in acute stages

* Need to look at ADC map as trace DWI images can look “normal”

2 PATIENTS WITH CYSTIC TYPE INJURY



WHITE MATTER INJURY (WMI) OF PREMATURITY FOCAL, CYSTIC

Declining incidence, <5% of WMI in VLBW

- Large cysts can be detected with US or MRI
- Cysts shrink - volume loss seen at follow-up MRI
- Risk Factor: NEC

Periventricular leukomalacia is most commonly seen adjacent to the trigones of the lateral ventricles and to the Monro foramen, areas that correspond to the watershed zones in periventricular white matter in the premature brain

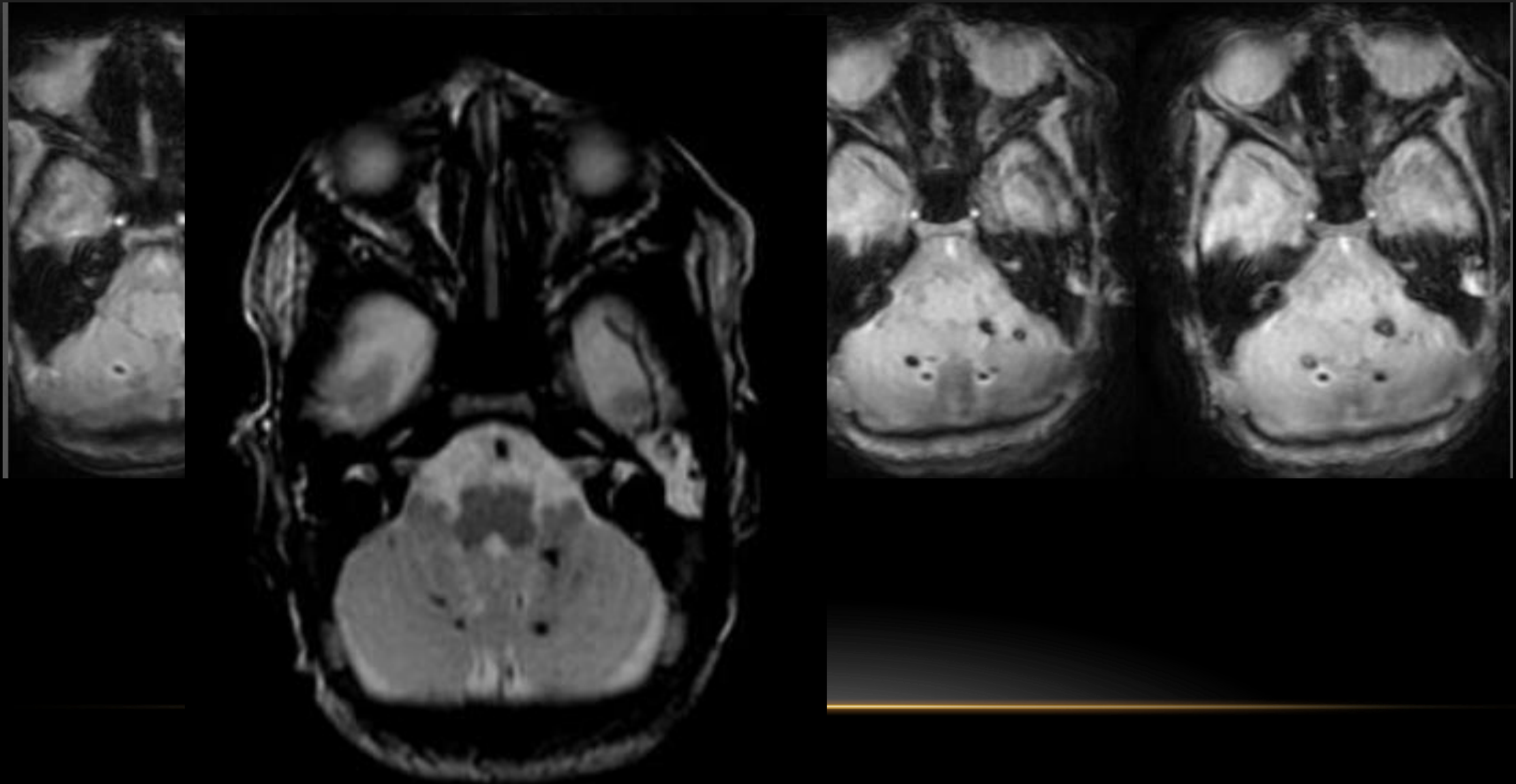
Kidokoro et al Peds 2014

WHITE MATTER INJURY (WMI) OF PREMATURITY FOCAL, CYSTIC

- The condition probably represents toxic injury -cerebral ischemia, reperfusion, or both

- End-stage periventricular leukomalacia manifests as a reduction in volume of the periventricular white matter and the centrum semiovale, with passive dilatation and irregularity of the ventricular wall

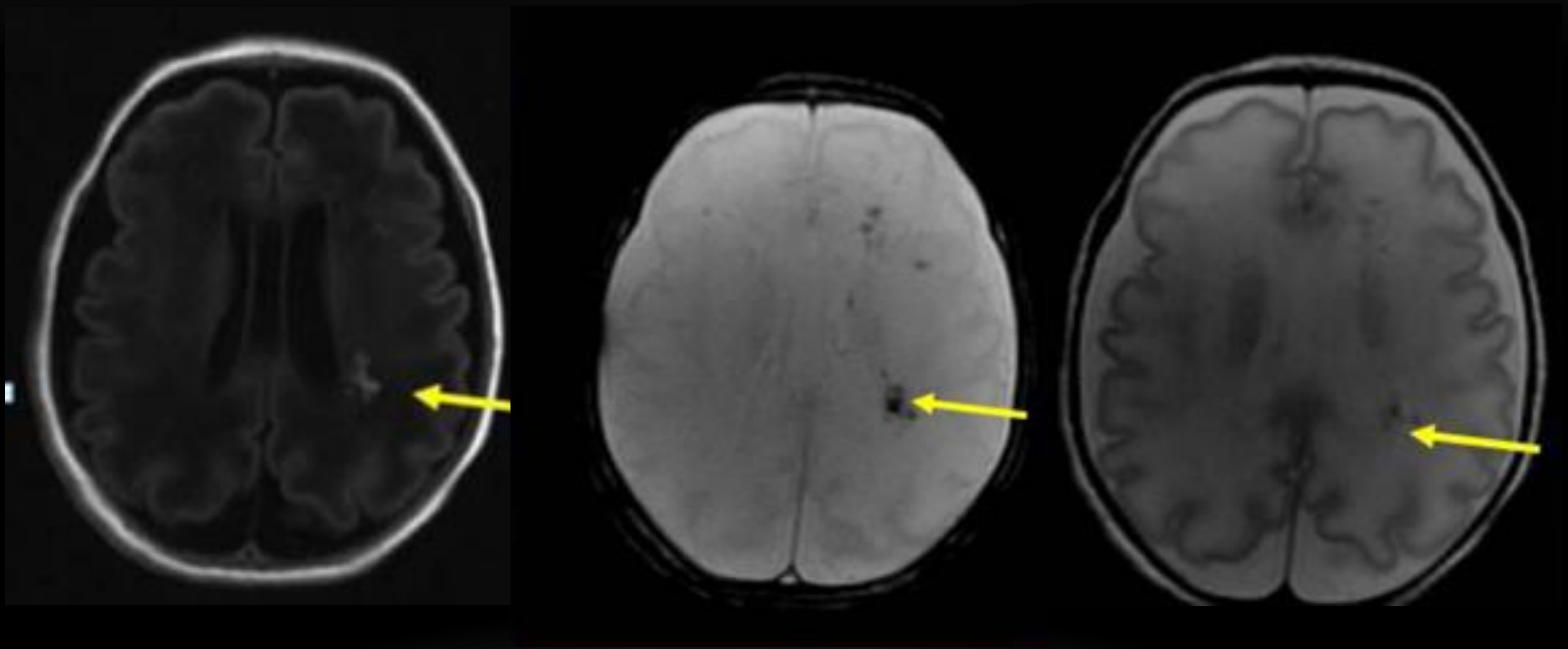
CEREBELLAR GM HEMORRHAGE



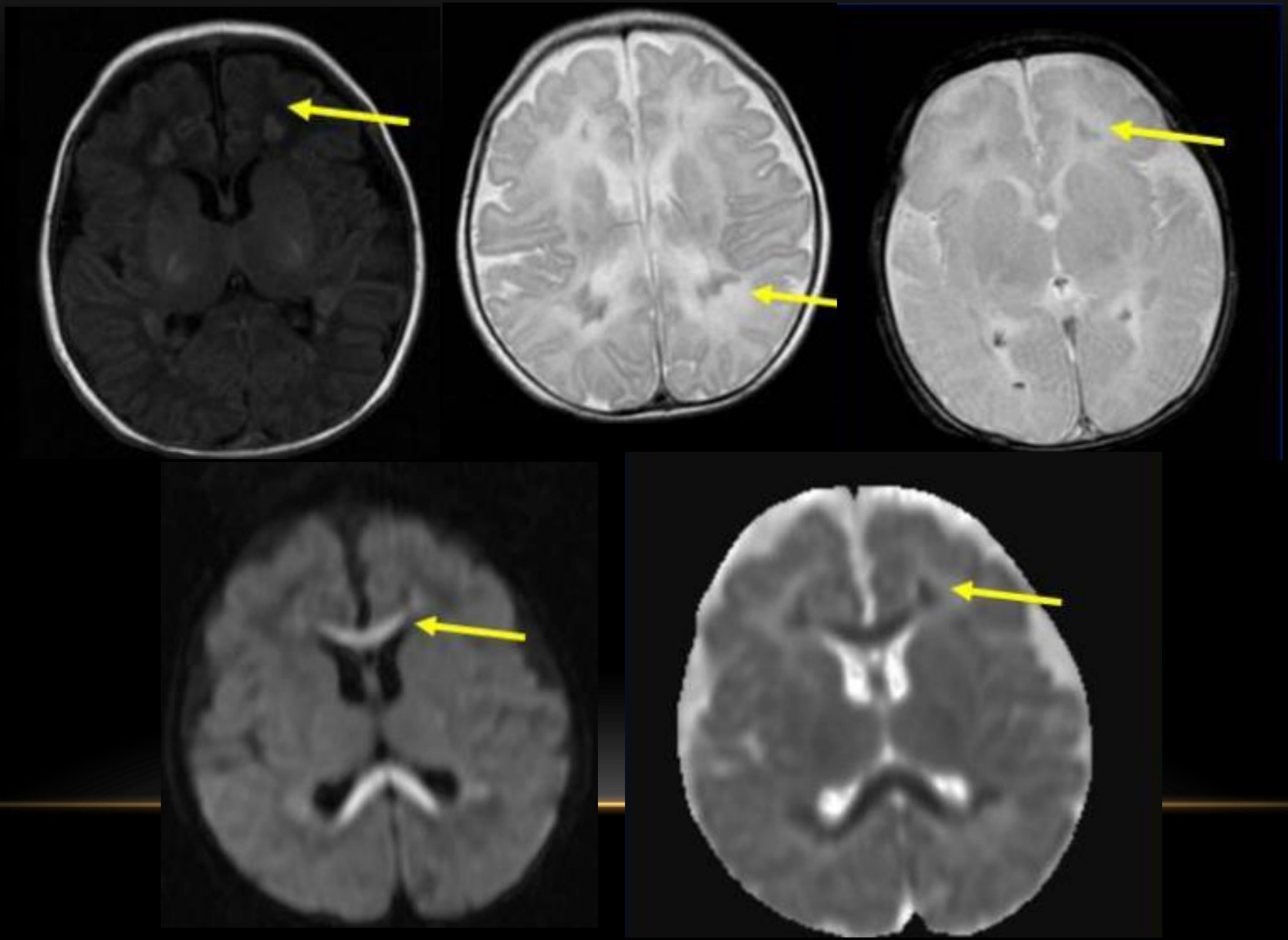
HEMORRHAGIC HIE OF PREMATURE-
CEREBELLAR INJURY

- Increasingly recognized form of preterm injury (10-40%)
- Common, esp in VLBW (<1500g)
- Germinal matrix hemorrhages in external granule cell layer- cerebellar germinal zone 28-40wks
- Large hemorrhages can be seen with US, MRI
- Small hemorrhages best seen with MRI
- Best seen on T2, SWI
- Increase detection with 3T
- Can lead to cerebellar hypoplasia

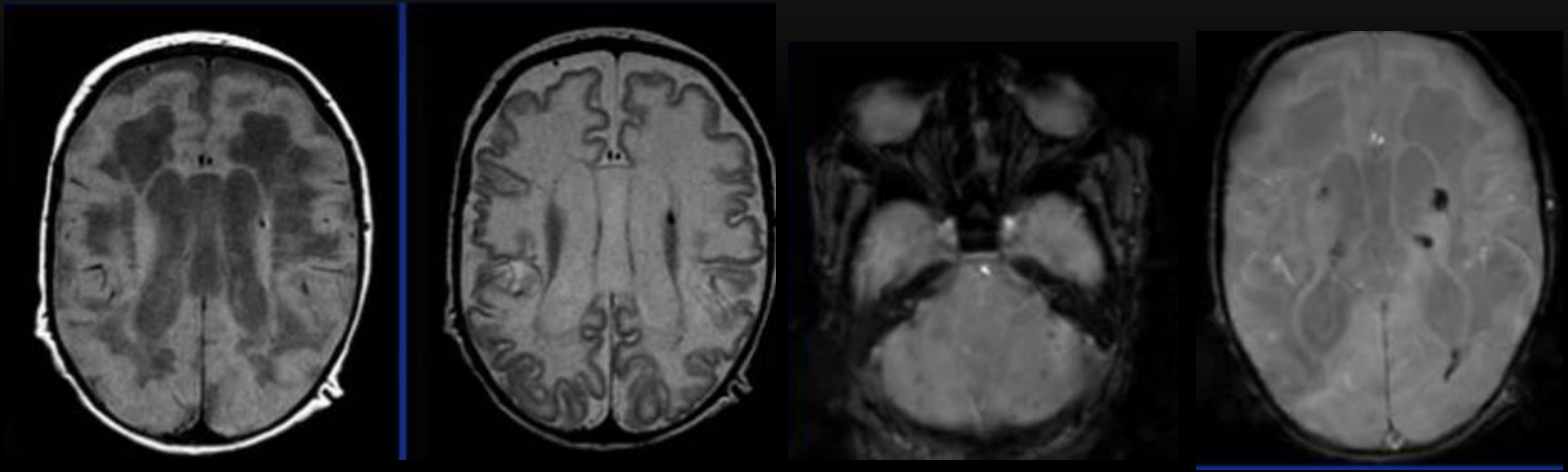
HEMORRHAGIC HIE OF PREMATURE-WM INJURY



MORE EXAMPLES



CHRONIC WM INJURY-MIXED PATTERN



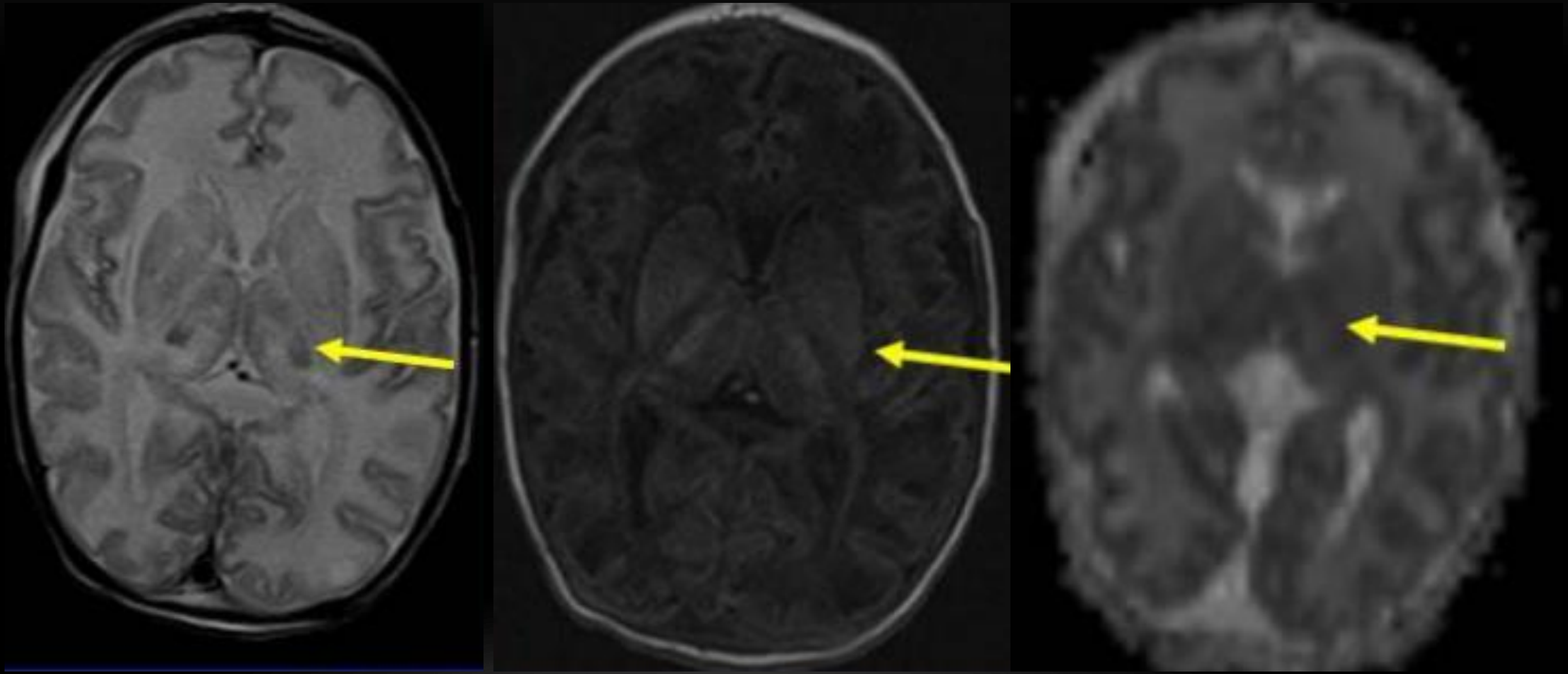
CHRONIC WM INJURY

Thinning of the corpus callosum, particularly in the posterior body and splenium, is a characteristic late feature of periventricular leukomalacia

PREMATURE- SEVERE INJURY

- Severe-deep gray nuclei/brainstem
- Thalami
- Dorsal brainstem
- Anterior vermis
- Lentiform nuclei
- Perirolandic gyri
- Cerebral cortex spared
- WM/GMH

31 WEEK EGA ABRUPTION



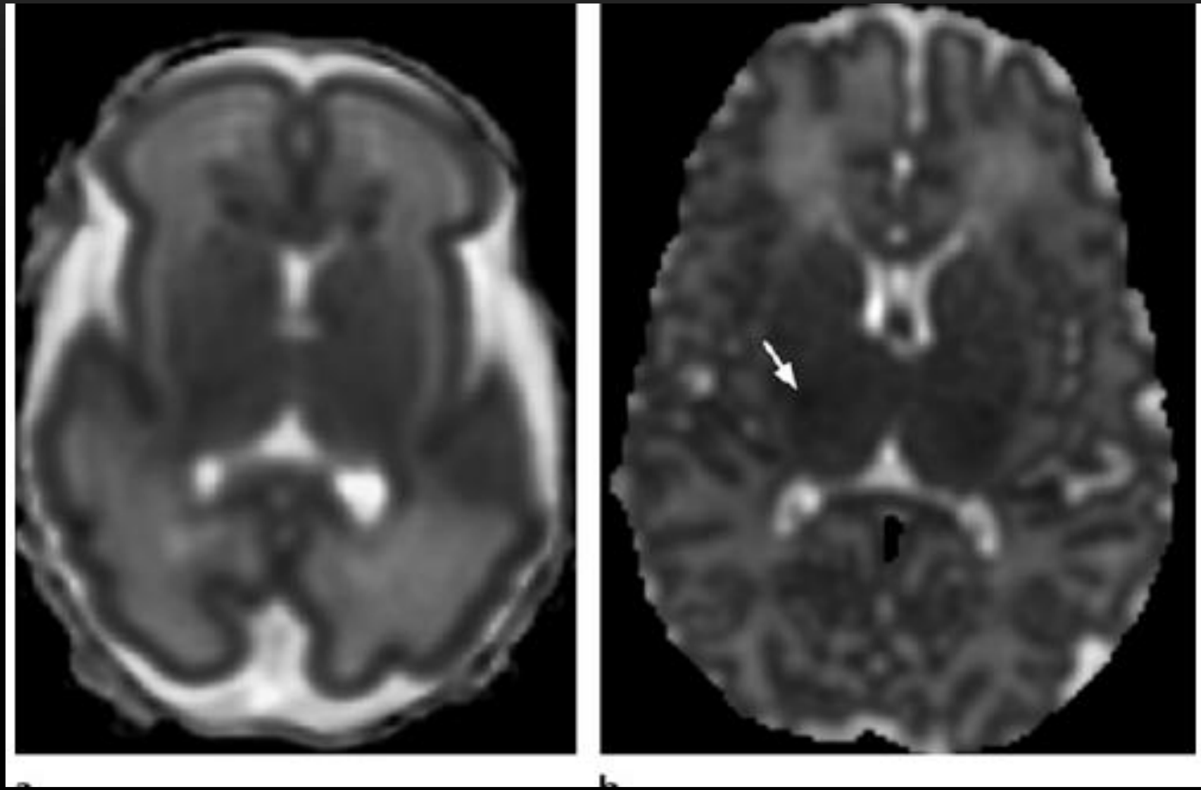


Figure 6. (**a**) ADC map obtained in a neonate at 26 weeks of gestation shows moderately decreased cortical water diffusion and increased white matter water diffusion. (**b**) ADC map obtained in a neonate at 38 weeks of gestation shows more limited water diffusion than in **a**, with resultant lower signal intensity in white matter. Note the region of slight signal hypointensity in the lateral aspect of the thalamus (arrow), a finding that represents myelination.

RG • Volume 30 Number 3

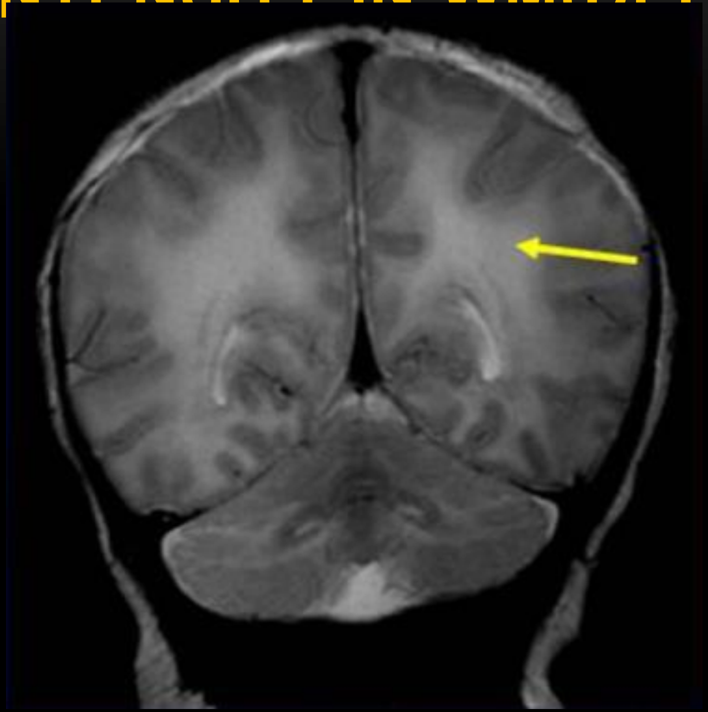
Diffusion in the cortex is more restricted because of the higher ratio of cells to extracellular space

NEURODEVELOPMENTAL DEFICITS IN WM DISEASE OF THE PREMATURE

- Outcomes:
  - Cognitive and motor delay-Spastic diplegia/quadriplegia
  - Neurosensory Impairment –Visual
- Predictors/Term equivalent
  - Moderate to severe WM abnormalities
  - Grey matter less strongly associated
  - US-III/IV;Cystic PVL
  - Postnatal steroids

Woodward et al, NEJM 2006

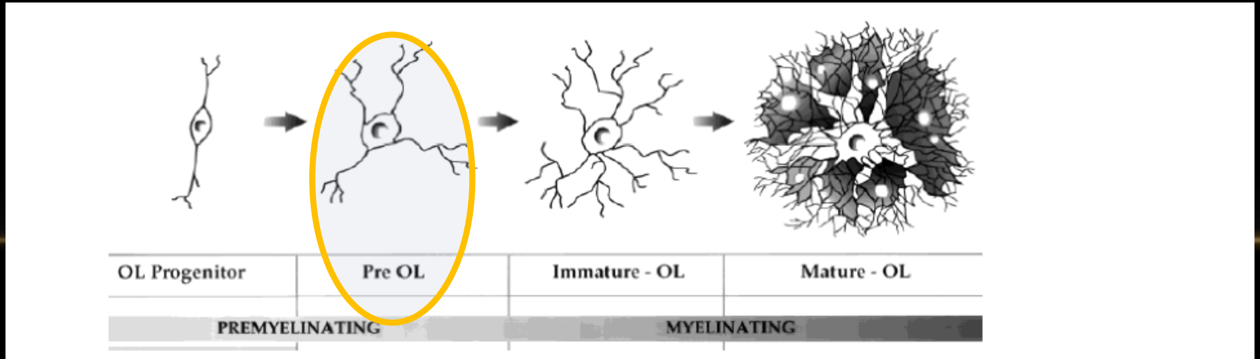
DIFFUSE EXCESSIVE HIGH SIGNAL INTENSITY IN WM(DEHSI)



- Controversial
  - WM
  - Increase diffusion
  - Poor neurologic outcome
- Transient normal process
- No difference; No difference ADC values with controls

ENCEPHALOPATHY OF PREMATURITY

- Selective vulnerability of pre-oligodendrocytes and immature oligodendrocytes AND subplate neurons to H-I and inflammtion
- Impaired pre oligodendrocyte maturation-decreased myelin
- Subplate neurons-role in thalamocortical and associative/commisural cortico-cortico connections
- Likely combination of 1° destructive process and 2° maturation/trophic disturbance



Back & Volpe 1997 MRDD Res Rev

FULL TERM INFANTS

- Severe, basal ganglia pattern
- Severe, total hypoxia
- Mixed pattern

NORMAL

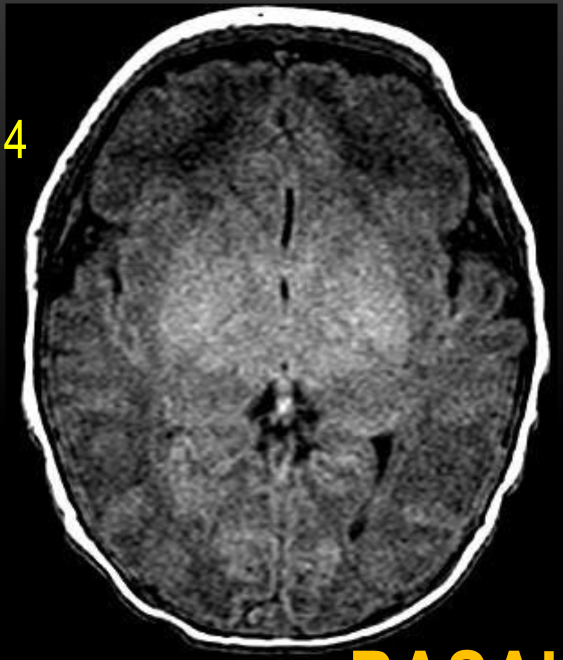
2 day old 36 week EGA boy

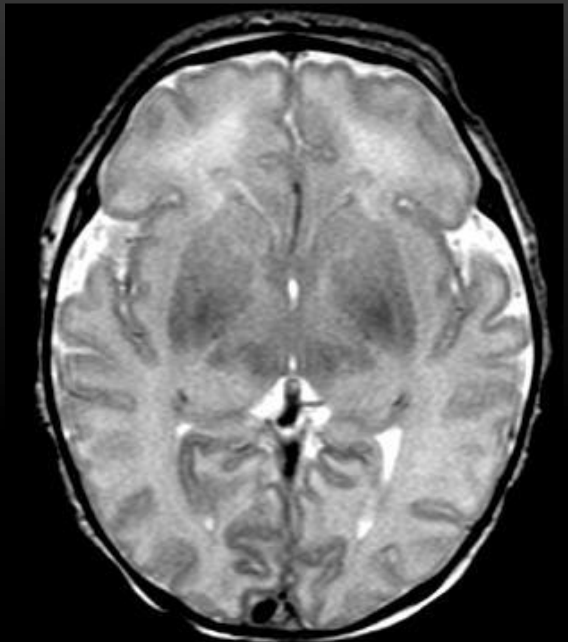
Hypointense T1 signal in post. Limb of internal capsule. This is normal for age in 36 wk EGA

Range of variation in signal intensity that can be seen in normal brain—basal ganglia show moderately hyperintense signal, although less than that typically seen in hypoxia

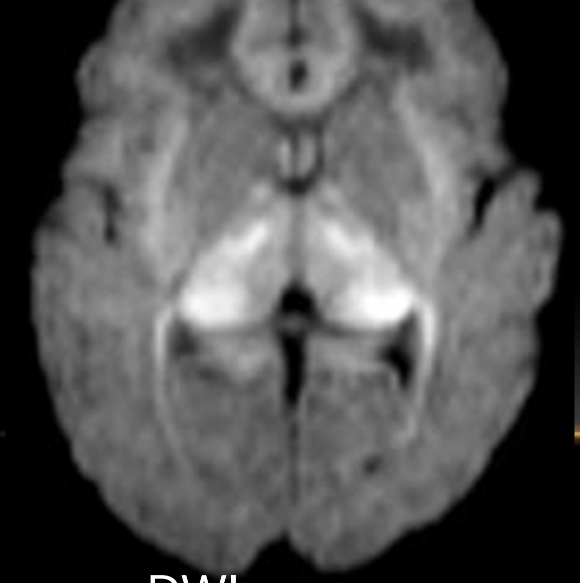
BASAL GANGLIA PATTERN

DAY 4

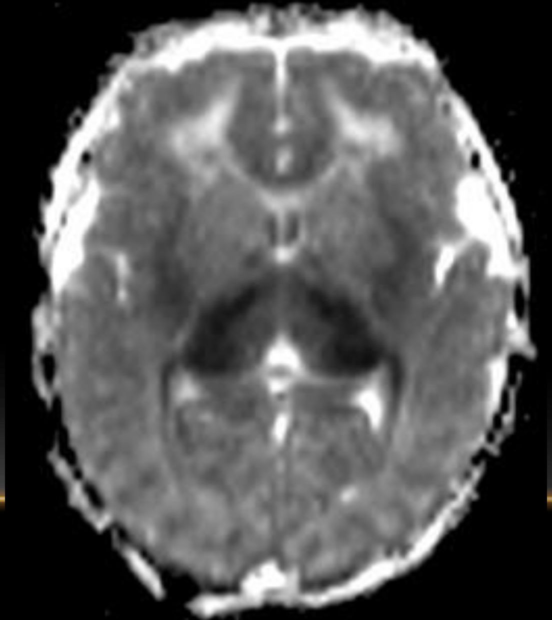




Injury to the basal ganglia and thalamus

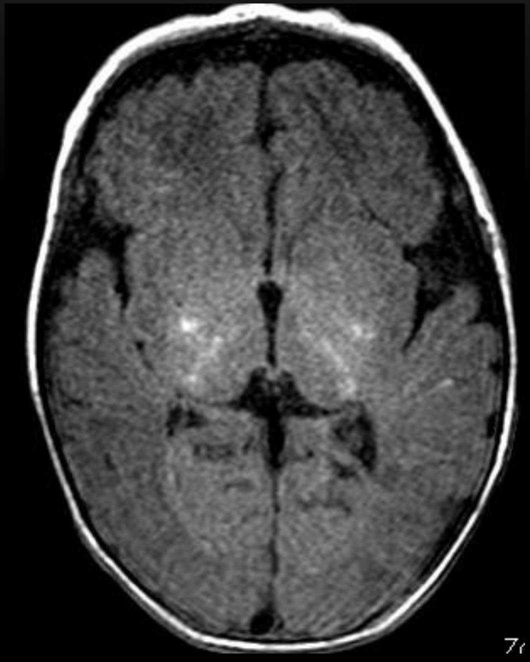


DWI



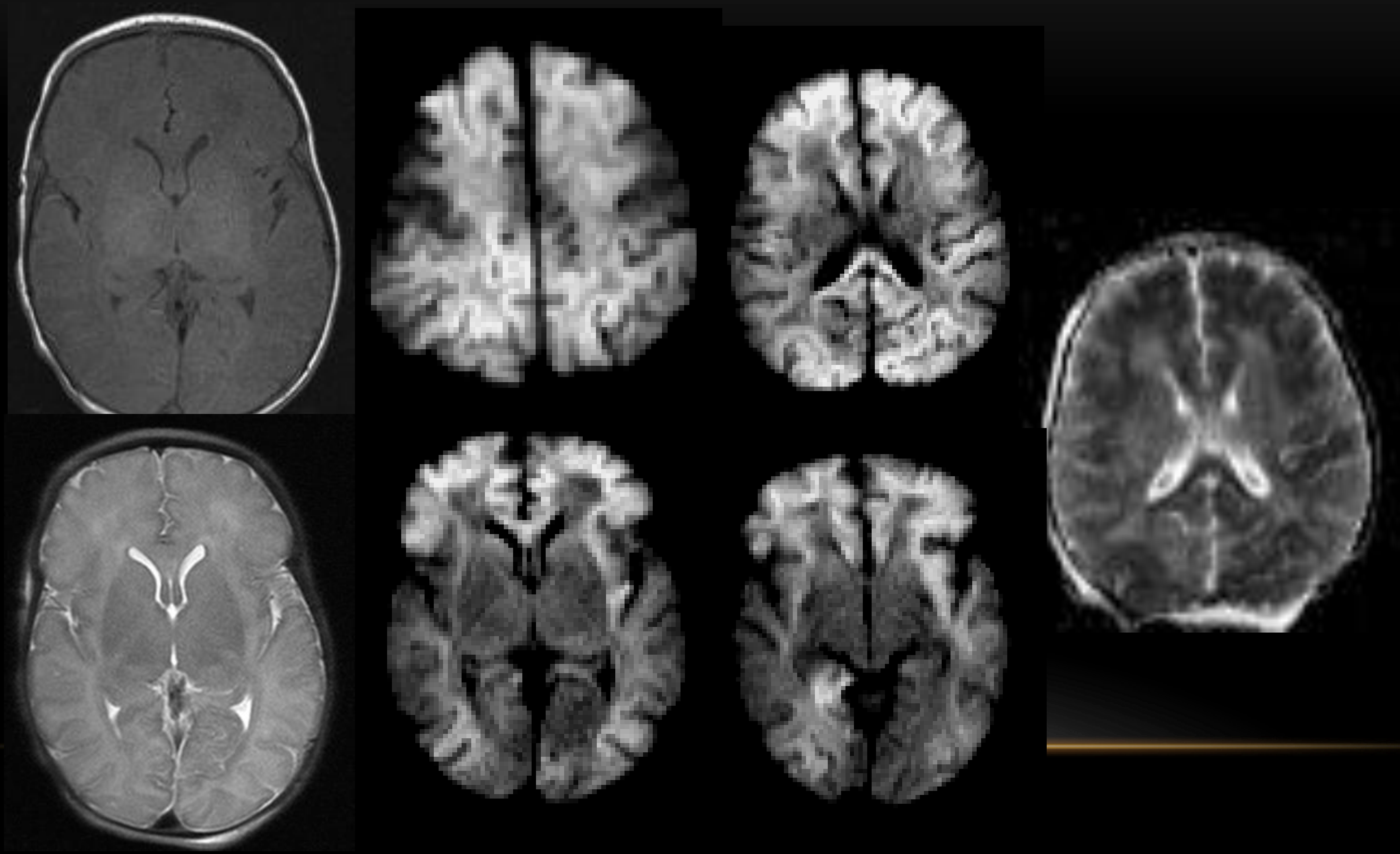
ADC

DAY 47



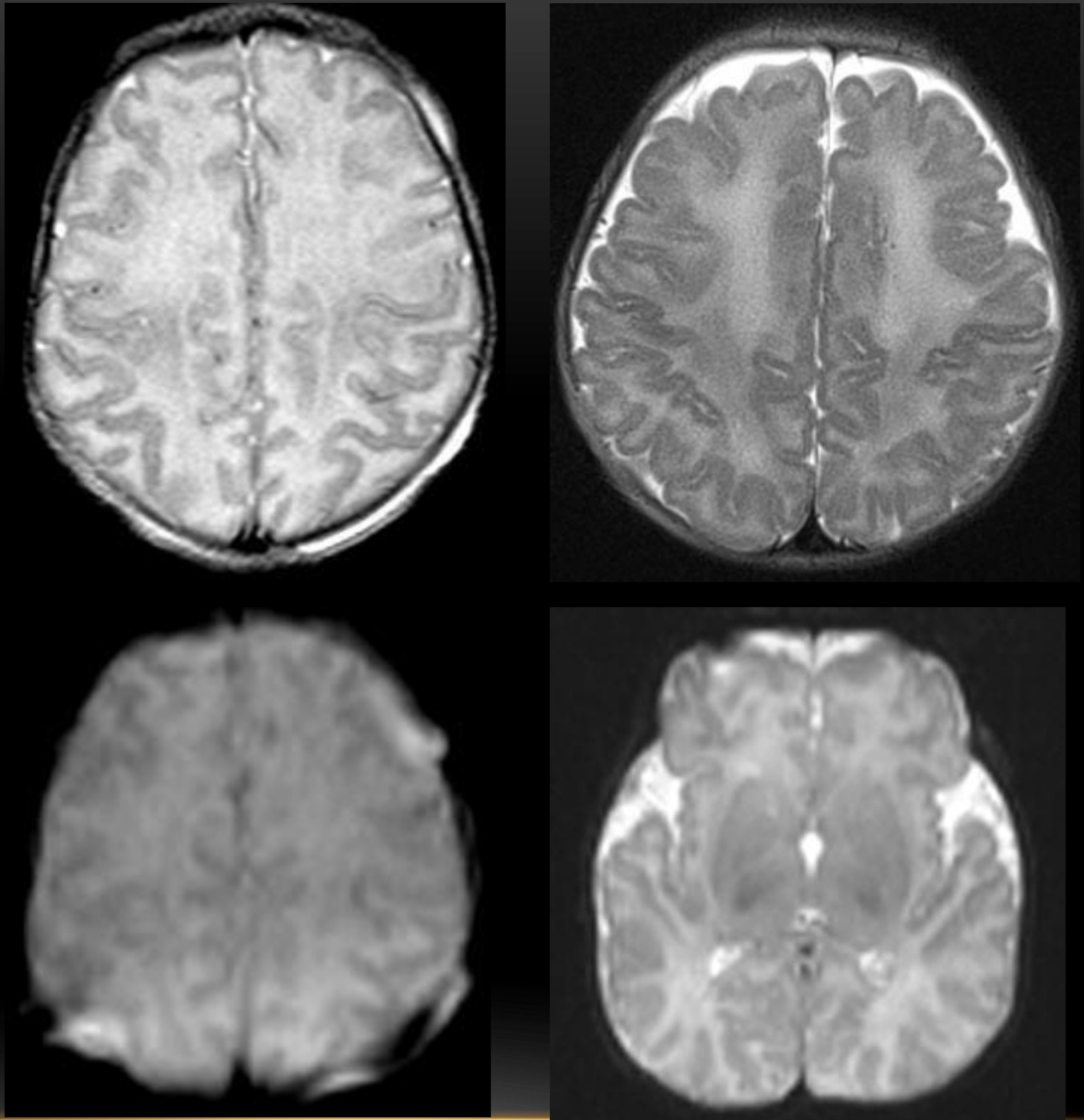
High T1 signal in basal ganglia and thalamus from intracellular calcium shift and necrosis

MRI FINDINGS IN THE NEONATE WITH SEVERE, TOTAL HYPOXIA



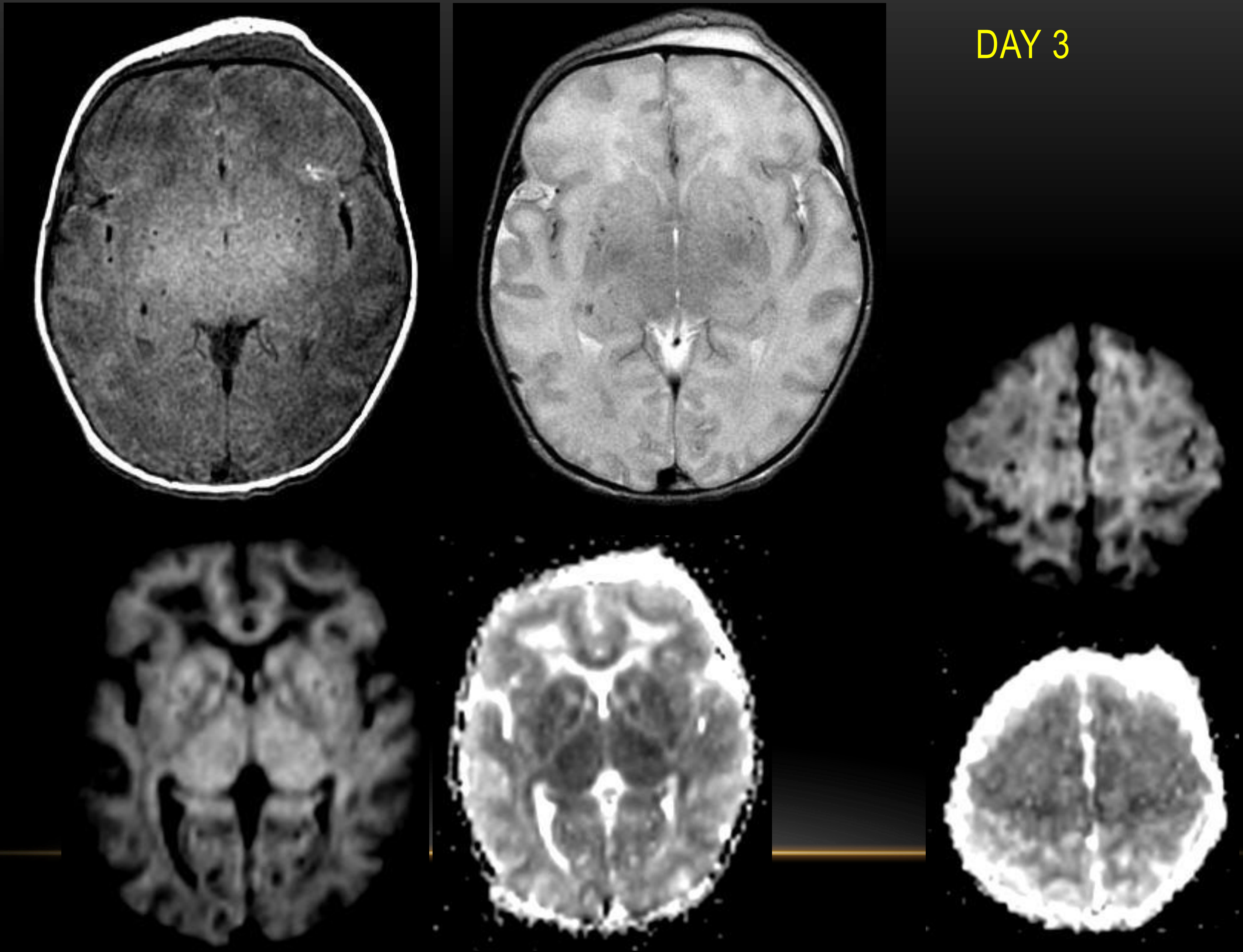
Abnormal high signal throughout the WM on T2

Blurring of GW differentiation more evident on B=0 than conventional T2-weighted images

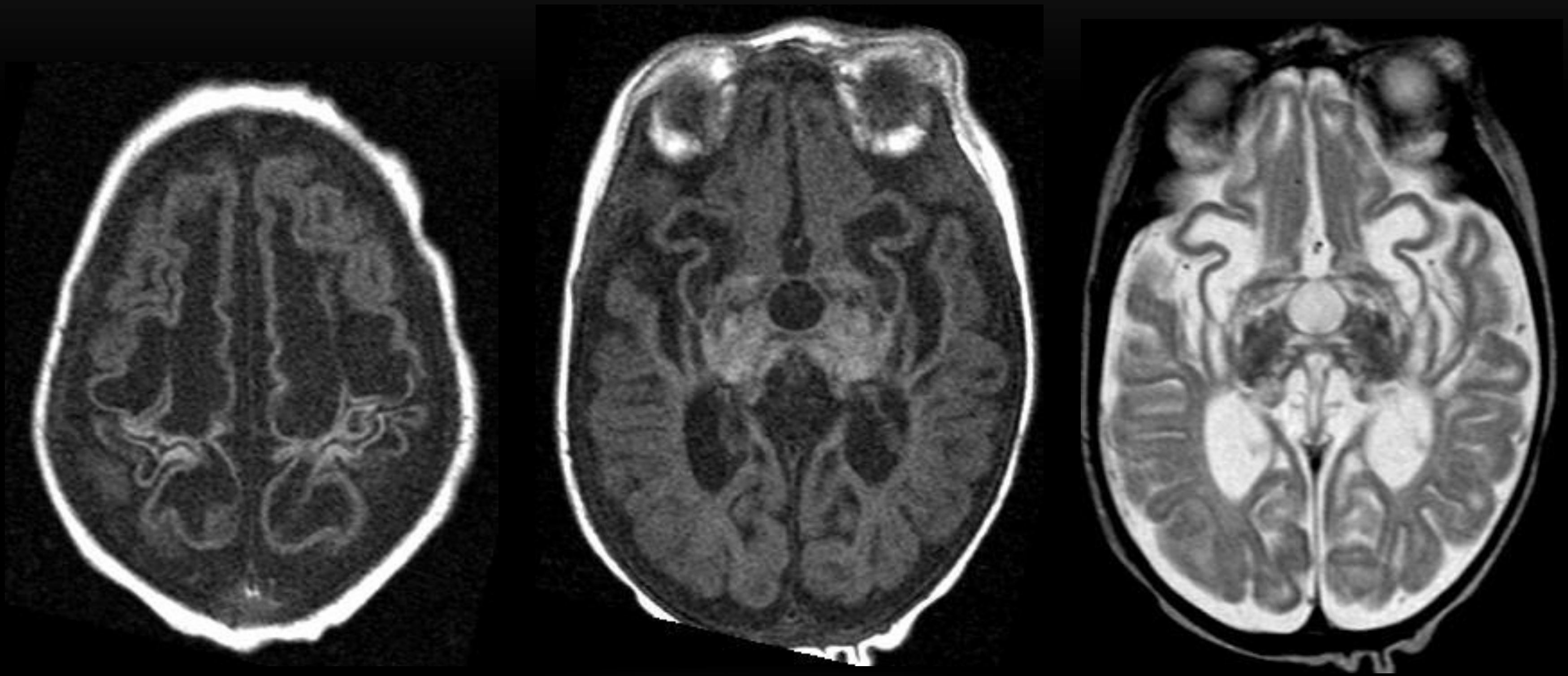


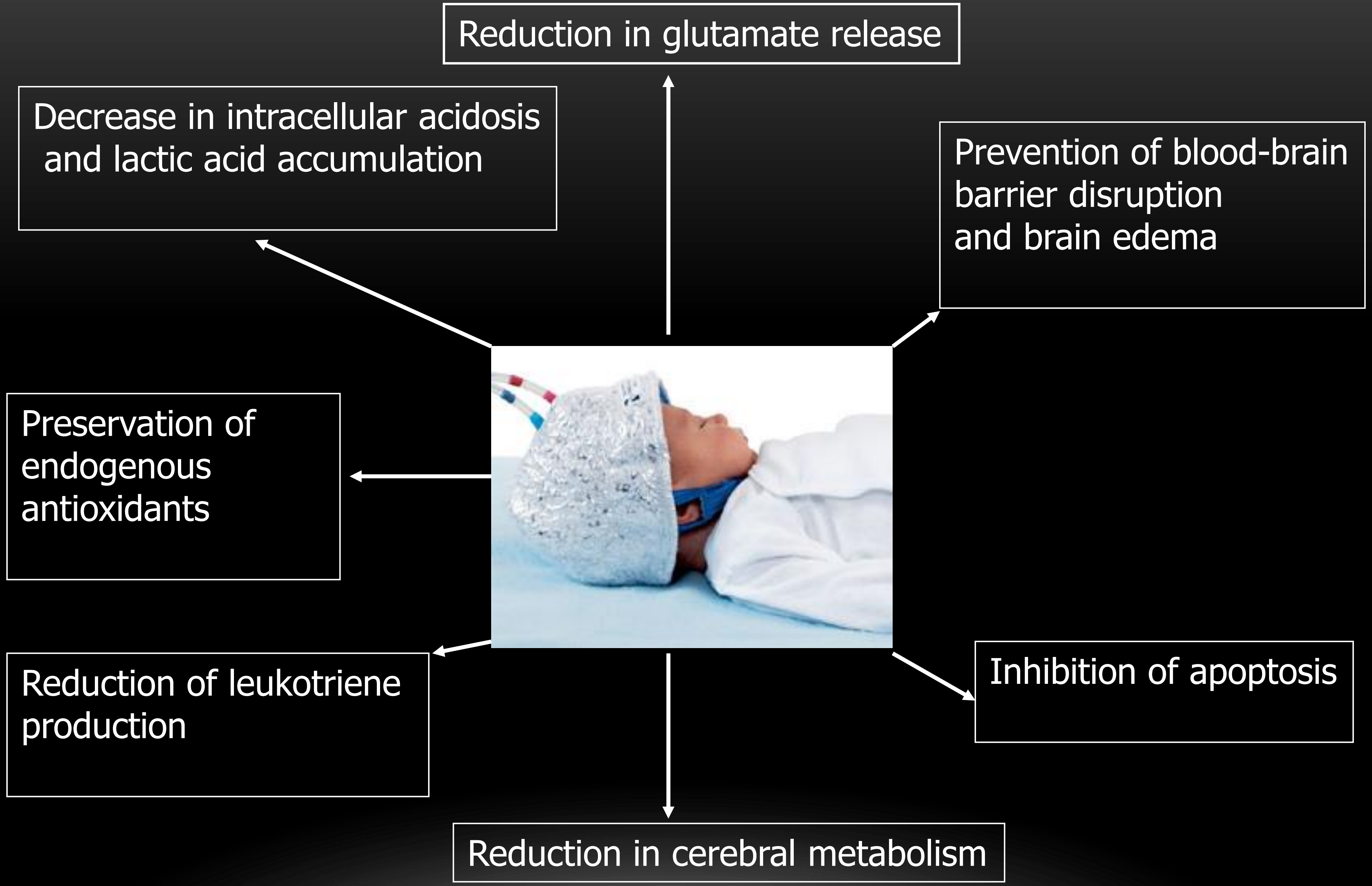
ABNORMAL NORMAL

DAY 3



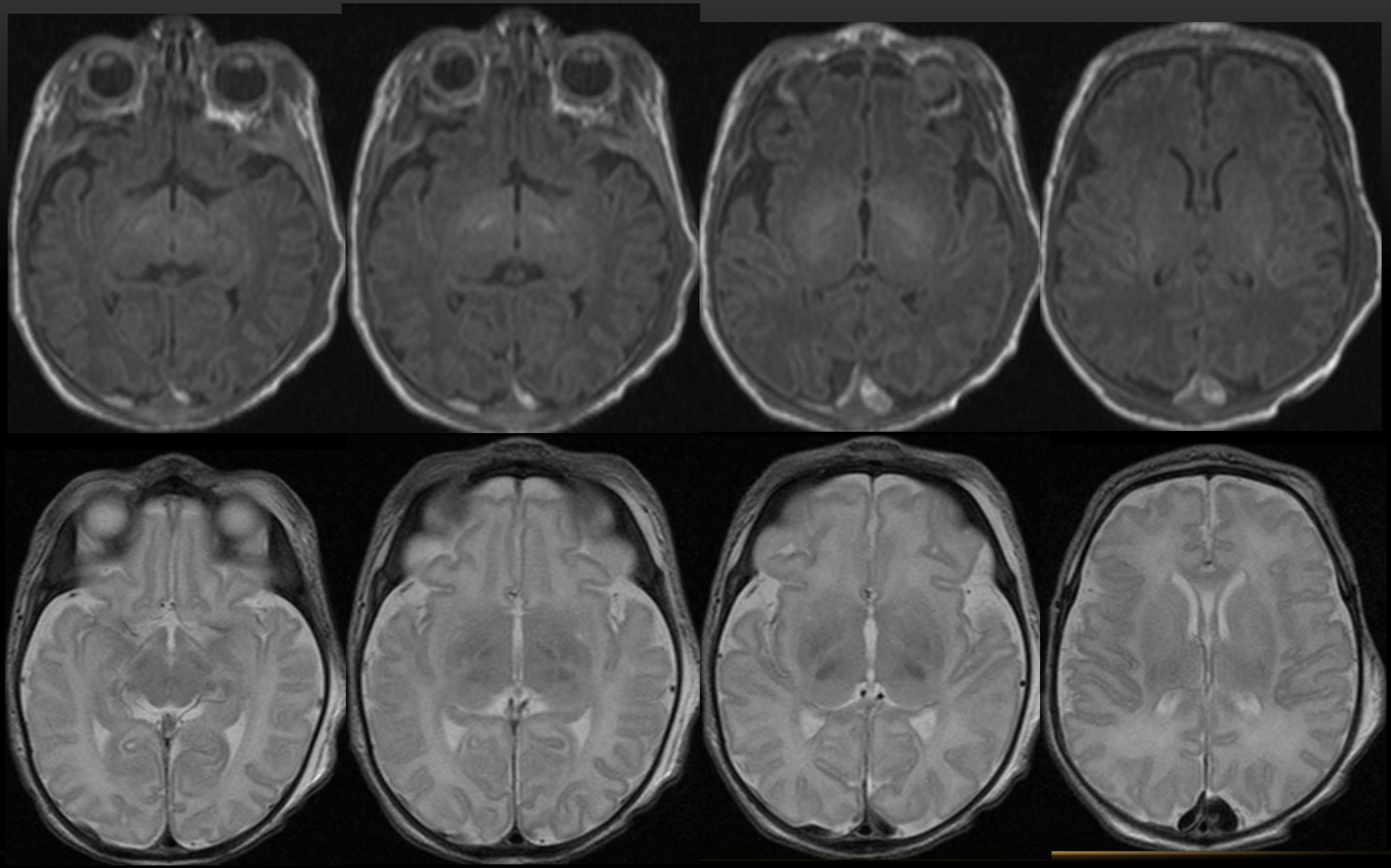
DAY 49



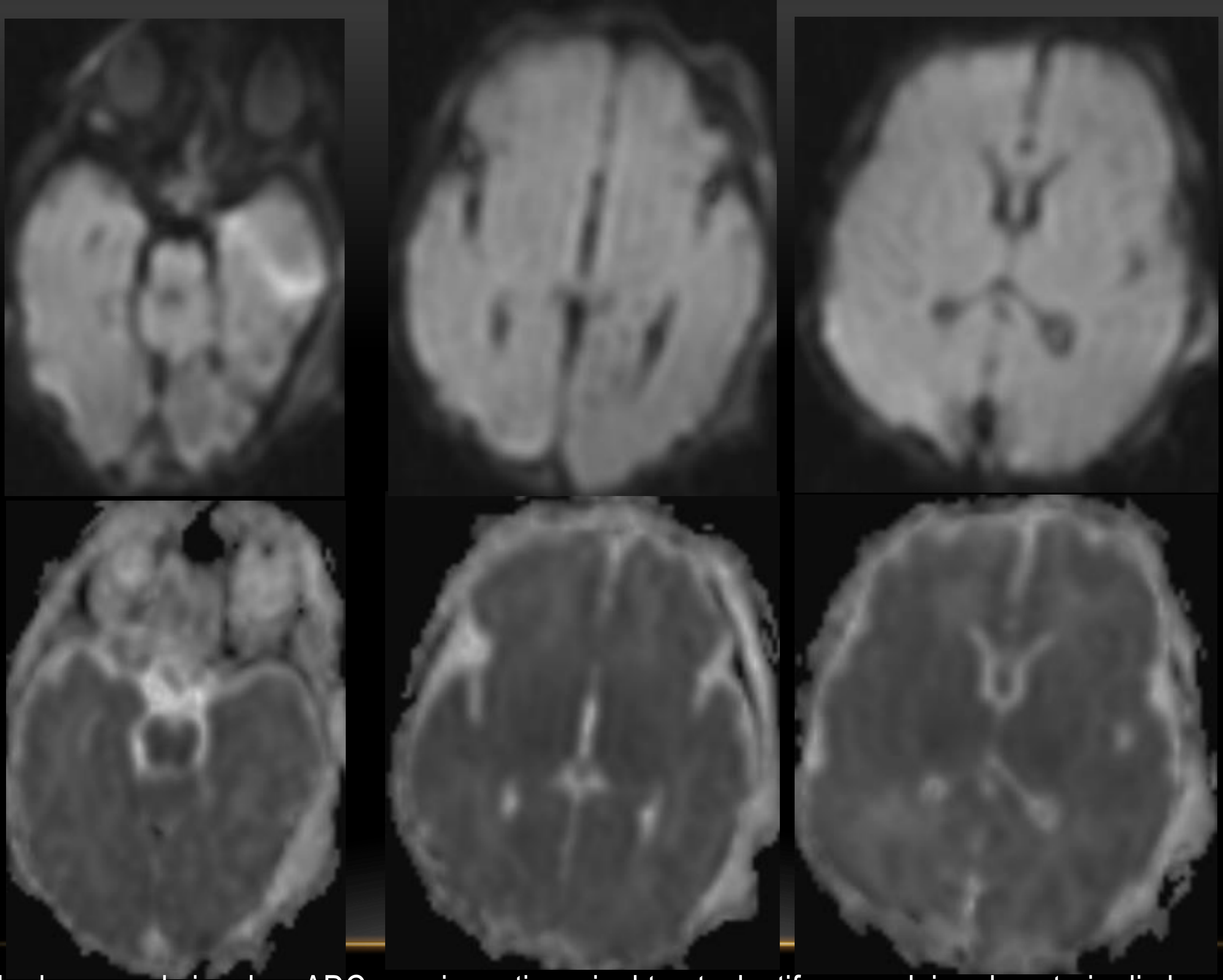

Reduction in glutamate release
Decrease in intracellular acidosis and lactic acid accumulation
Prevention of blood-brain barrier disruption and brain edema
Preservation of endogenous antioxidants
Reduction of leukotriene production
Inhibition of apoptosis
Reduction in cerebral metabolism

38 WEEK EGA GIRL INFANT BORN AFTER INDUCTION FOR MATERNAL PRE-ECLAMPSIA

Hypoxic ischemic injury s/p cooling. Infant is now 5 days old and is being re-warmed



Inc T1 signal in corticospinal tracts, lentiform nuclei and thalami (subtle), and decreased T1 signal in posterior limbs of internal capsule



Subtle decreased signal on ADC map in corticospinal tracts, lentiform nuclei and posterior limbs of internal capsules. No DWI changes because they've already normalized.

KEY POINTS

- HIE usually manifests within the first few hours after birth
- A few days after birth - without an obvious reason, metabolic and infectious causes must be considered
- Normal Neonate MR Findings->37 weeks EGA
  - ↑ T1 & ↓T2 signal in posterior half of posterior limb of internal capsule
  - At a minimum, 1/3 of the length should be T1 hyperintense
  - Usually seen during first 24 hours of life
- If ≤36 weeks EGA: no ↑ T1 in this region = normal finding

PRETERM

Severe hypoxic-ischemic insults to the premature brain typically affects:

- Thalamus
- Anterior part of the vermis
- Dorsal brainstem
- Injury to the basal ganglia is usually less severe and common

TERM

- Severe hypoxic-ischemic injury in term baby involves:
- Ventral and lateral aspects of the thalamus
- Posterior aspect of the putamen
- Perirolandic regions
- Corticospinal tracts

PRETERM

- Mild to moderate hypoxic-ischemic injury may result in a germinal matrix hemorrhage, periventricular leukomalacia, or both
- Hypoperfusion causes periventricular border zone of white matter injury

TERM

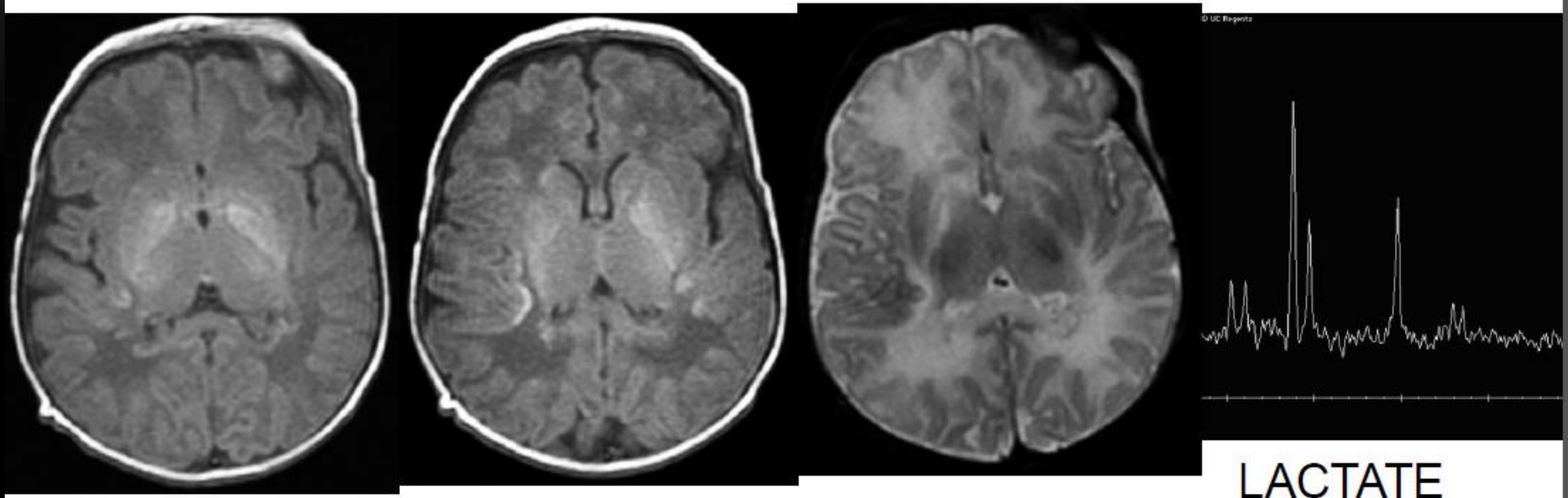
- Mild to moderate hypoxic-ischemic injury in term baby causes lesions in
  - Watershed areas
  - Parasagittal cortex
  - Subcortical white matter
  - Spares the brainstem, cerebellum, and deep gray matter structures

RG • Volume 30 Number 3

METABOLIC DISORDERS PRESENTING WITH ENCEPHALOPATHY IN NEONATAL PERIOD

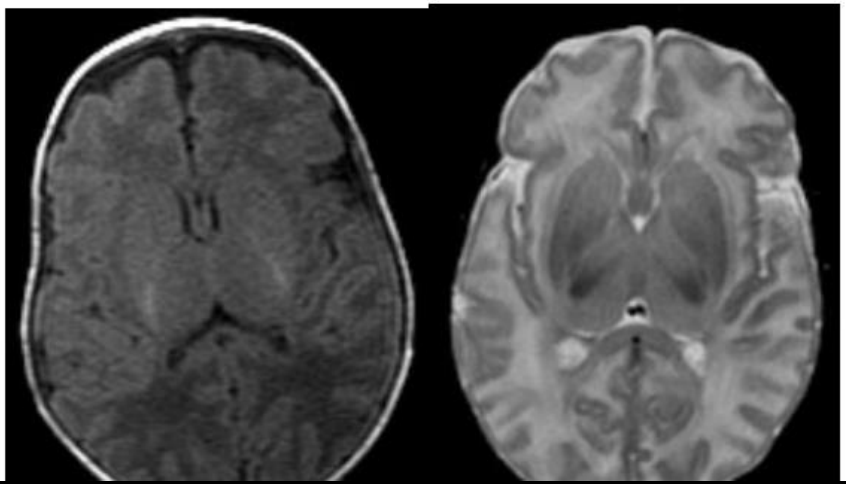
- Amino/organic acidopathies:
- Nonketotic hyperglycinemia
- Glutaric aciduria I and II
- Sulfite oxidase deficiency
- Maple syrup urine disease
- Proprionic Acidemia
  - Urea Cycle disorders
  - Mitochondrial/respiratory chain abnormalities
  - Peroxisomal biogenesis disorders

11 day old w/encephalopathy and high ammonia:



LACTATE
Low NAA

Compare with normal term neonate…



IMPORTANT CLINICALCORRELATES

- Long-term studies of the outcome of very prematurely born infants - significant motor, cognitive, and behavioral deficits
- More prone to develop encephalopathies
- In comparison to the term-born infants, the premature infants at term demonstrated prominent reductions in cerebral cortical and deep GM volume
- The major predictors of altered cerebral volumes were gestational age at birth and the presence of cerebral WM injury

IMPORTANT CLINICALCORRELATES

- Infants with significantly reduced cortical GM and deep nuclear GM volumes and increased CSF volume volumes exhibited moderate to severe neurodevelopmental disability at 1 year of age
- The nature of the cerebral abnormalities that underlie these common and serious developmental disabilities is not entirely understood
- Postulated-WM injury and delayed WM and GM gyral development

CONCLUSIONS:

- Hypoxic ischemic injury manifests differently in a full term than in a premature on MRI
- USG of head serves as a baseline examination to enroll a patient in the PENUT trial AND a routine baseline scan on day 7 of a premature baby
- Imaging of the patients who have undergone cooling demonstrate lesser extent of brain injury


A four-day reduction in hospital stay,
multiplied by the number of preemies
born each year, would result in
a $2.4 billion annual cost savings
for the national healthcare system.