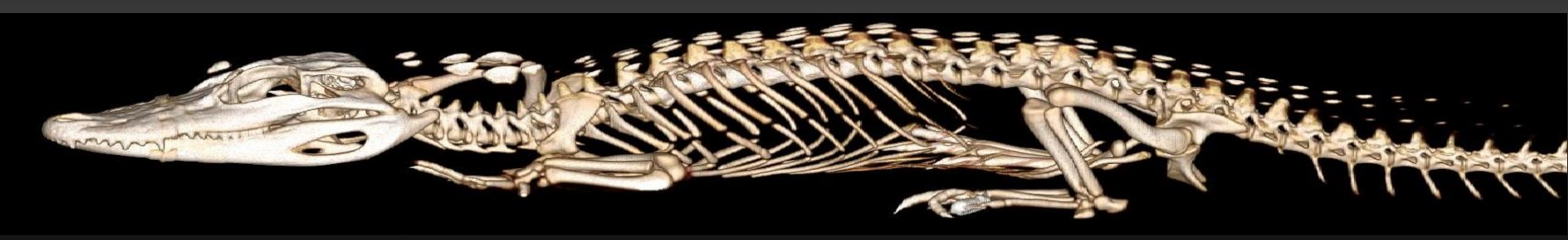

IMAGING OF HYPOXIC ISCHEMIC INJURY IN A NEONATE

FN3 STATE MEETING

NEMOURS CHILDREN'S HOSPITAL ORLANDO,FL

08/05/17

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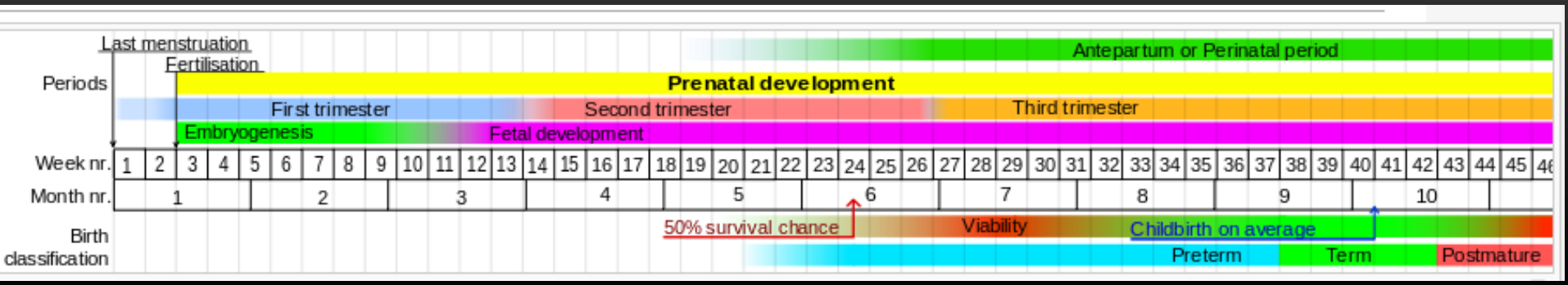
UF | UNIVERSITY of FLORIDA

PURPOSE:

- 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
- To discuss the patterns of HI injury in term versus premature infants



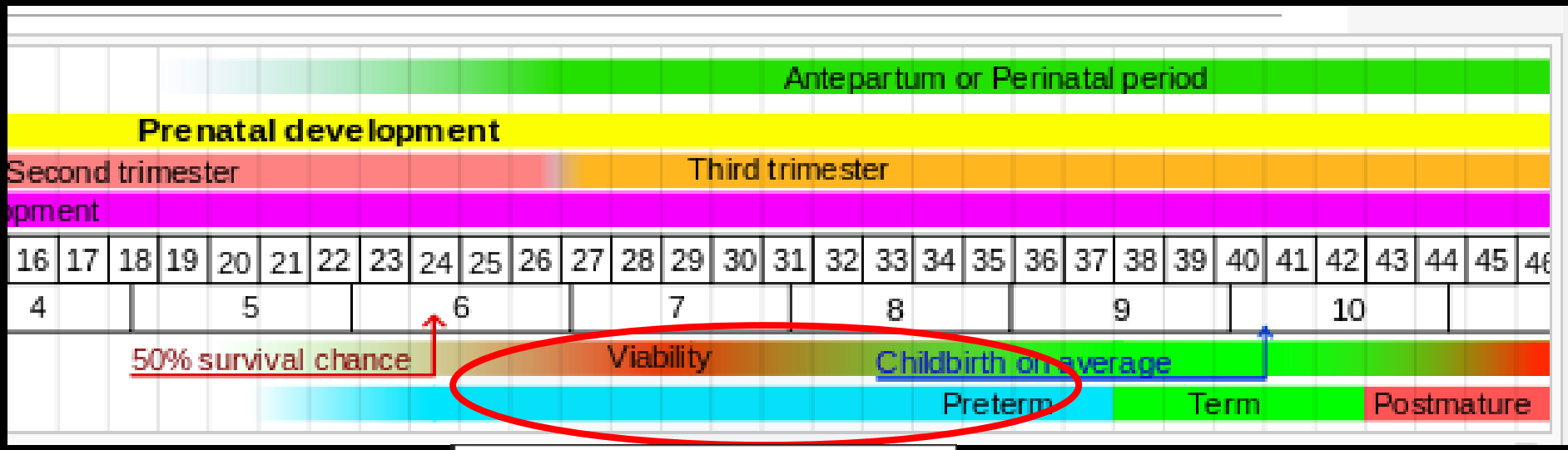


Table 1. Classification of Prematurity

Gestational Age

LPT: between 34 weeks and 36 weeks + 6 days
VPT: ≤32 weeks
EPT: ≤28 weeks

Birthweight

LBW: <2,500 g (5 lb, 8 oz.)
VLBW: <1,500 g (3 lb, 4 oz.)
ELBW: <1,000 g (2 lb, 3 oz.)

ELBW: extremely low birthweight; EPT: extremely preterm; LBW: low birthweight; LPT: late preterm; VLBW: very low birthweight; VPT: very preterm.
Source: Reference 1.

DEFINITIONS

- Hypoxic-ischemic injury to designate any brain impairment caused by insufficient oxygenation and blood flow
- Hypoxic-ischemic encephalopathy, a condition that is diagnosed on the basis of specific clinical findings of profound acidosis, a poor Apgar score (0–3) at birth, seizure, coma, hypotonia, and multiorgan dysfunction
- Brain ischemia leads to a shift in metabolism from oxidative phosphorylation to anaerobic oxidation

HEAD US: INDICATIONS-PREMATURE INFANTS

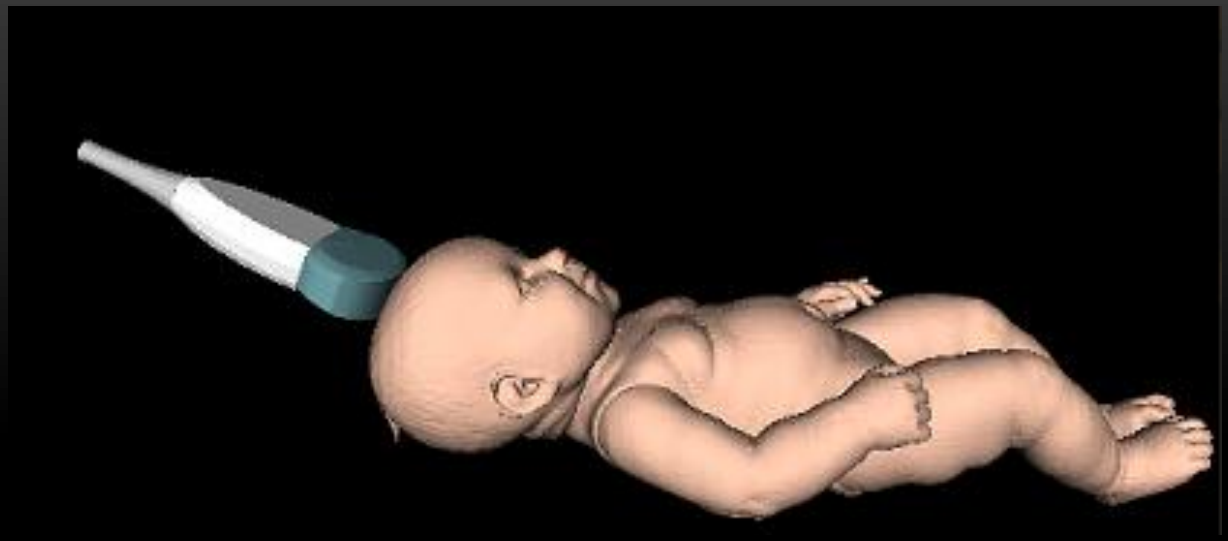
- To detect
  - Intracranial hemorrhage
  - Periventricular leukomalacia/ischemia
  - Hydrocephalus
  - Extra-axial fluid collections

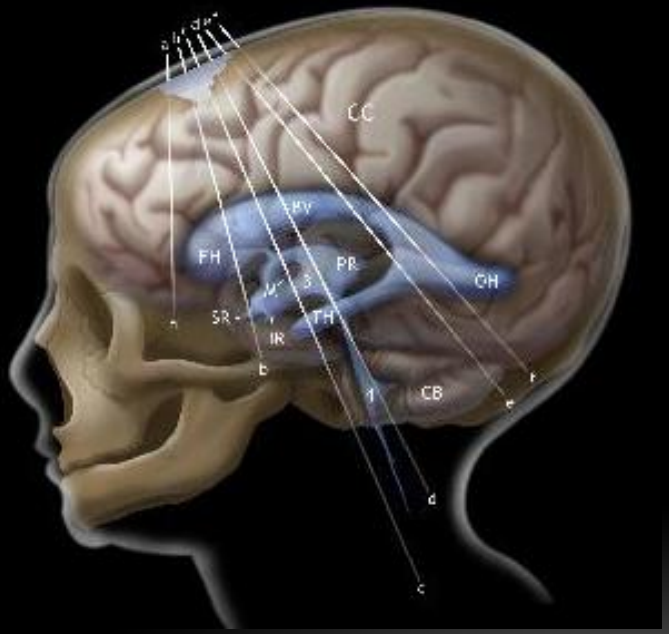
HEAD US: INDICATIONS-PREMATURE INFANTS

- **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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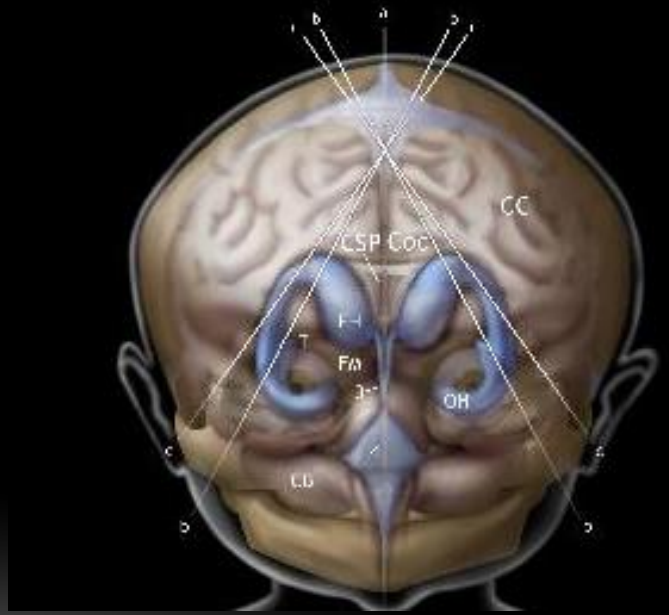
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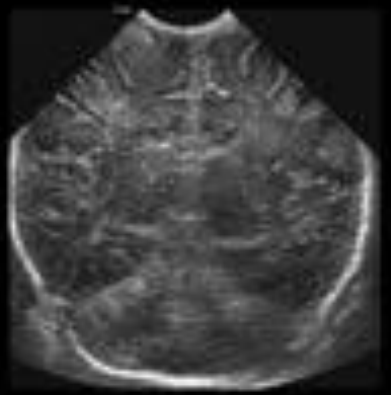
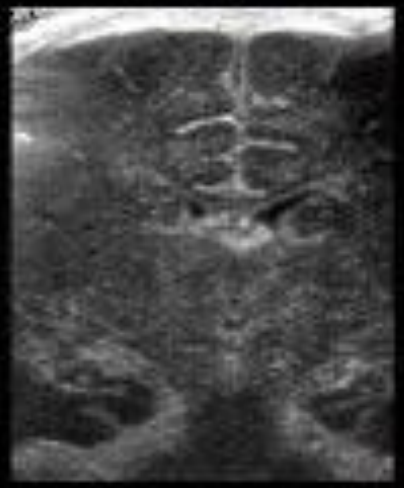
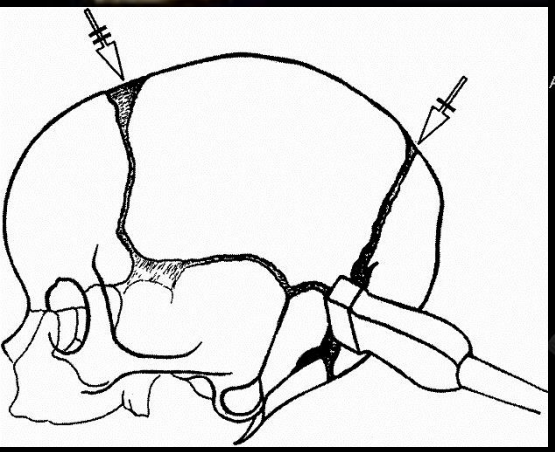
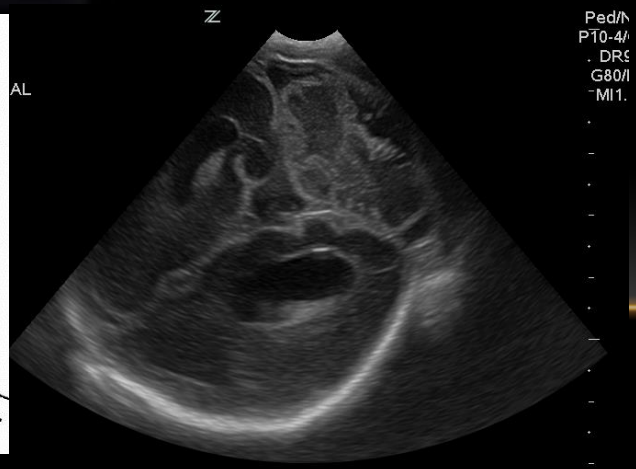
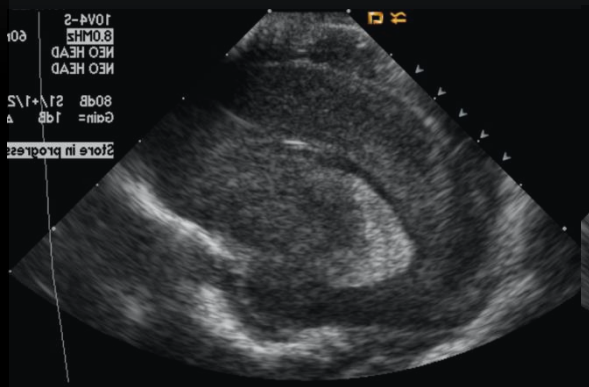
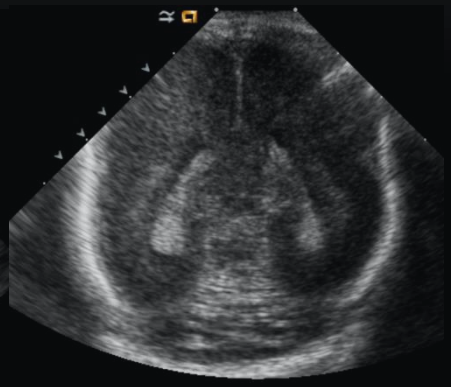





Premature brain-normal

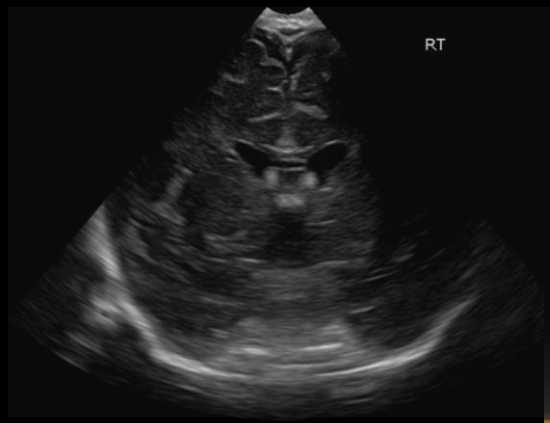
- < 32 weeks - smooth surface
- 36 weeks - reaches adult configuration
- Subarachnoid space should be < 5 mm in premature infants; less in term
- Cavum septum pellucidum – usually closes by 2-6 months
- Normal cisterna magna height 3-8 mm

Premature brain-normal

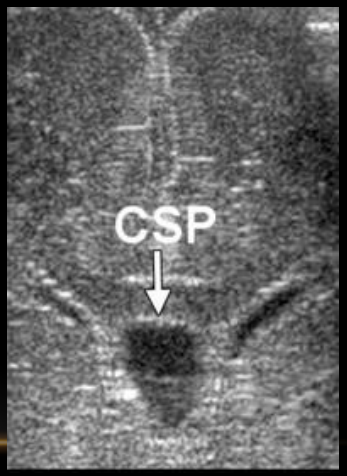




Undersulcation



Venticular prominence,
prominent extraaxial spaces,
open sylvian cistern



Cavum septum pellucidum

INTRACRANIAL HEMORRHAGE

- Premature Infants:

  - Incidence : 20-25%

  - Risks: < 30 wks / < 1500 g

- Germinal matrix
- 67% of premature infant less than 32 weeks have ICH versus 5% for term
- 25-50%-clinically silent, 50%-Day 1, 90% Day 3

INTRACRANIAL HEMORRHAGE

- Predisposing factors
- Increased systemic BP- Increased pCO2, increased IV vol,decreased Hb
- Increased CNS venous pressure-Tension pneumothorax, asphxyia, CHF, mechanical ventilation
- Decreased CNS perfusion-Hypotension, decreased pO2,Hb

Germinal matrix

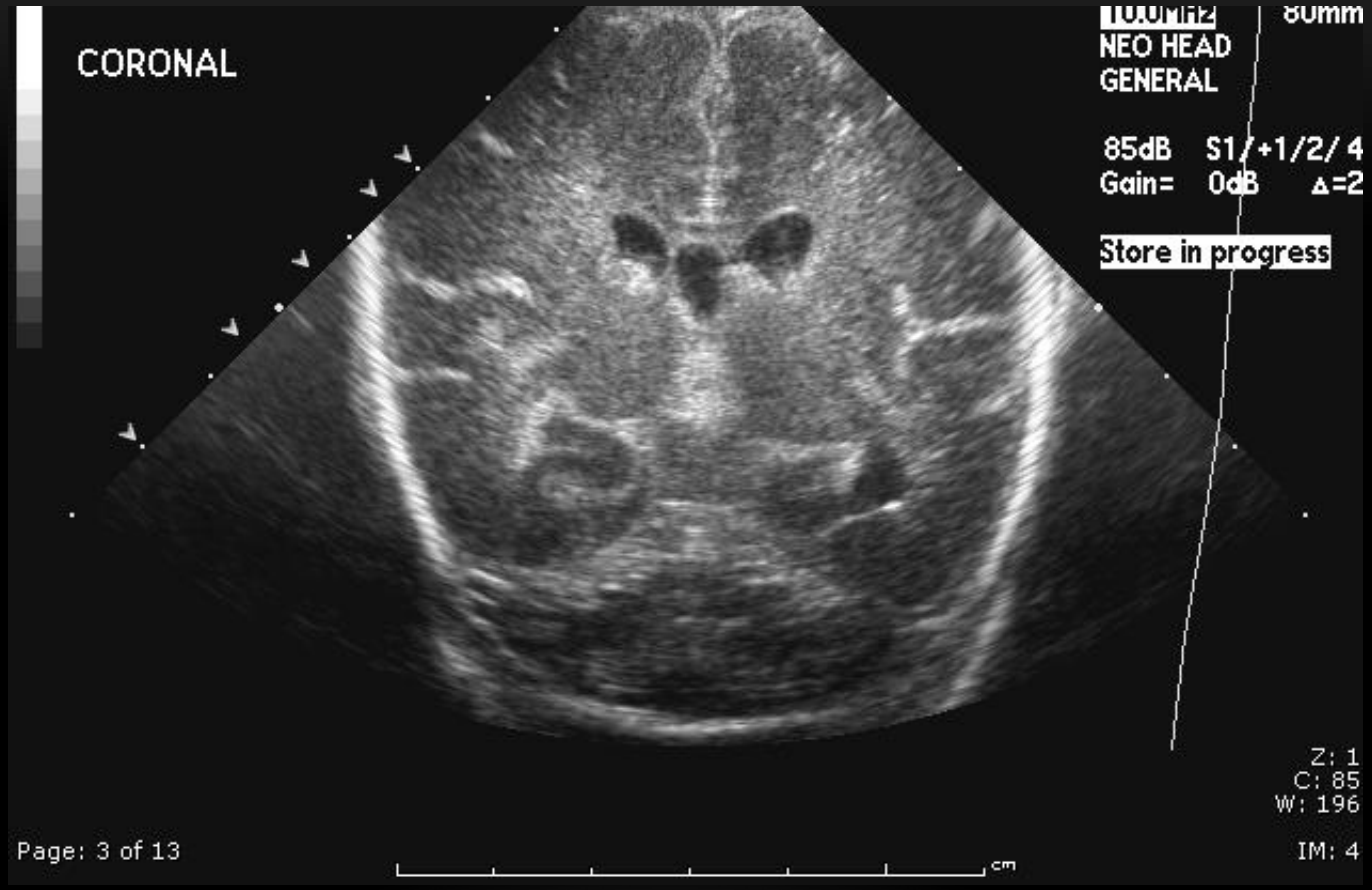
- Involution-3mth-9mths of gestation
- 28-32 weeks: only small amount left in caudothalamic groove
- By 36 weeks: involution is complete
- Premature-Lack of autoregulation-High risk of bleed-Capillary-Venous level hemorrhage

Burstein and Papile grading system

- Grade 1
  - Subependymal hemorrhage only
- Grade 2
  - Subependymal hemorrhage with blood in nondilated ventricles
- Grade 3 -35%
  - Subependymal hemorrhage with blood in **dilated** lateral ventricles
- Grade 4
  - Subependymal, blood in dilated ventricles, intraparenchymal blood

Grade 1 Hemorrhage

- Coronal image:
  - Echogenic mass inferior and lateral to floor of frontal horns
- Parasagittal image:
  - Echogenicity anterior to caudothalamic groove
- Clot liquefies over days to weeks, may form small 3-5 mm subependymal cysts


CORONAL
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Z: 1
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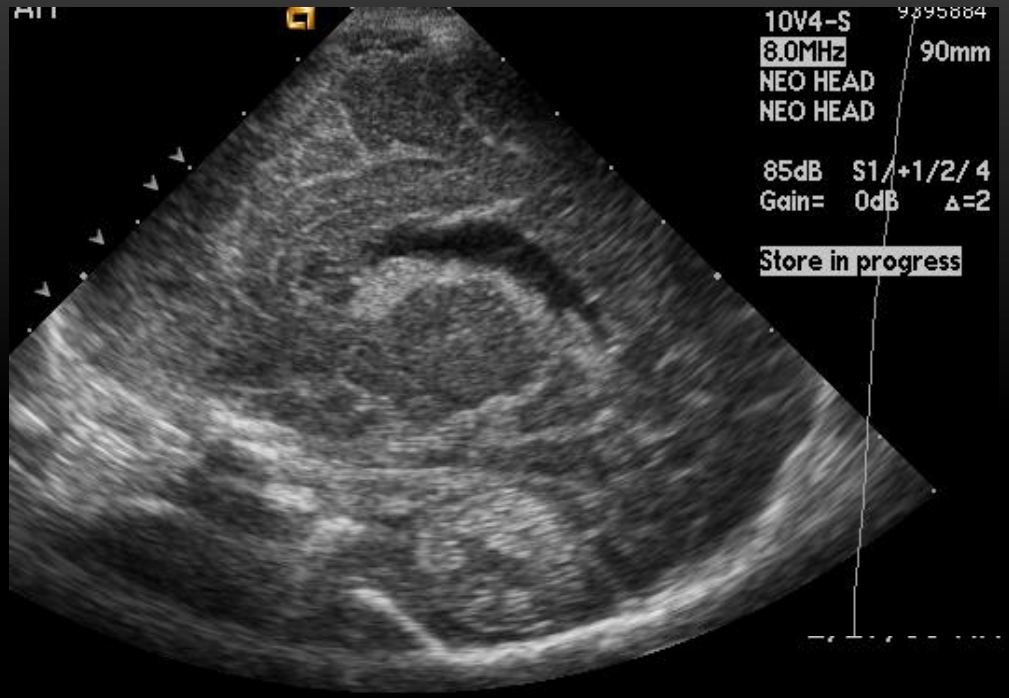
cm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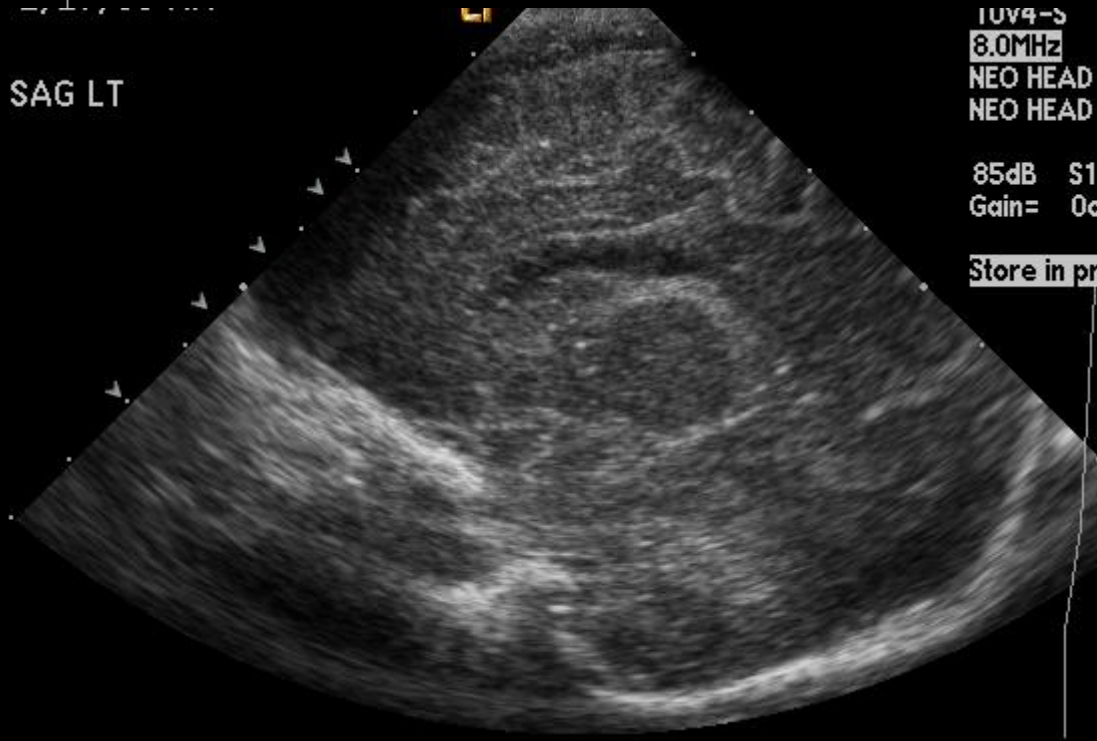
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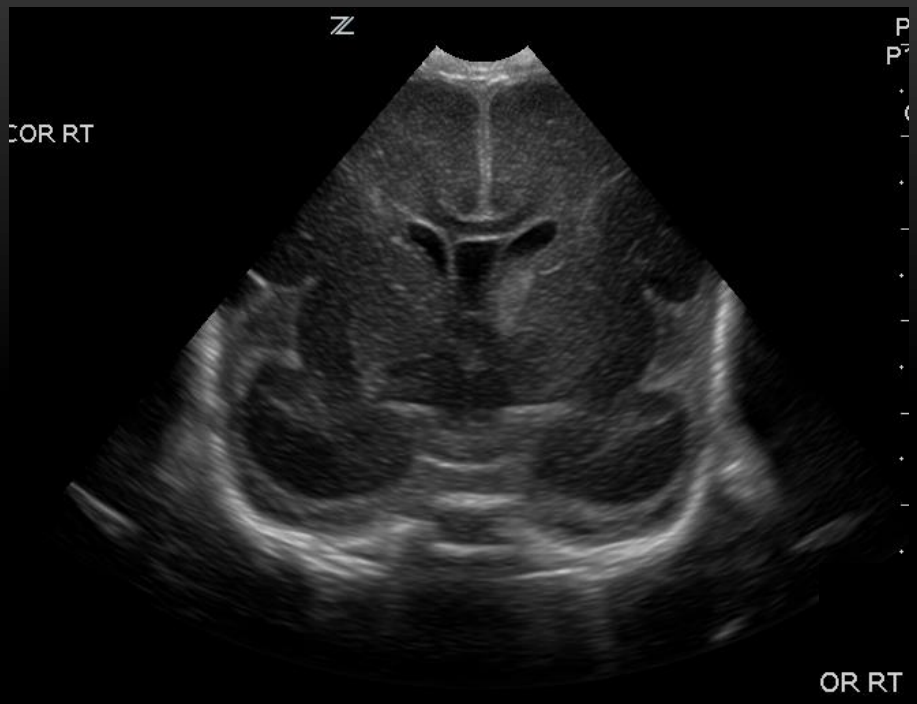
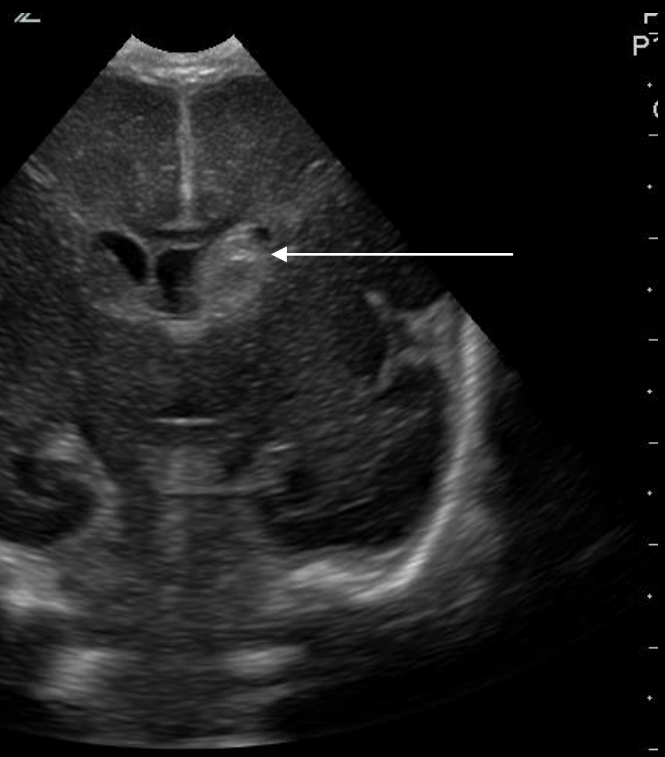
Gain=

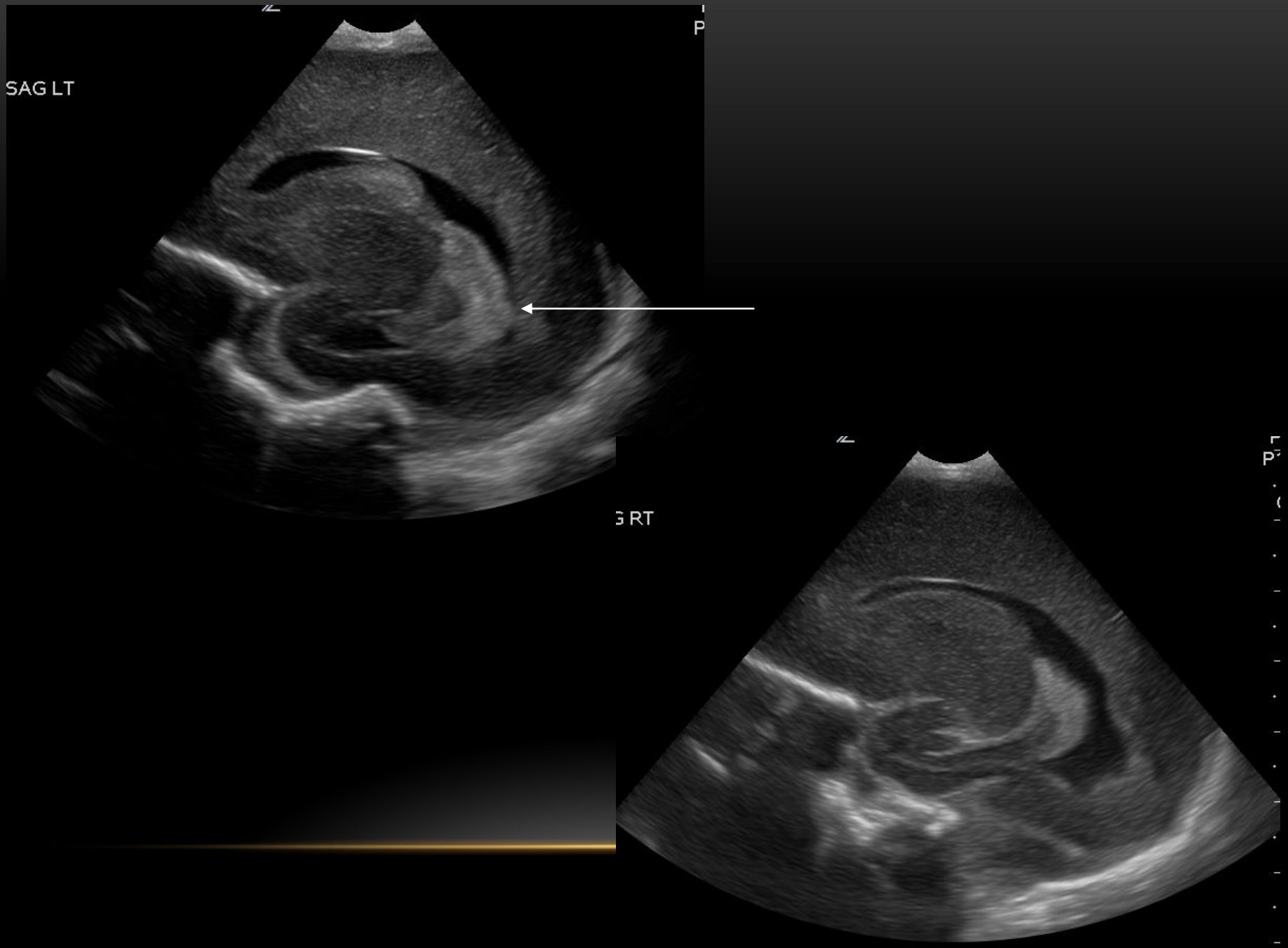
Grade 2 Hemorrhage

- Most difficult to diagnose
- Germinal matrix hemorrhage ruptures through ependyma, entering lateral ventricle
- No choroid plexus in occipital horns or frontal horns, so echogenicity anterior to foramen of monroe is clot
- Clot avascular / choroid plexus is not
- Can develop hydrocephalus





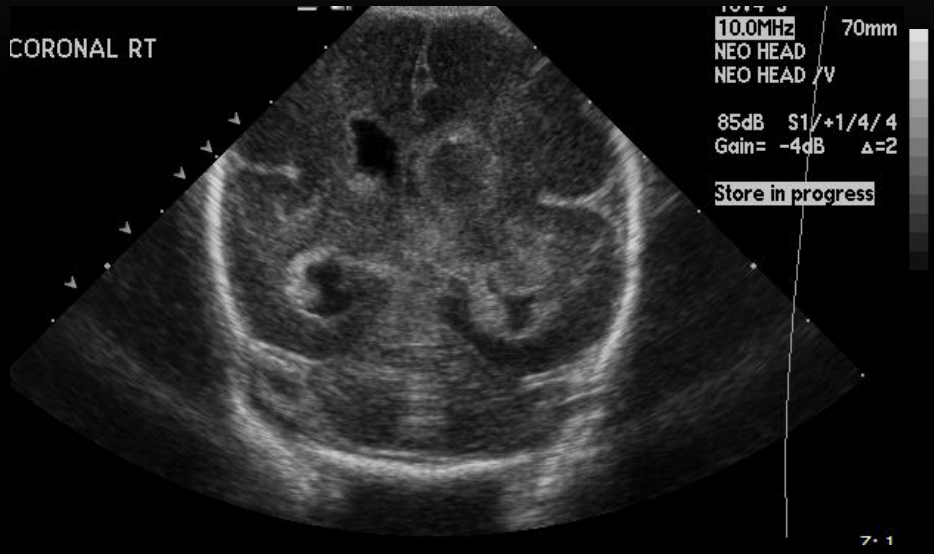
Intraventricular extension



Normal Right side

Grade 3 Hemorrhage

- Expands the lateral ventricles, 3rd, 4th ventricle
- Resolves over 5-6 weeks
  - Low level echoes, CSF/blood levels
- Hydrocephalus –Arrest/resolve-75%
- 10% require shunting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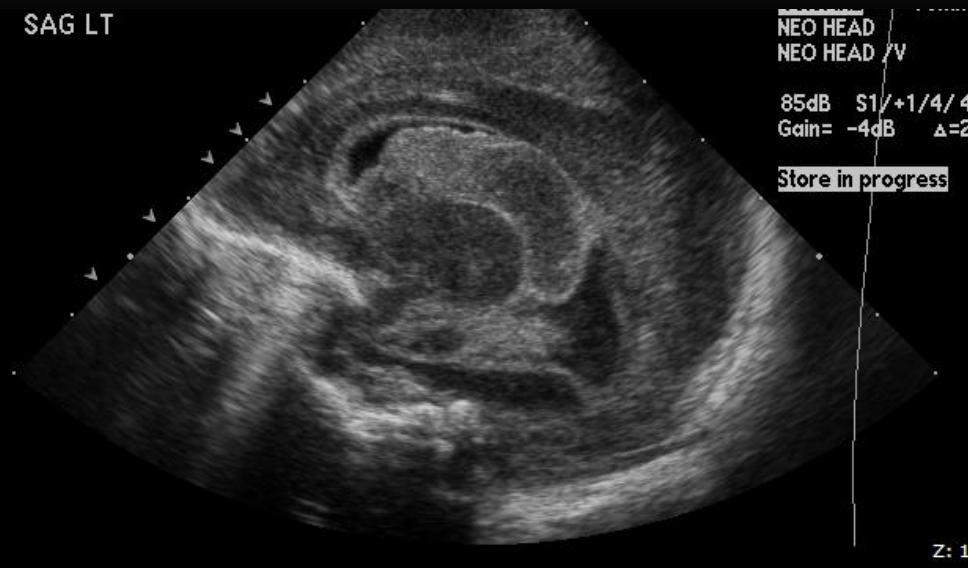
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Gain= -4dB Δ=2
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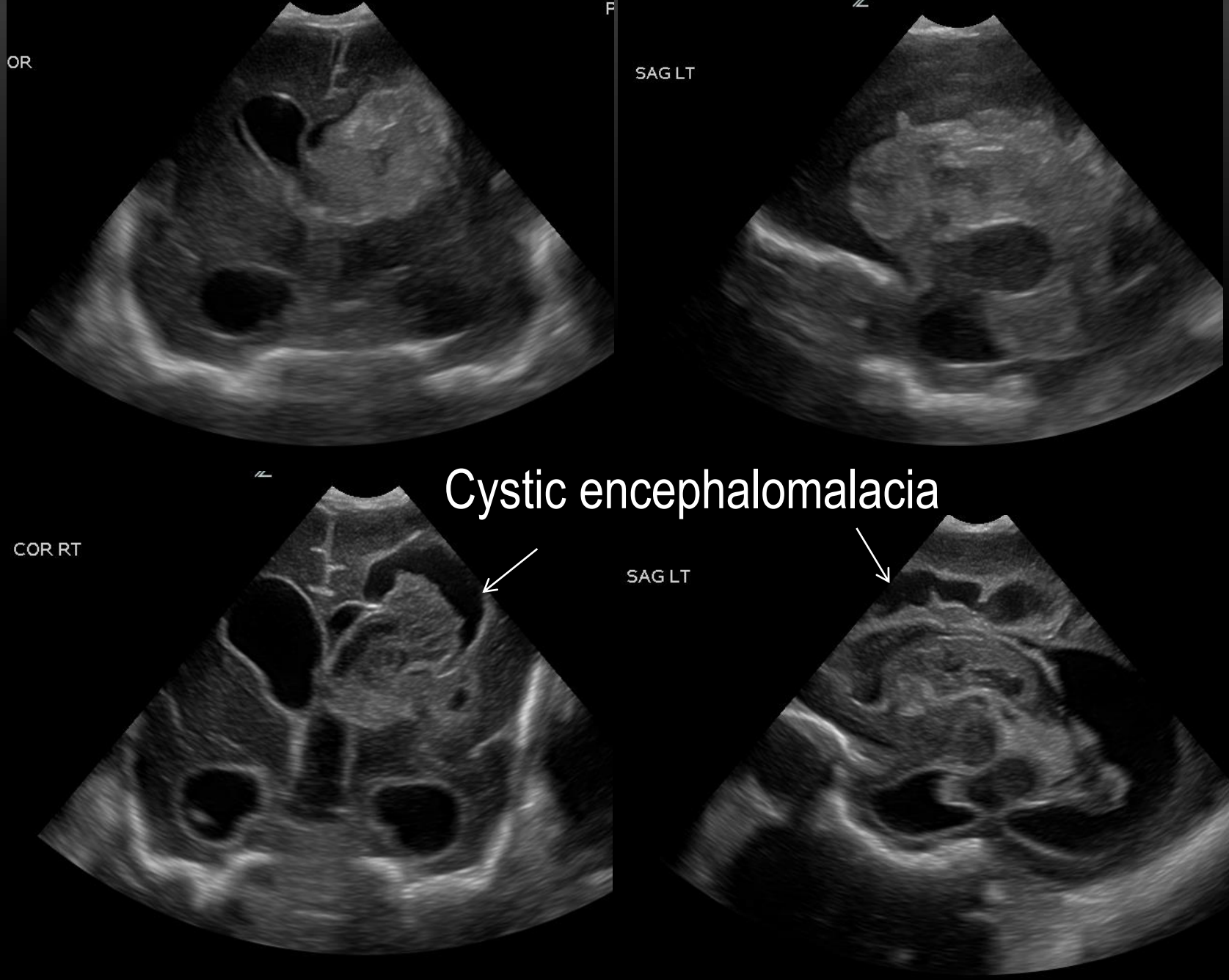
Grade 4 Hemorrhage

- Intraparenchymal hemorrhage
- Causes mass effect (vs PVL)
- Hemorrhagic venous infarct resulting from germinal matrix bleed compressing / thrombosis of periventricular veins
- Liquefies and retracts over several weeks
  - Hypoechoic center
  - Large porencephalic cysts (vs PVL) 2-3 months



Cystic encephalomalacia

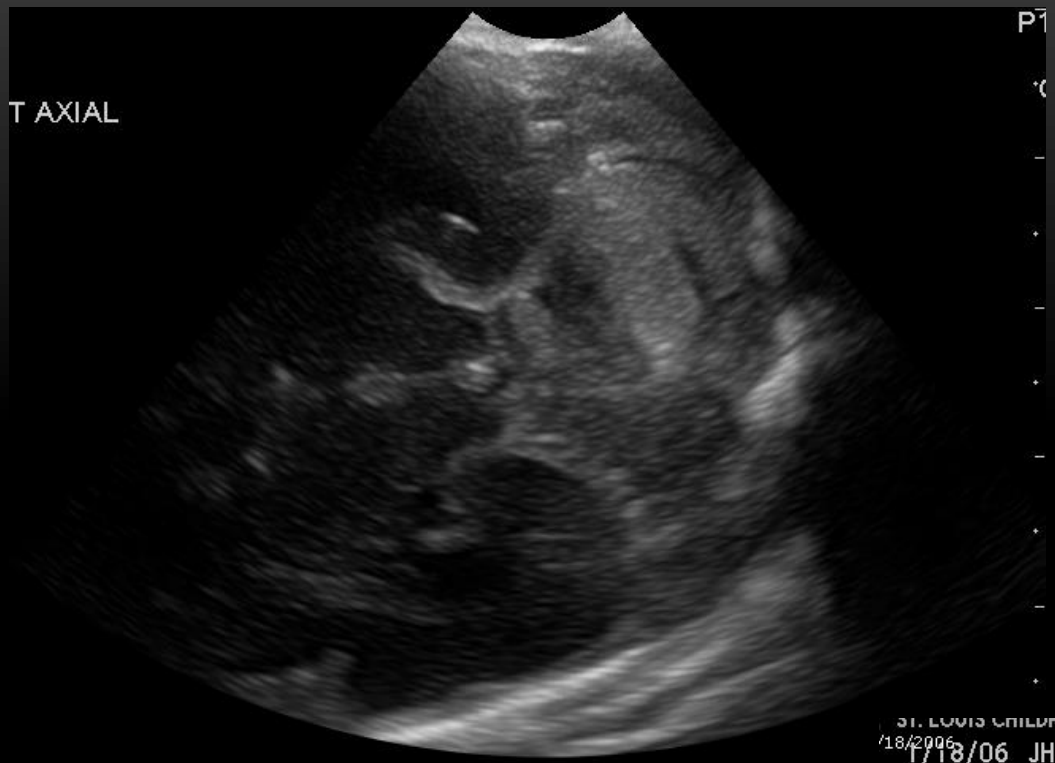
Prognosis

Grade	Mortality	Neuro Sequelae
1	5 %	5 %
2	10 %	15 %
3	20 %	35 %
4	50 %	90 %

Neurologic Sequelae –
Mental retardation, visual impairment,spastic diplegia or quadriplegia

Cerebellar hemorrhage

- Cerebellar hemorrhages occur in approximately 25% of preterm infants with very low birth weight
- External granular layer of cerebellum is also a germinal zone
- Best imaged through post/post-lateral fontanelle
- Can result in brainstem compression, increased ICP, cerebellar atrophy
- US: echogenic SOL in cerebellar hemisphere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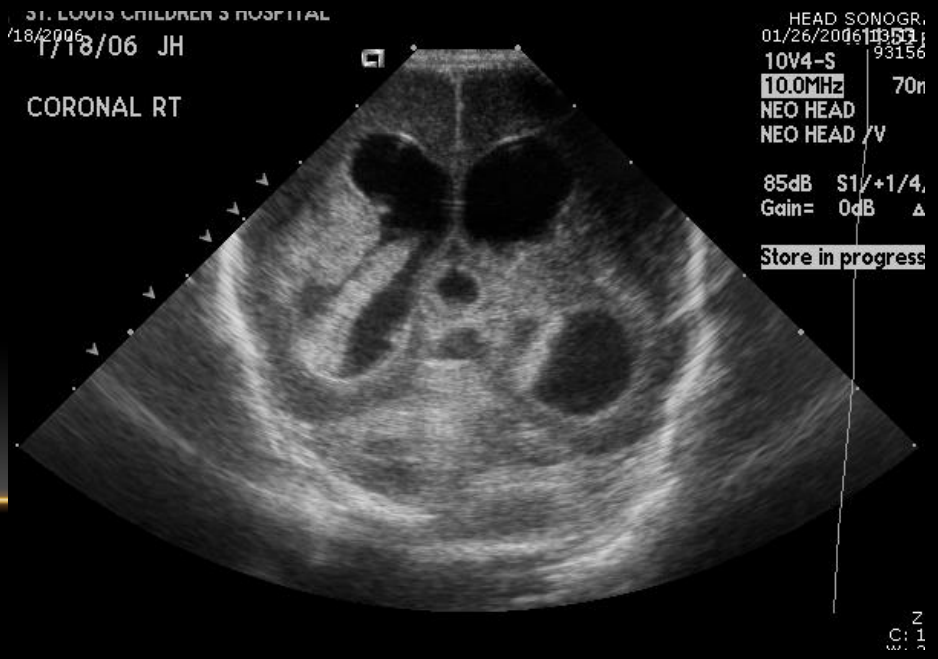
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Gain= 0dB
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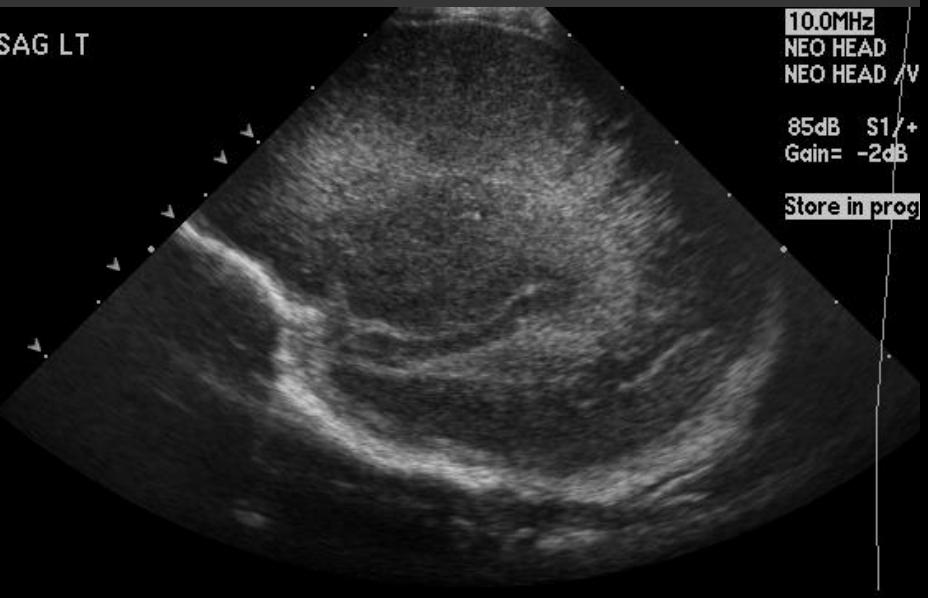
WHITE MATTER INJURY /HIEOF PREMATURITY

- Old term “periventricular leukomalacia”
- Lack of autoregulation
- Periventricular white matter adjacent to trigones and frontal horns; Deep or subcortical WM
- Secondary gray matter-thalami,BG, cortex,cerebellum
- US not sensitive to noncavitary white matter injury and underestimates
- Increased echogenicity of periventricular white matter > choroid plexus
- Definitive diagnosis: cystic necrosis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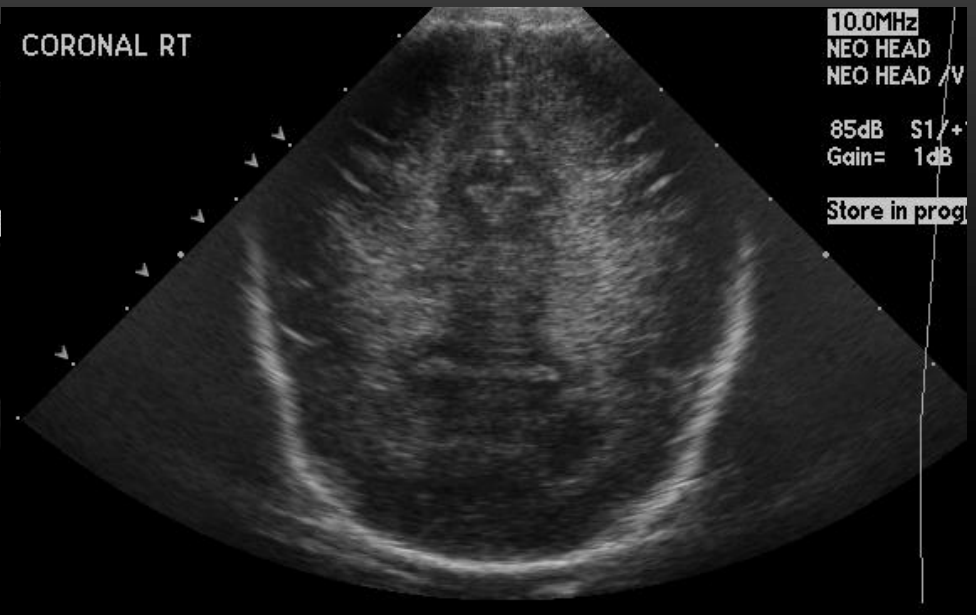
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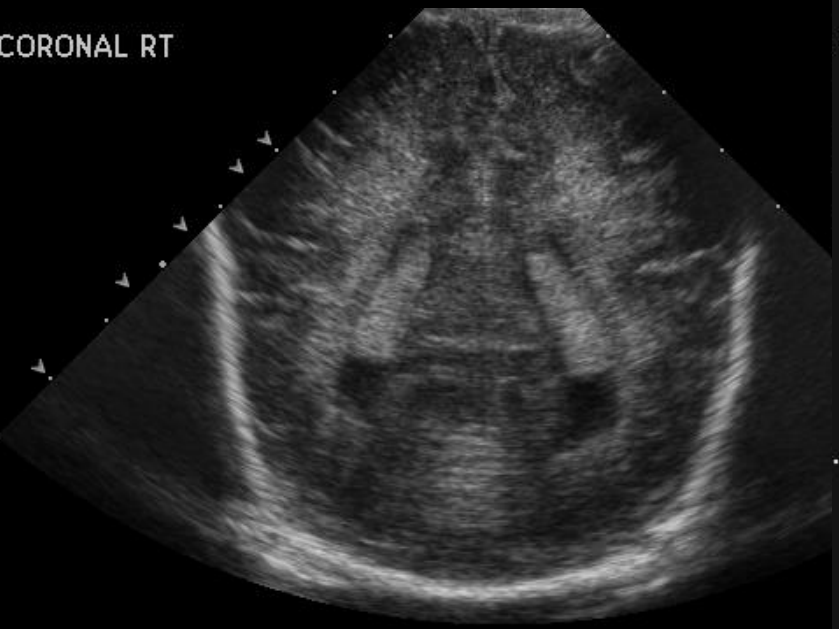
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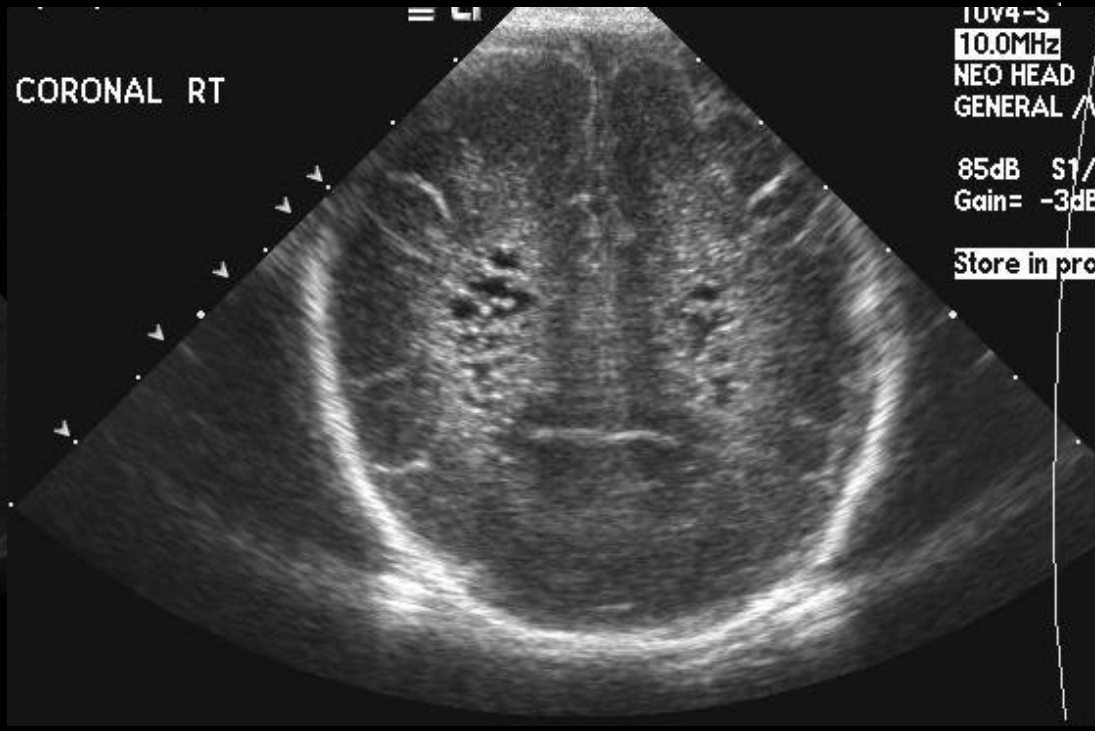
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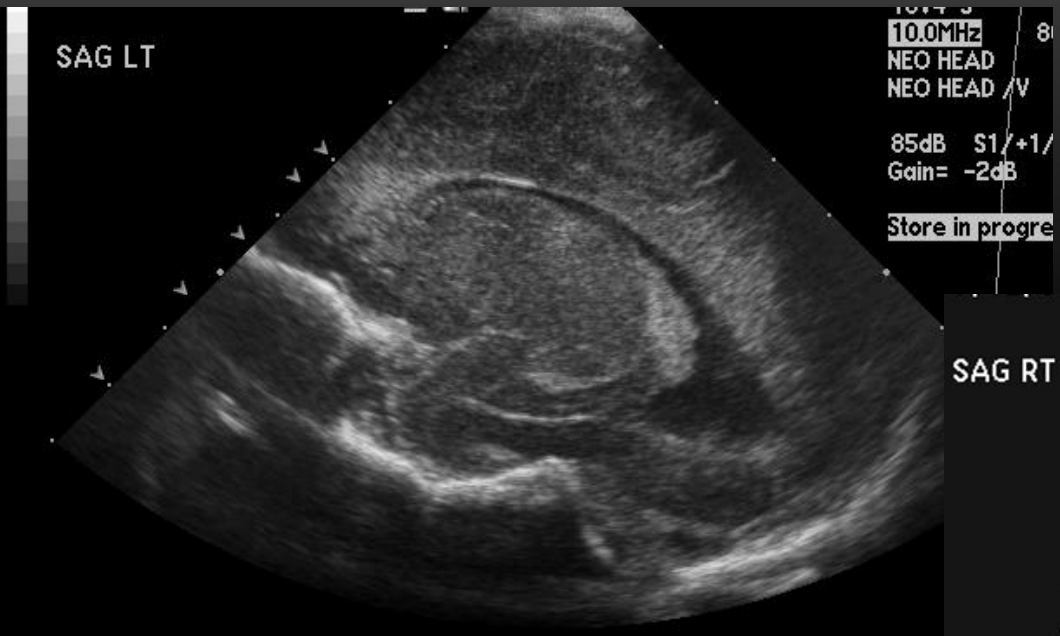
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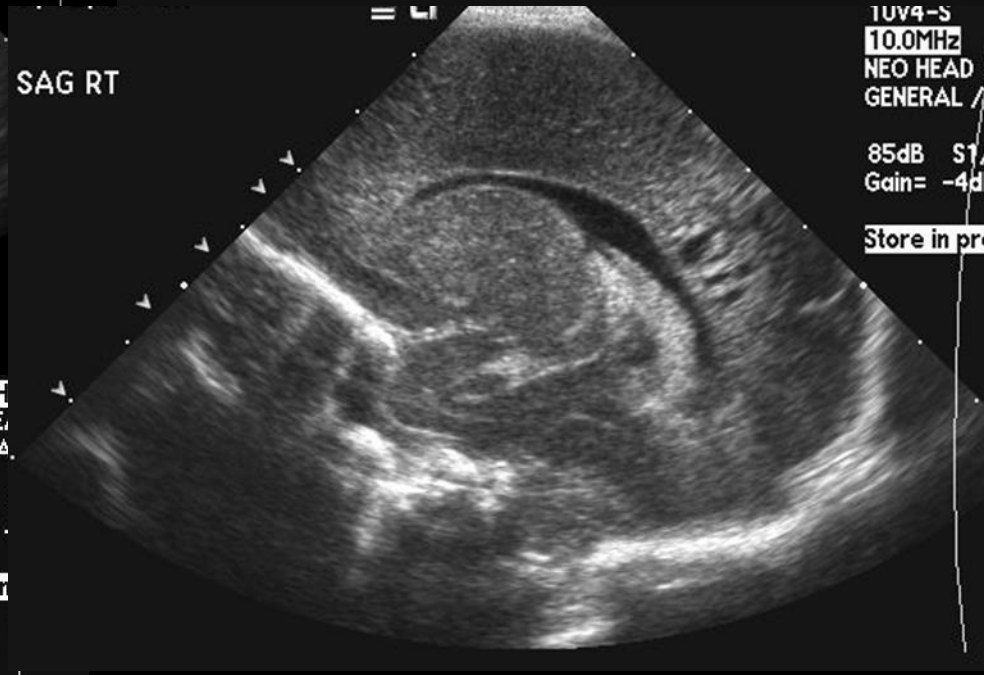
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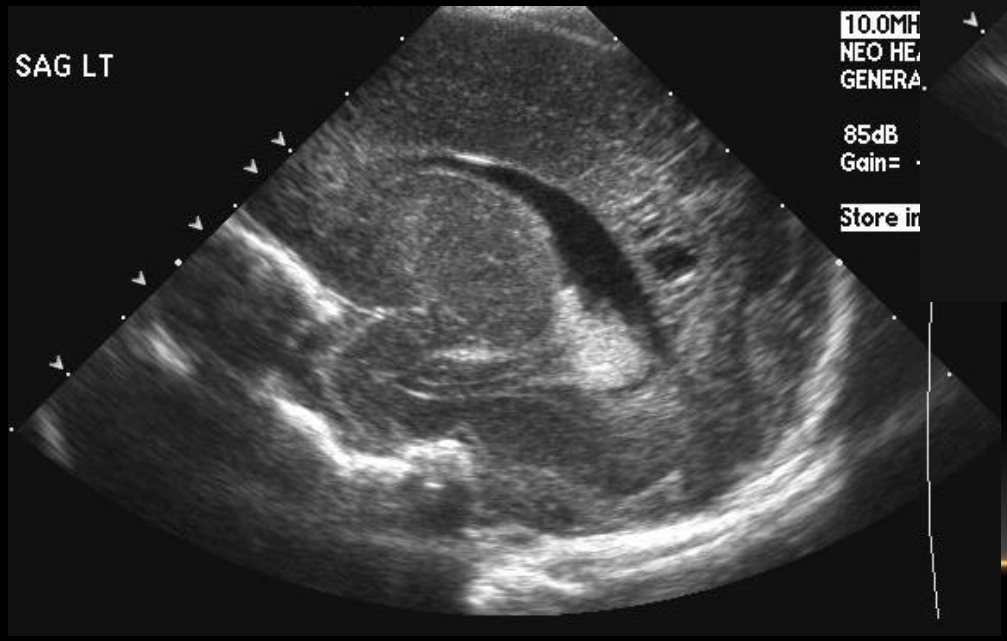
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Store in

SUMMARY USG

- Ultrasound fast and convenient for unstable infants
- Better at detecting hemorrhage than ischemia/hypoxia
- Initial evaluation in term infants-ischemia/hypoxia, congenital malformations, infection


Kartikeya
2015

MRI

PATIENT IMAGING-MRI

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

MRI

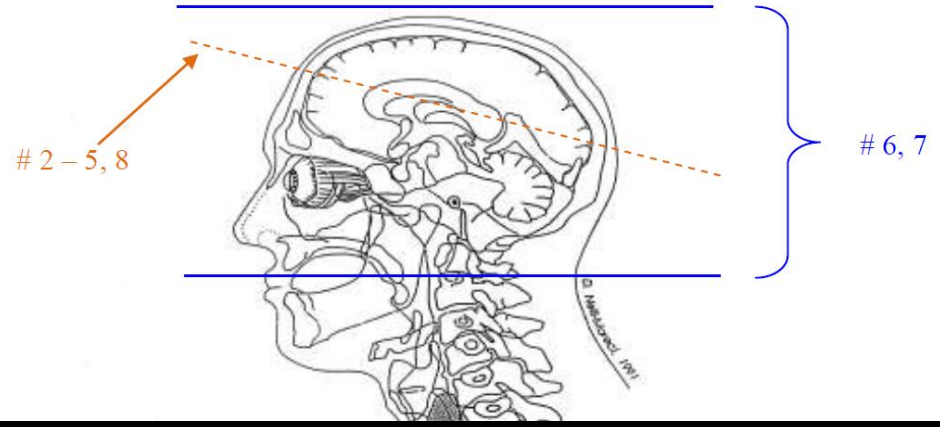
- Neonates' vital signs are prone to fluctuate, and several parameters must be closely monitored
- STABLE- sugar, temperature, artificial breathing, blood pressure, and laboratory test results
- ***High-quality coronal diffusion-weighted images also can be obtained-neonates lack pneumatized paranasal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

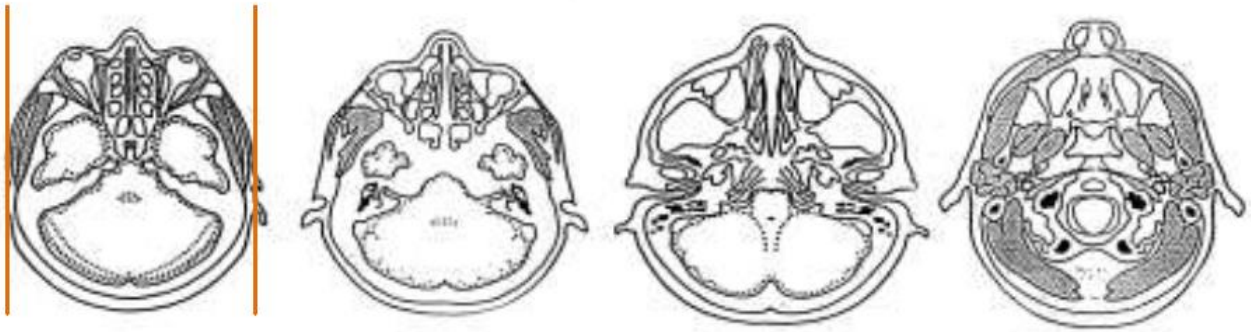
MR Brain Neonatal Screen without IV Contrast

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**





Indications

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

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

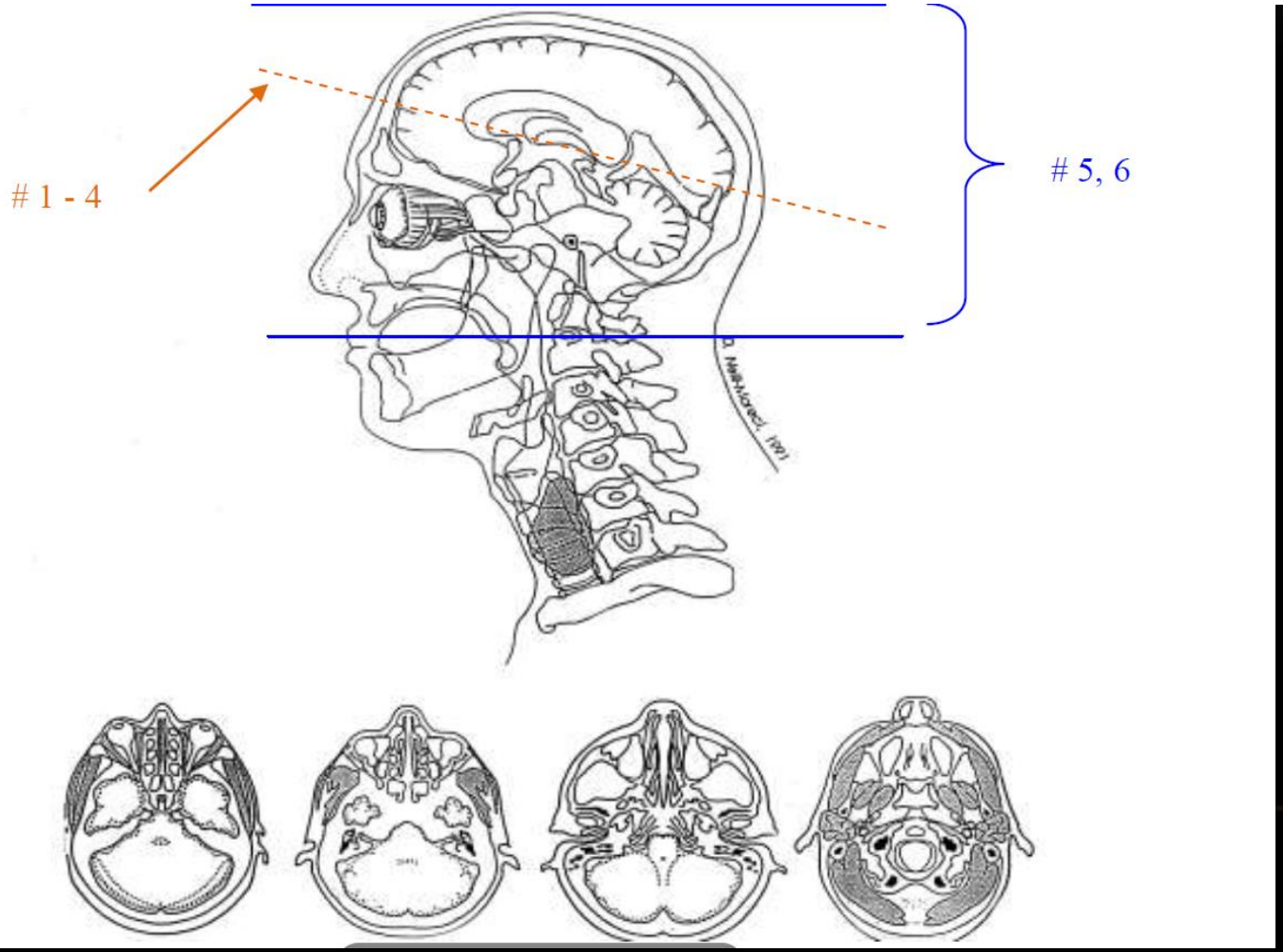
FLAIR-Poor due to high water content
Imaging best -1-2 week
Diffusion-False negative < 24 hrs
Pseudonormalize- 6 day

SPECIAL INSTRUCTIONS:

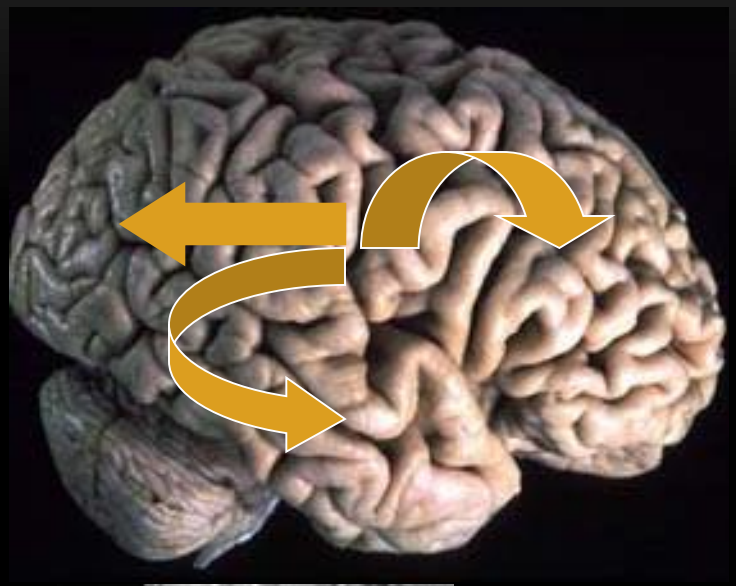
For neonatal brains, post warming protocol

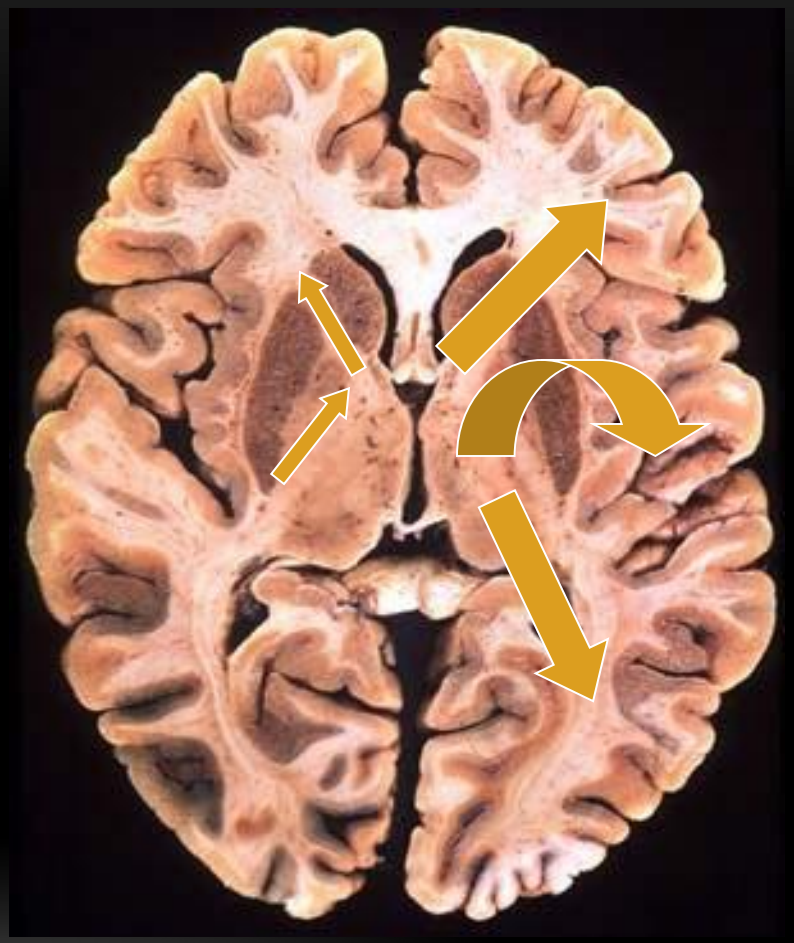
*** Do NOT angle volume slab.**

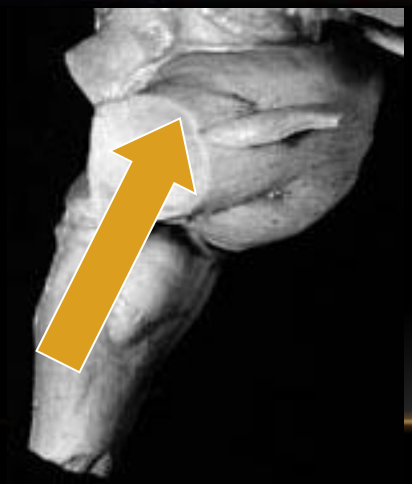
** Place slab for multi-voxel MRS in right or left basal ganglia region. Voxel volume has to be > 2.5 cc.



PROGRESSION OF MYELINATION



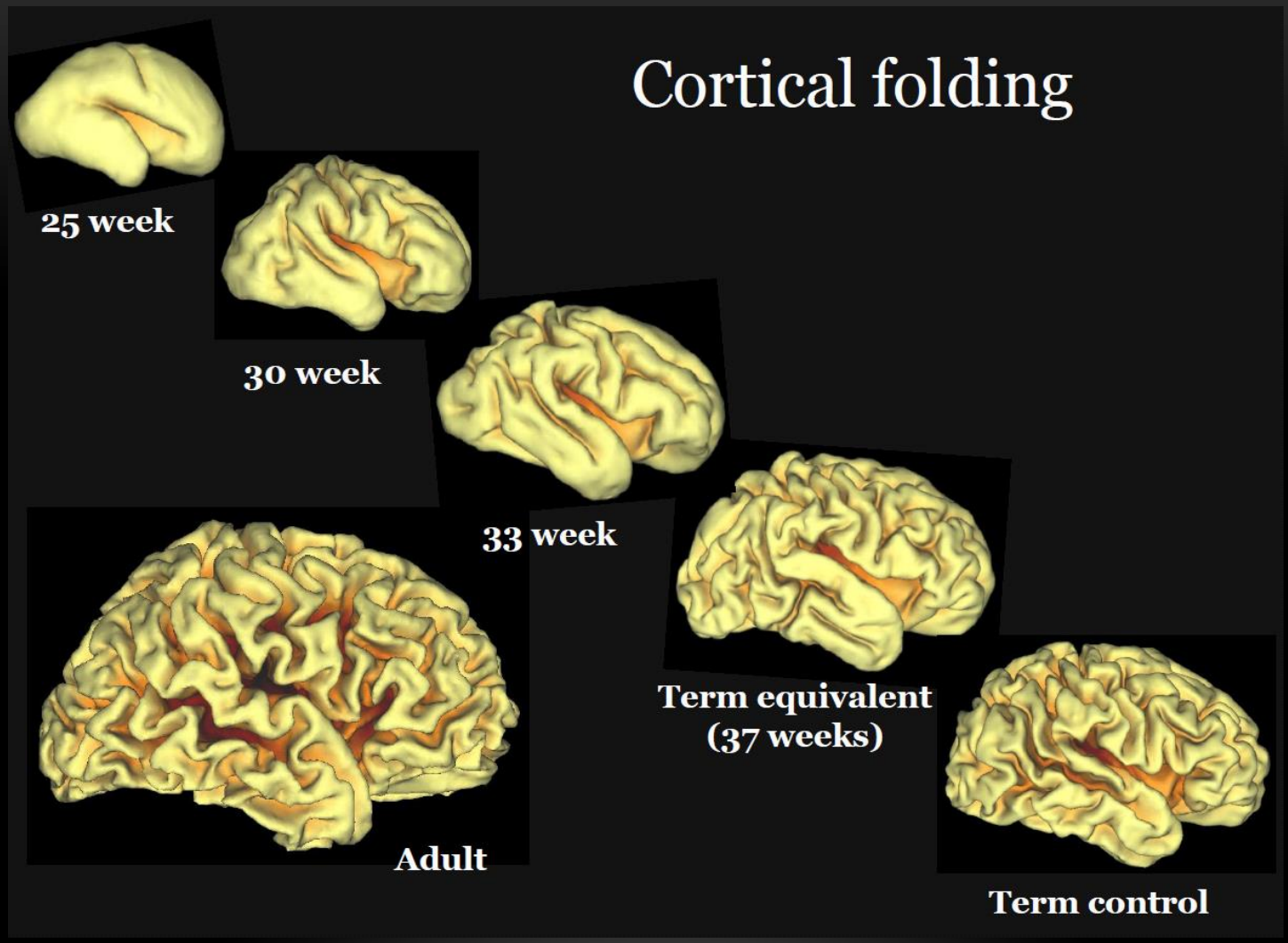




Rostral to caudal; Posterior to anterior; Central to peripheral

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

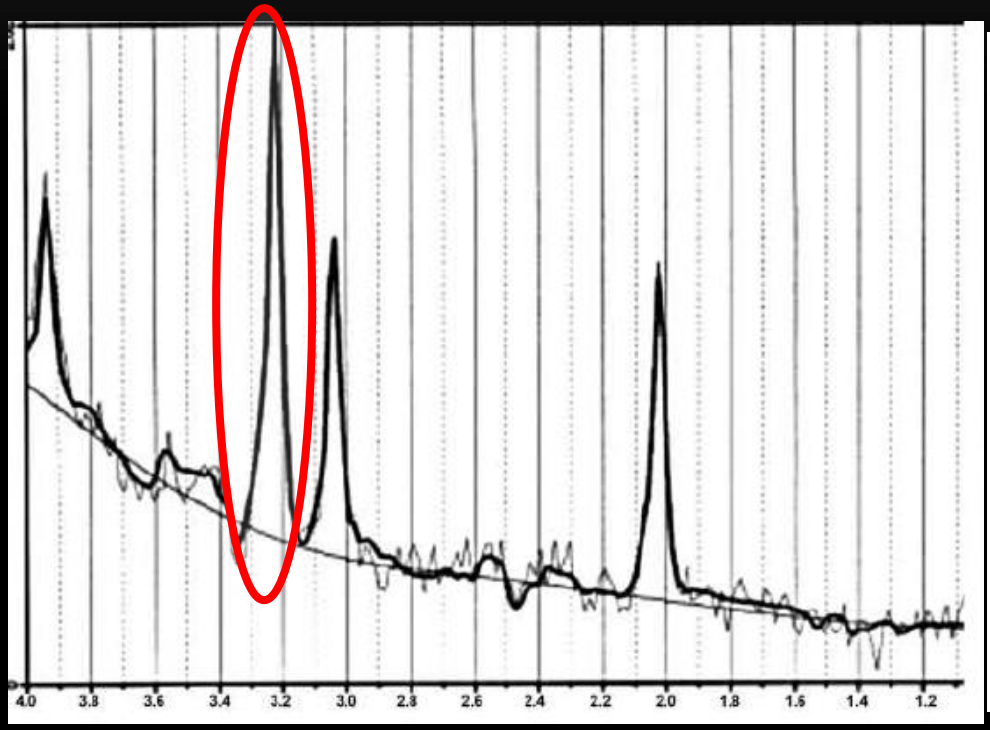


Courtesy: Dr. Robert McKinstry

Sulcation

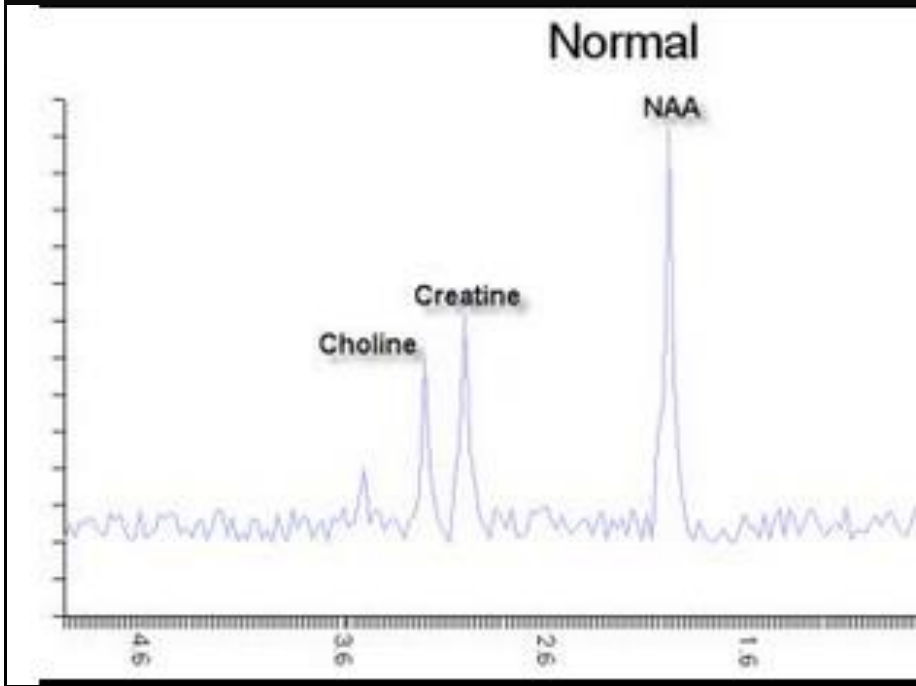
- 16 weeks-Interhemispheric and sylvian
- 22 weeks-Parietooccipital, Hippocampal,Callosal
- 23-24 weeks- Calcarine
- 24 weeks-Cingulate
- 26 weeks-Central
- 27-Precentral,Superior temporal,marginal
- 28 weeks-Post central
- 29 weeks-Superior frontal,Inferior frontal
- 33 weeks-Inferior temporal

NORMAL MRS IN A TERM INFANT



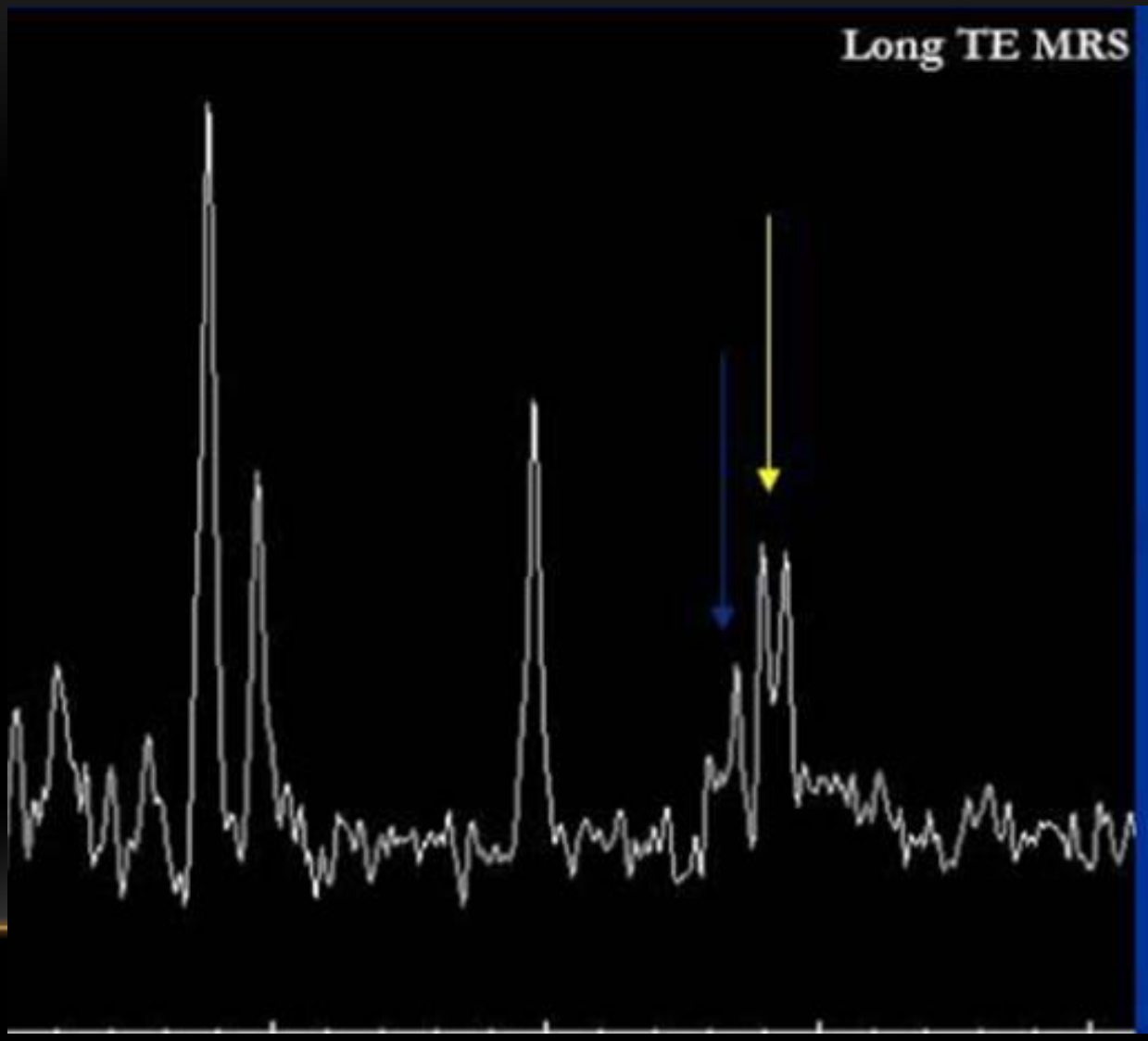
RadioGraphics 2010; 30:763–780

NORMAL MRS IN AN ADULT



Premie MRSpectroscopy

Varies
Preterm may contain lactate




Kartikey 2016

HIE IN PRETERM

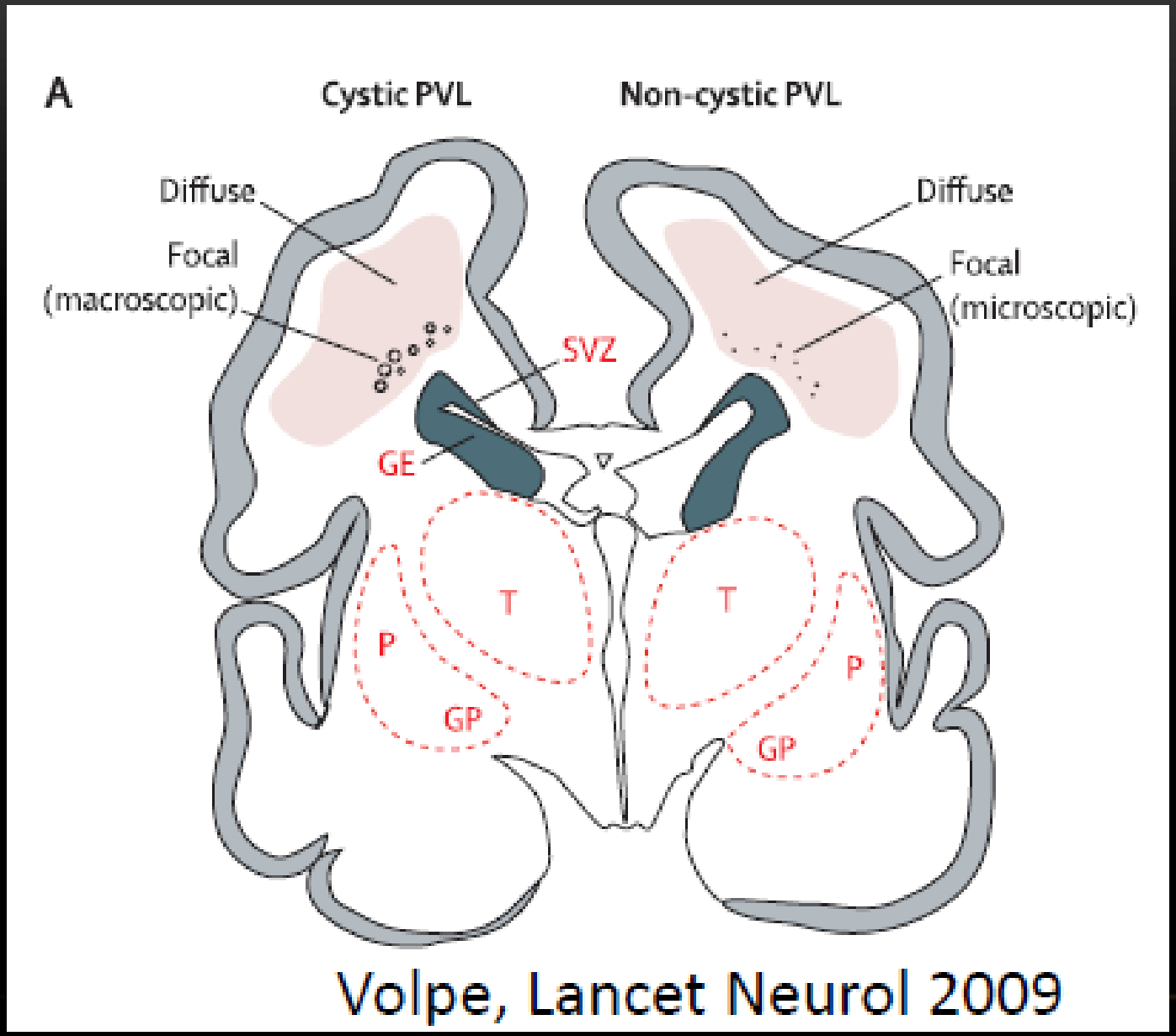
- 50% of cases of cerebral palsy –Premature infants
- Up to 19% of infants born before 28 weeks of gestation develop cerebral palsy
- Hypoperfusion –Watershed Ischemia- Premyelinating neurons
- Lack of autoregulation

HIE IN PRETERM

- **Severe** hypoxic-ischemic insults to the premature brain typically injure the thalamus, anterior part of the vermis, and dorsal brainstem. Involvement of the basal ganglia, hippocampus, cerebellum, and corticospinal tracts also may be seen
- **Mild to moderate** hypoxic-ischemic injury may result in a germinal matrix hemorrhage, periventricular leukomalacia, or both

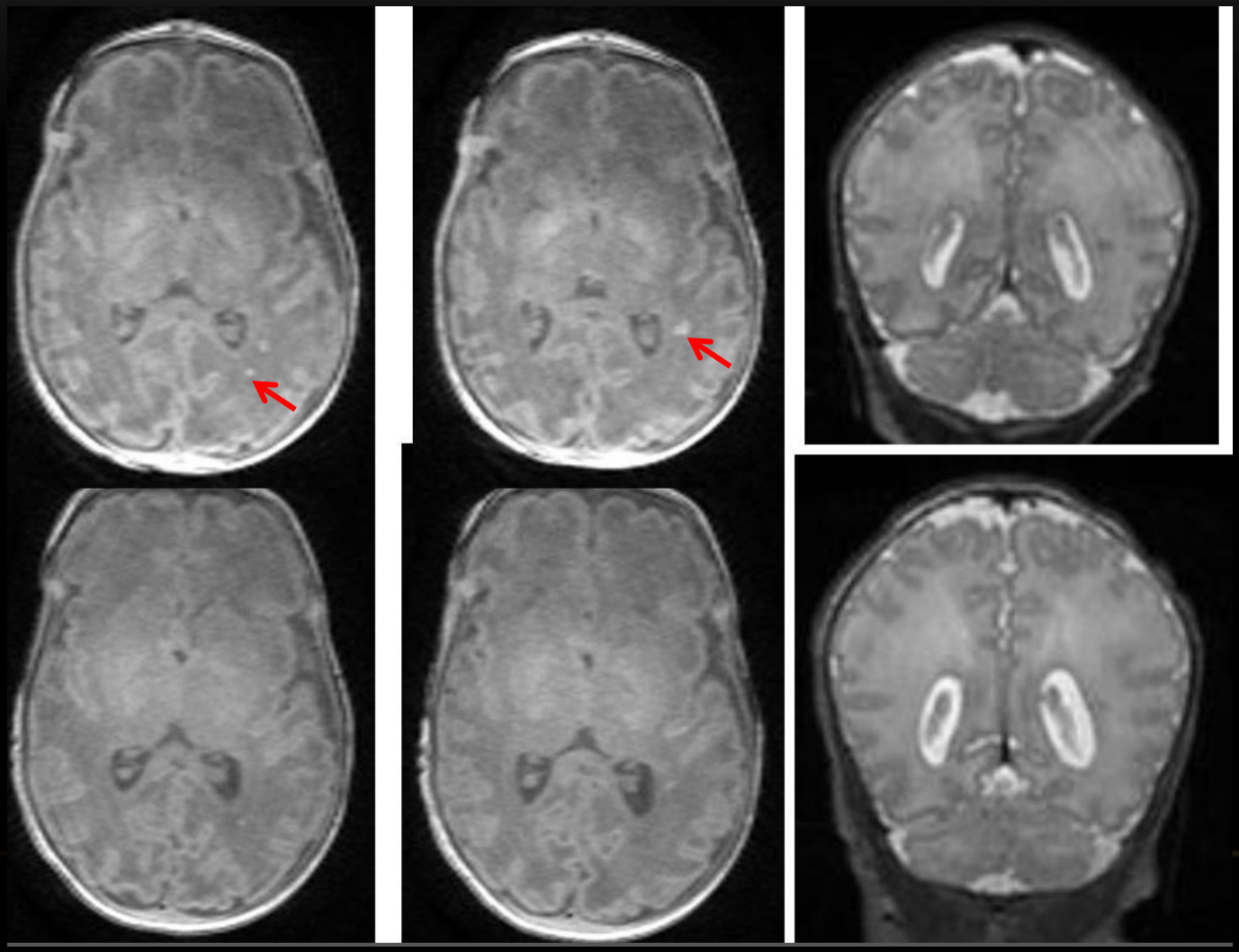
PREMATURE INFANTS

- 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

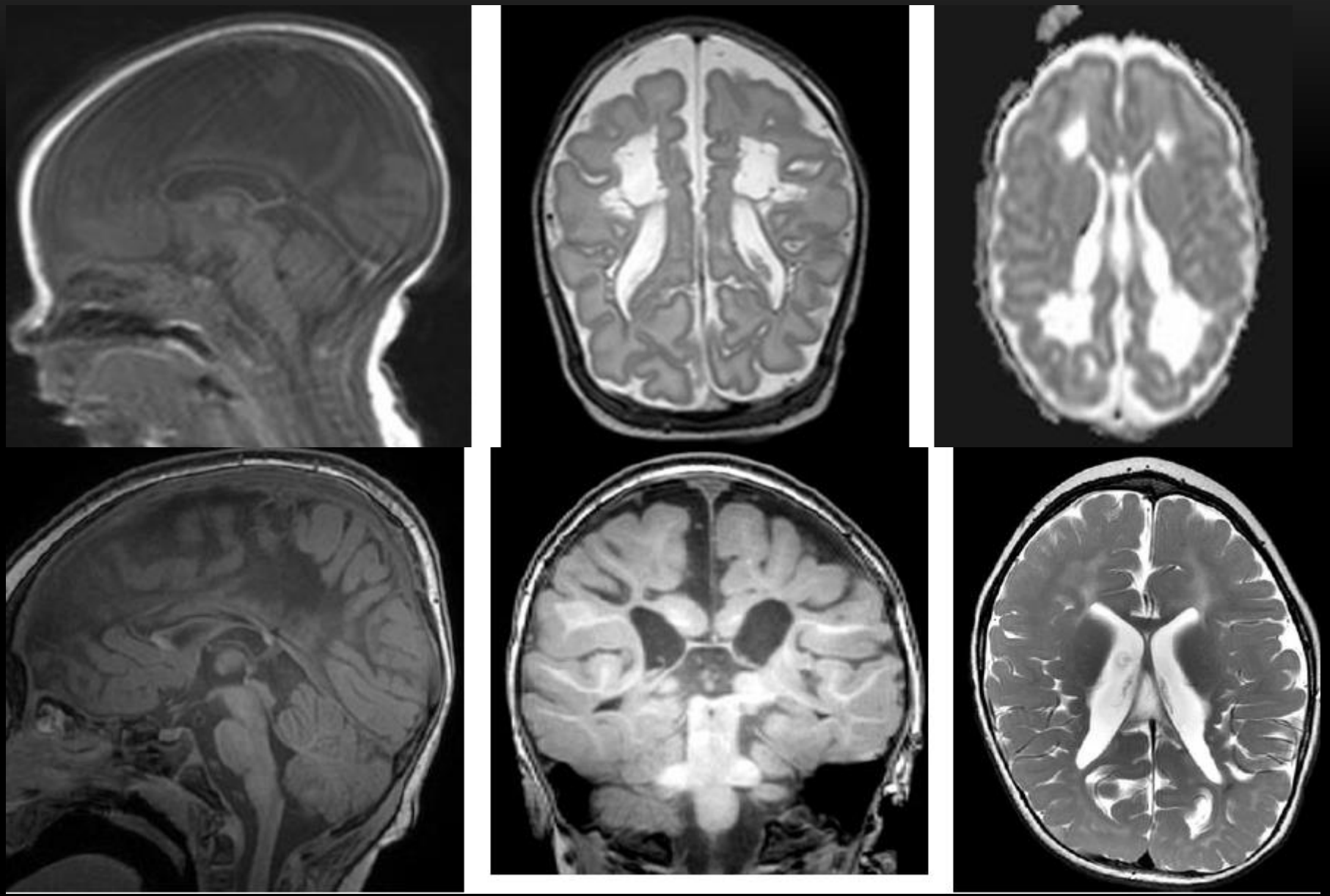


Volpe, Lancet Neurol 2009

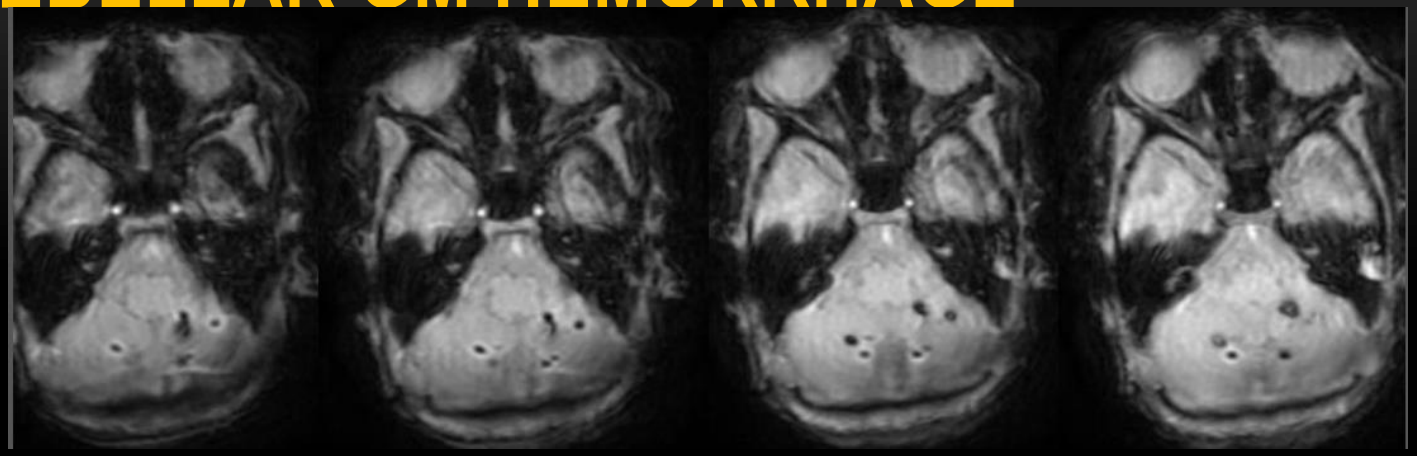
FOCAL NON CYSTIC EX 30 WEEK EGA



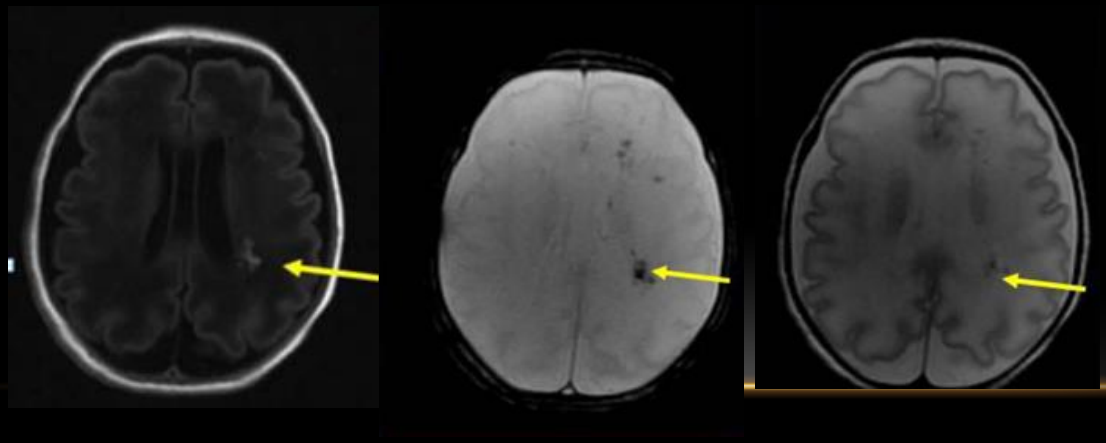
2 PATIENTS WITH CYSTIC TYPE INJURY



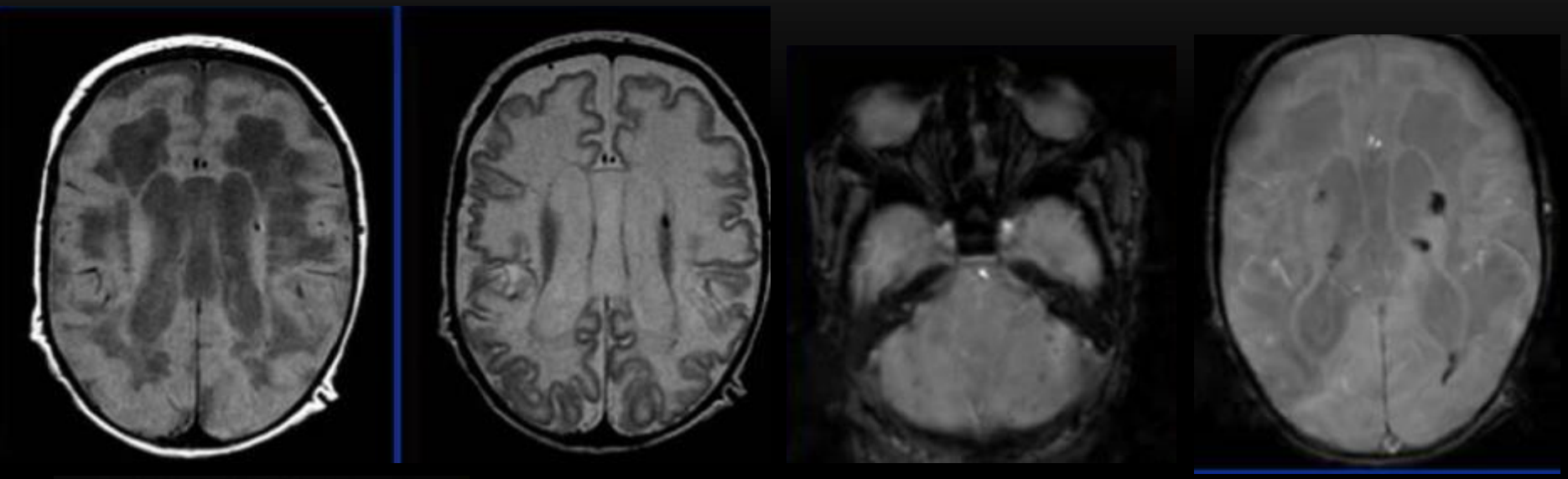
CEREBELLAR GM HEMORRHAGE

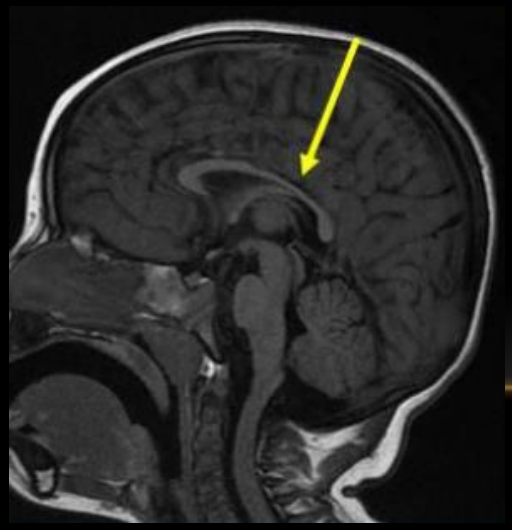


HEMORRHAGIC HIE OF PREMATURE-WM INJURY



CHRONIC WM INJURY-MIXED PATTERN

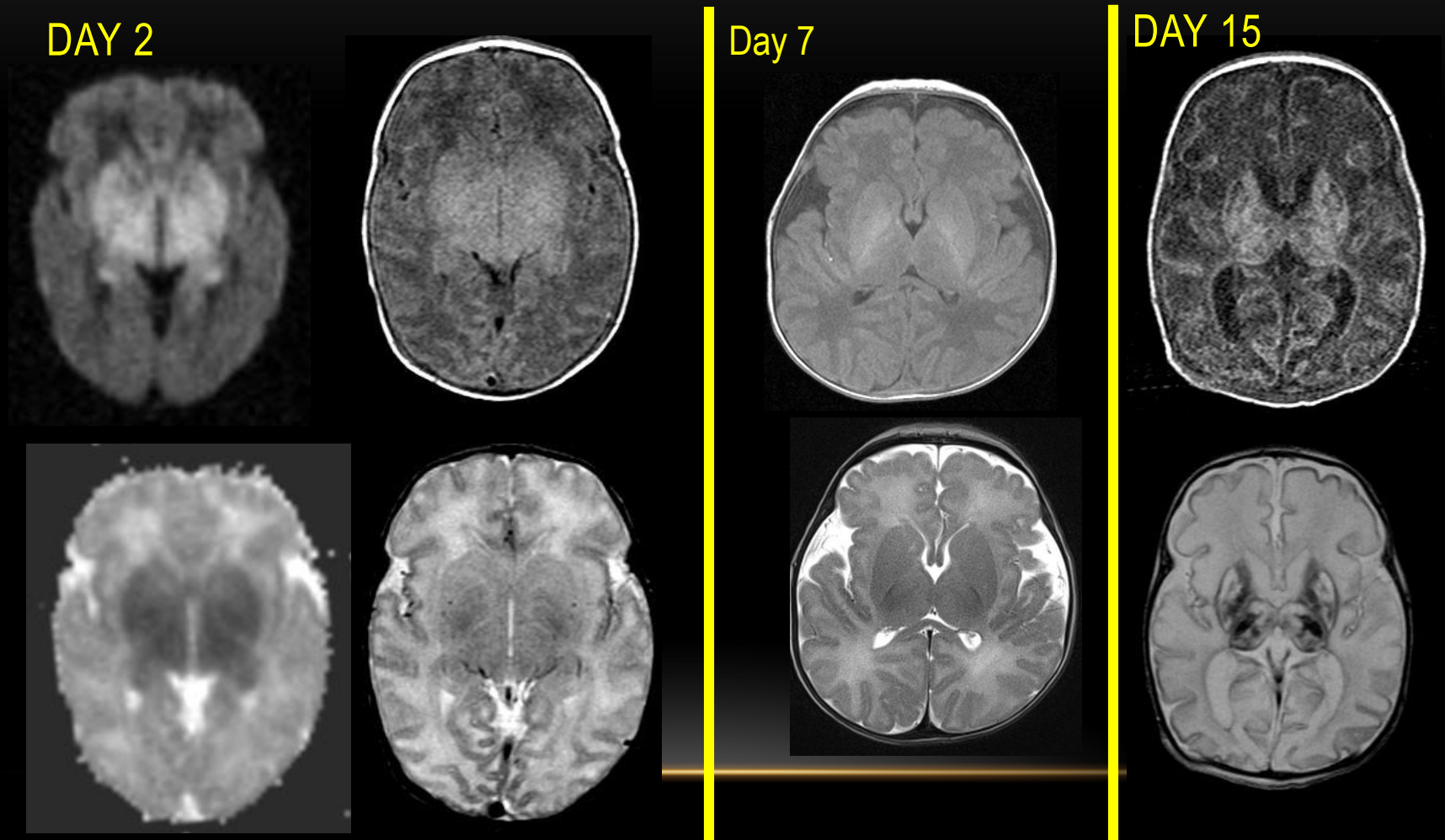




CHRONIC WM INJURY

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

PREMATURE- SEVERE INJURY



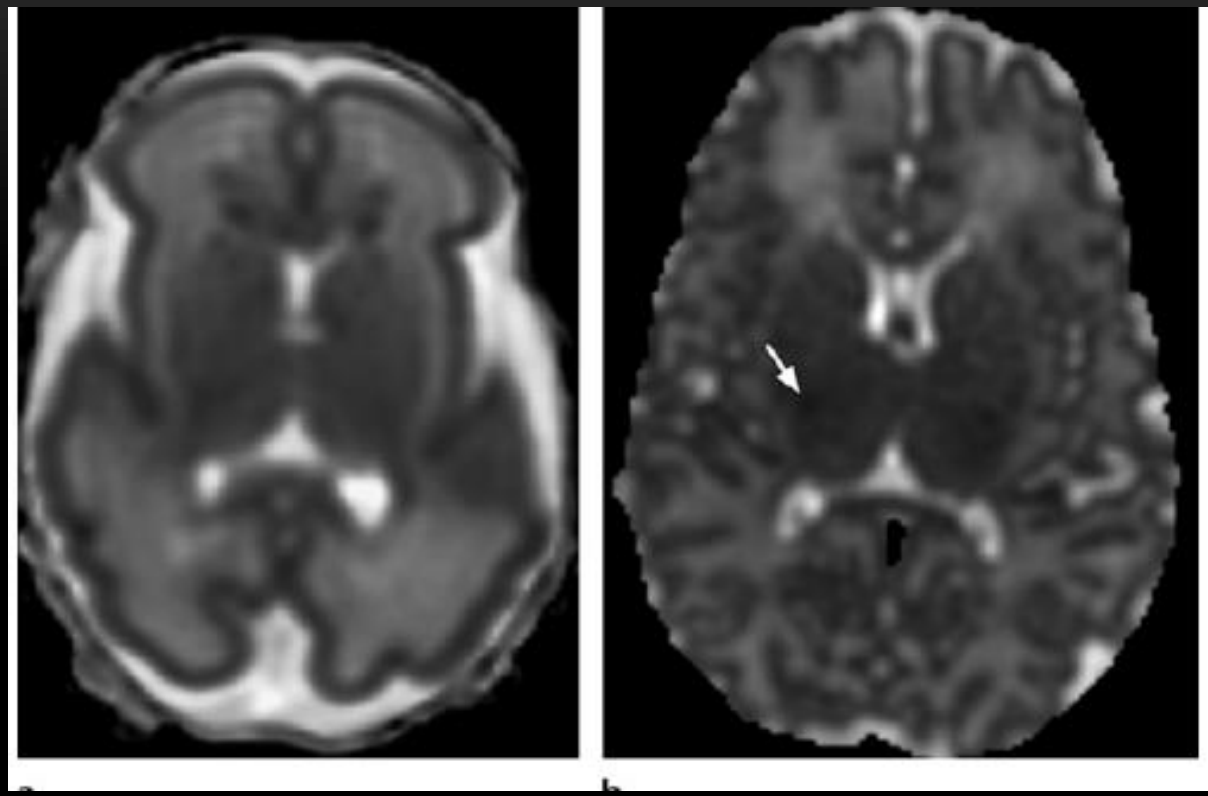


Figure 6. (a) ADC map obtained in a neonate at 26 weeks of gestation shows moderately decreased cortical water diffusion and increased white matter water diffusion. (b) ADC map obtained in a neonate at 38 weeks of gestation shows more limited water diffusion than in a, with resultant lower signal intensity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

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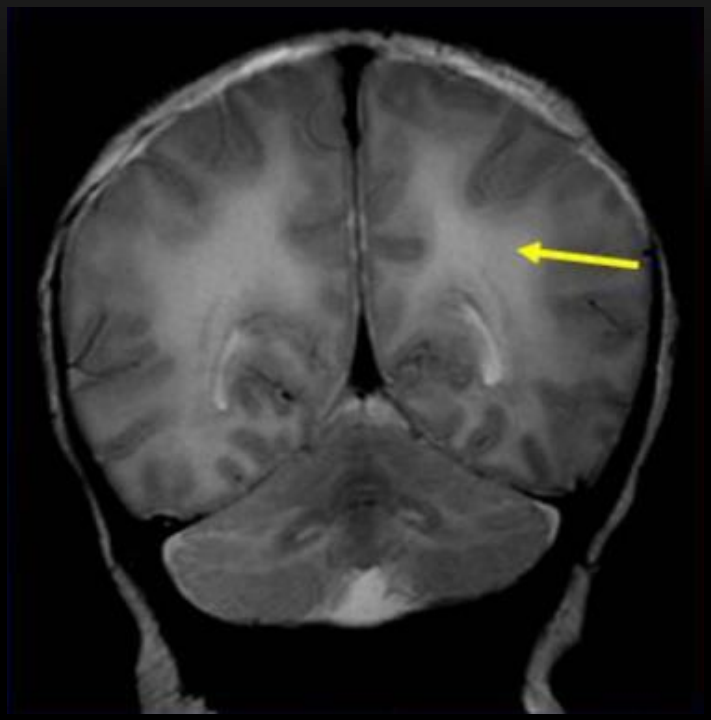
Diffusion in the cortex is more restricted because of the higher ratio of cells to extracellular space

DIFFUSE EXCESSIVE HIGH SIGNAL INTENSITY IN WM(DEHSI)

- Controversial
  - WM
  - Increase diffusion
  - Poor neurologic outcome



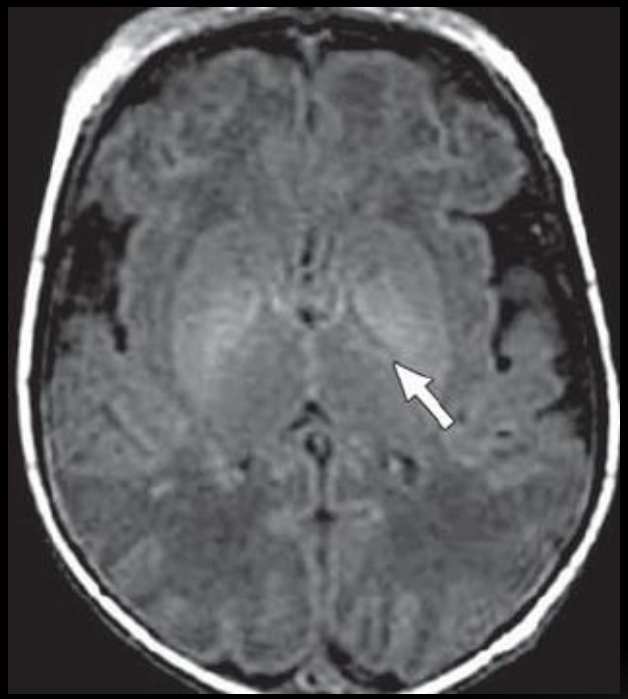
- Transient normal process
- No difference; No difference ADC values with controls

FULL TERM INFANTS

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

NORMAL

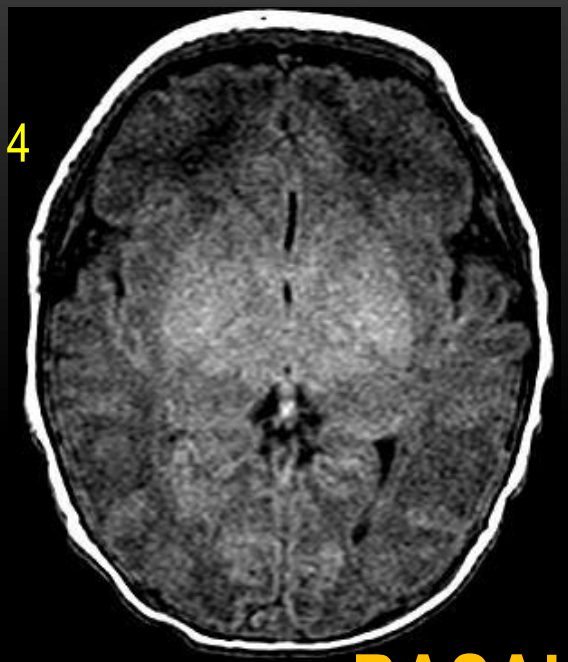
2 day old 36 week EGA boy

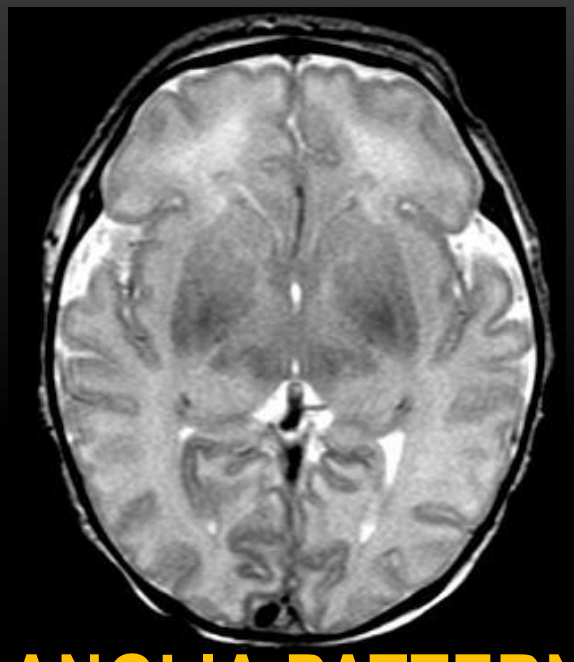


Hypointense T1 signal in post. Limb of internal capsule. This is normal for age in 36 wk EGA

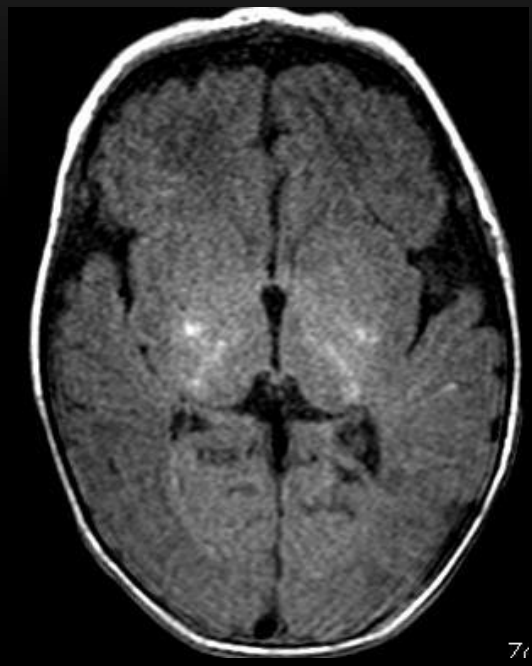
Range of variation in signal intensity that can be seen in normal brain—basal ganglia show moderately hyperintense signal, although less than that typically seen in hypoxia

DAY 4



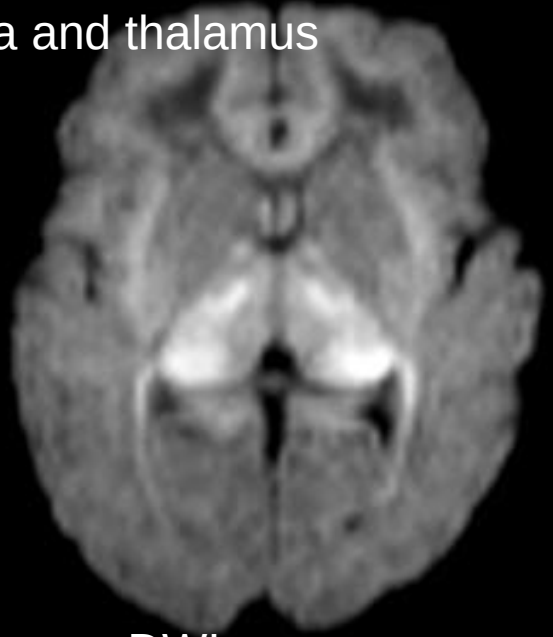


DAY 47

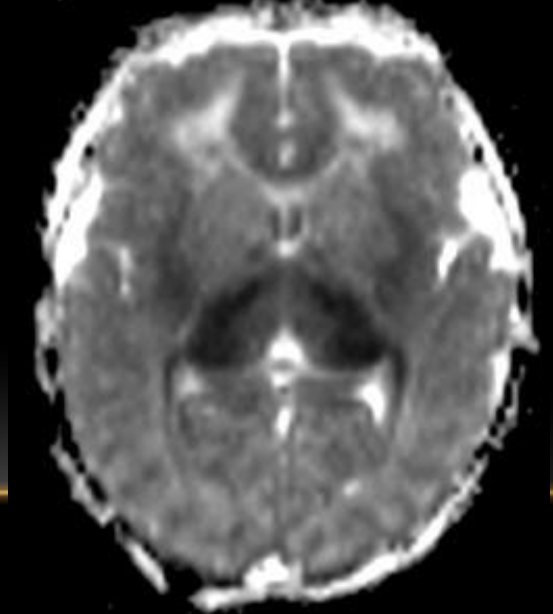


BASAL GANGLIA PATTERN

Injury to the basal ganglia and thalamus



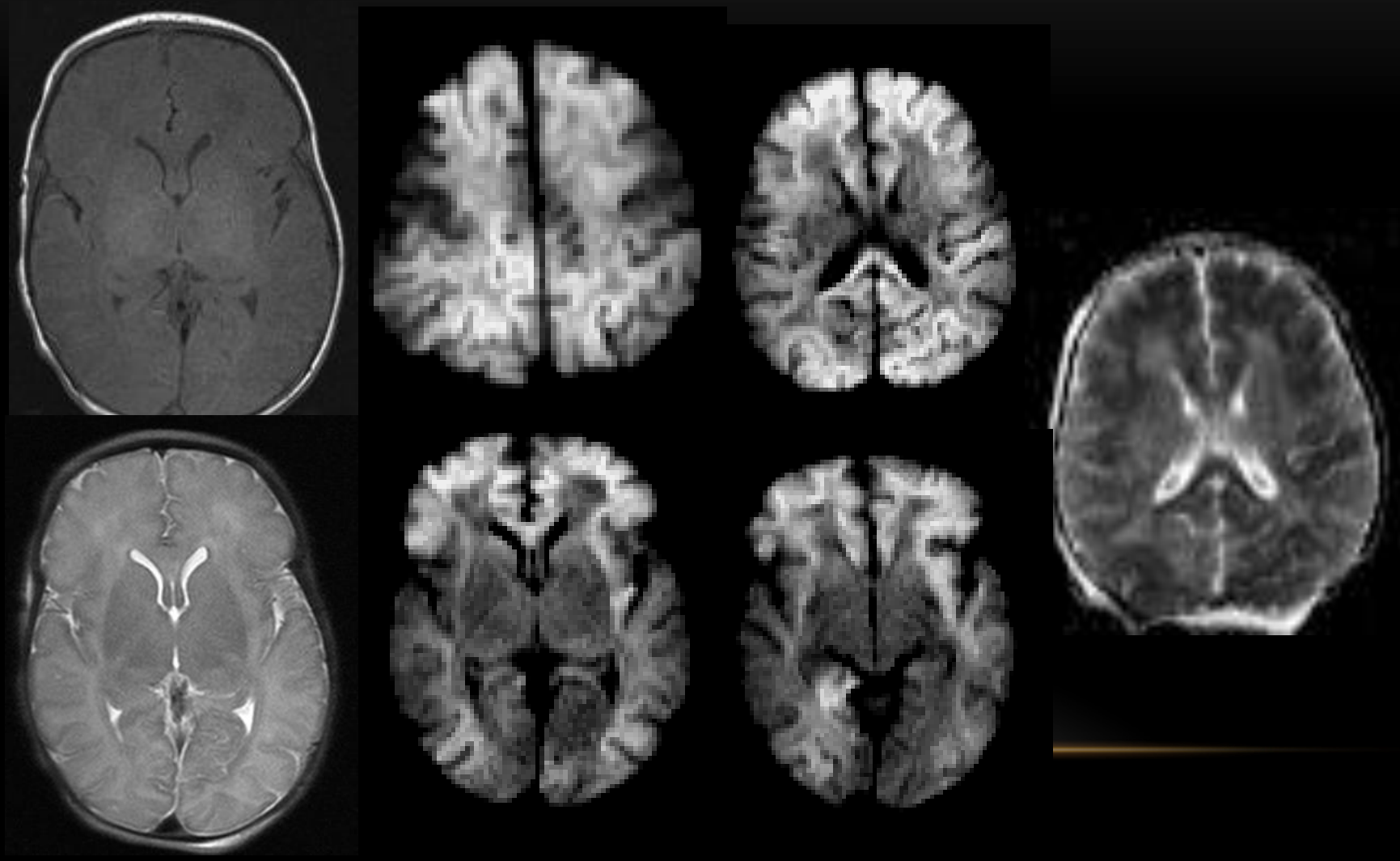
DWI



ADC

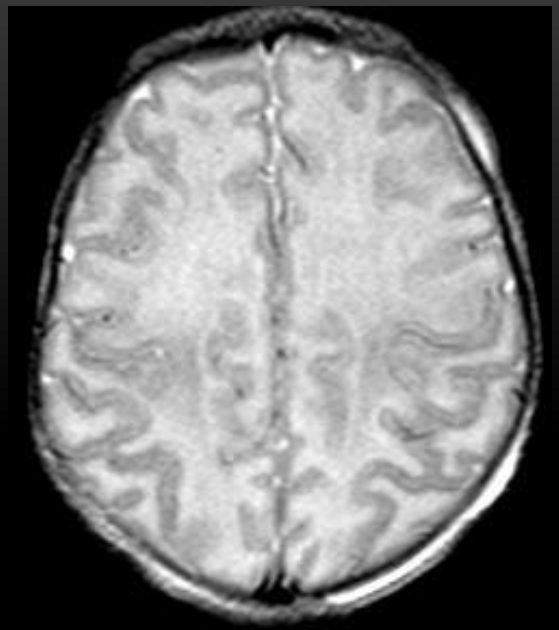
High T1 signal in basal ganglia and thalamus from intracellular calcium shift and necrosis

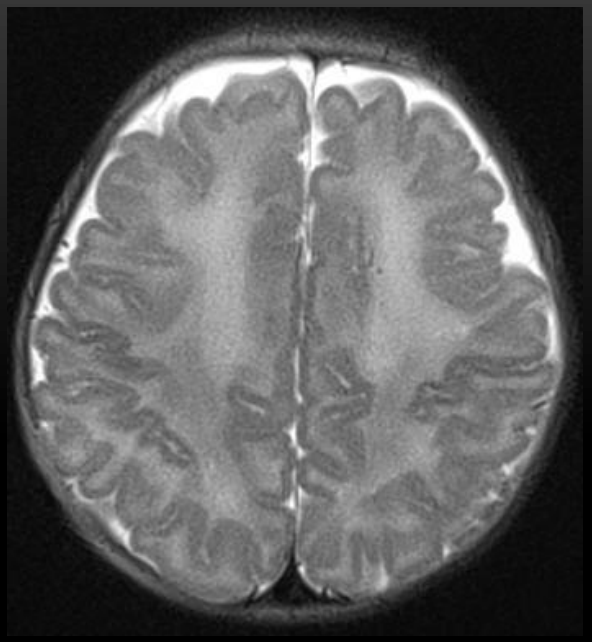
MRI FINDINGS IN THE NEONATE WITH SEVERE, TOTAL HYPOXIA

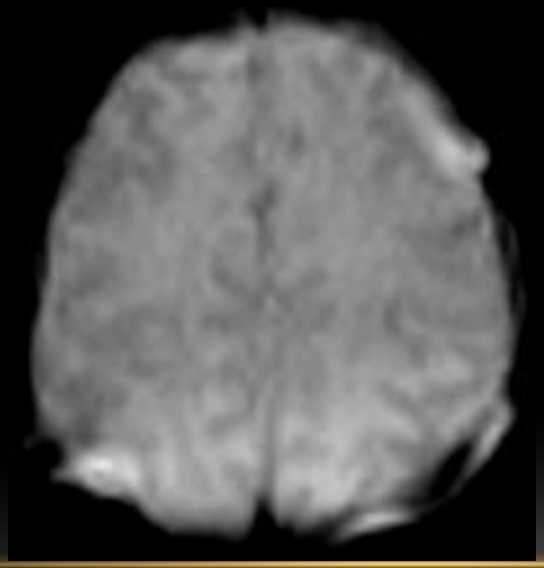


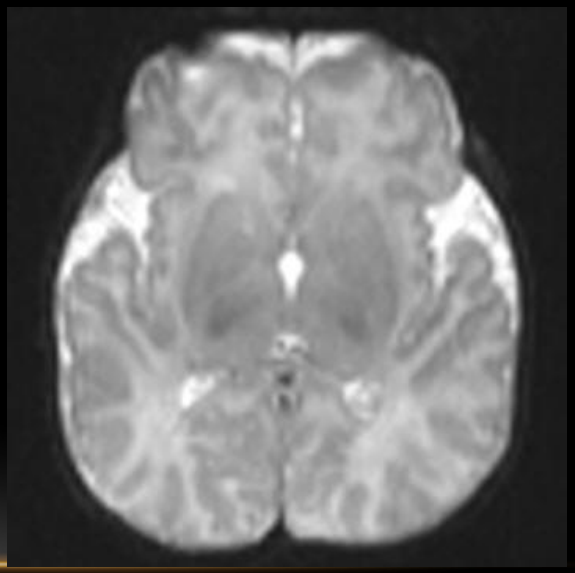
Abnormal high signal throughout the WM on T2

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

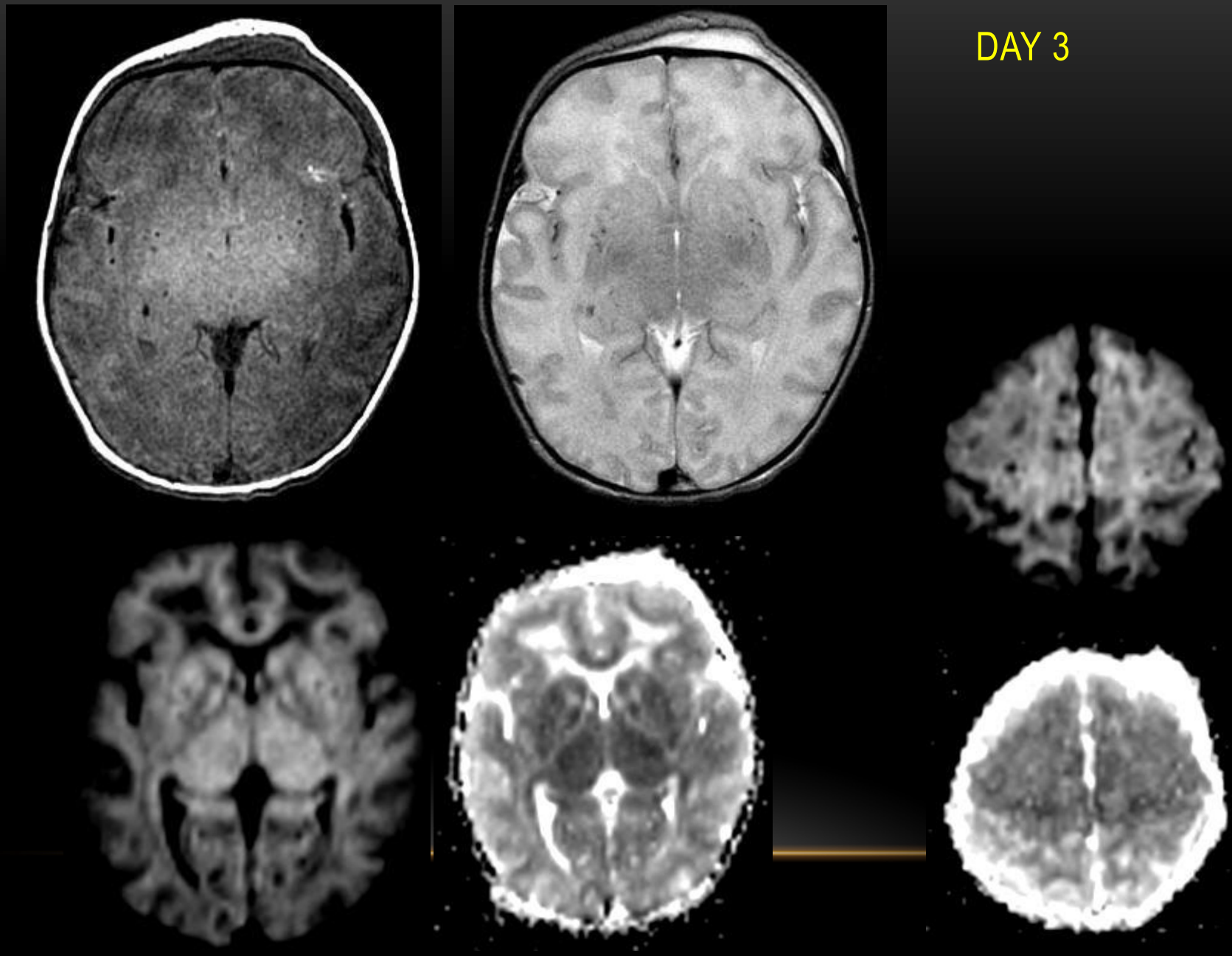




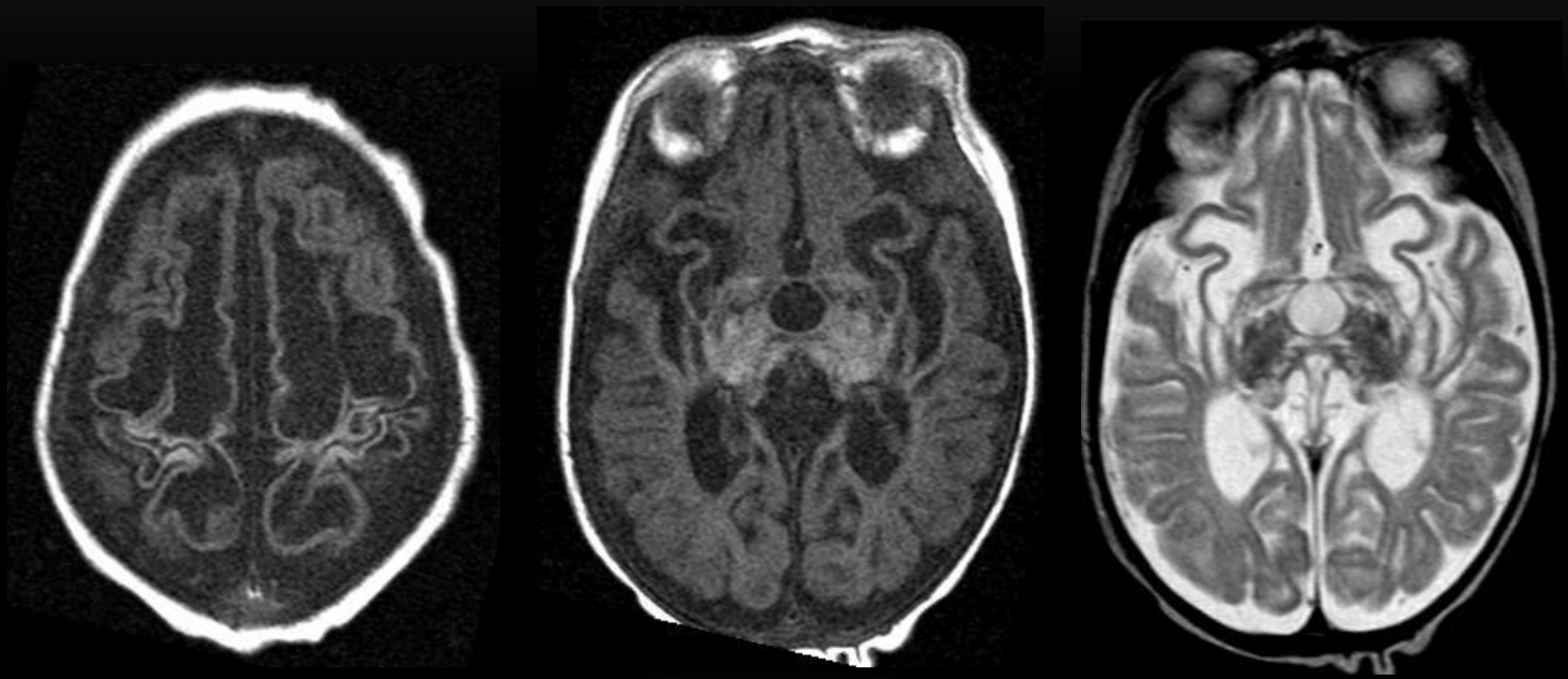




ABNORMAL **NORMAL**


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

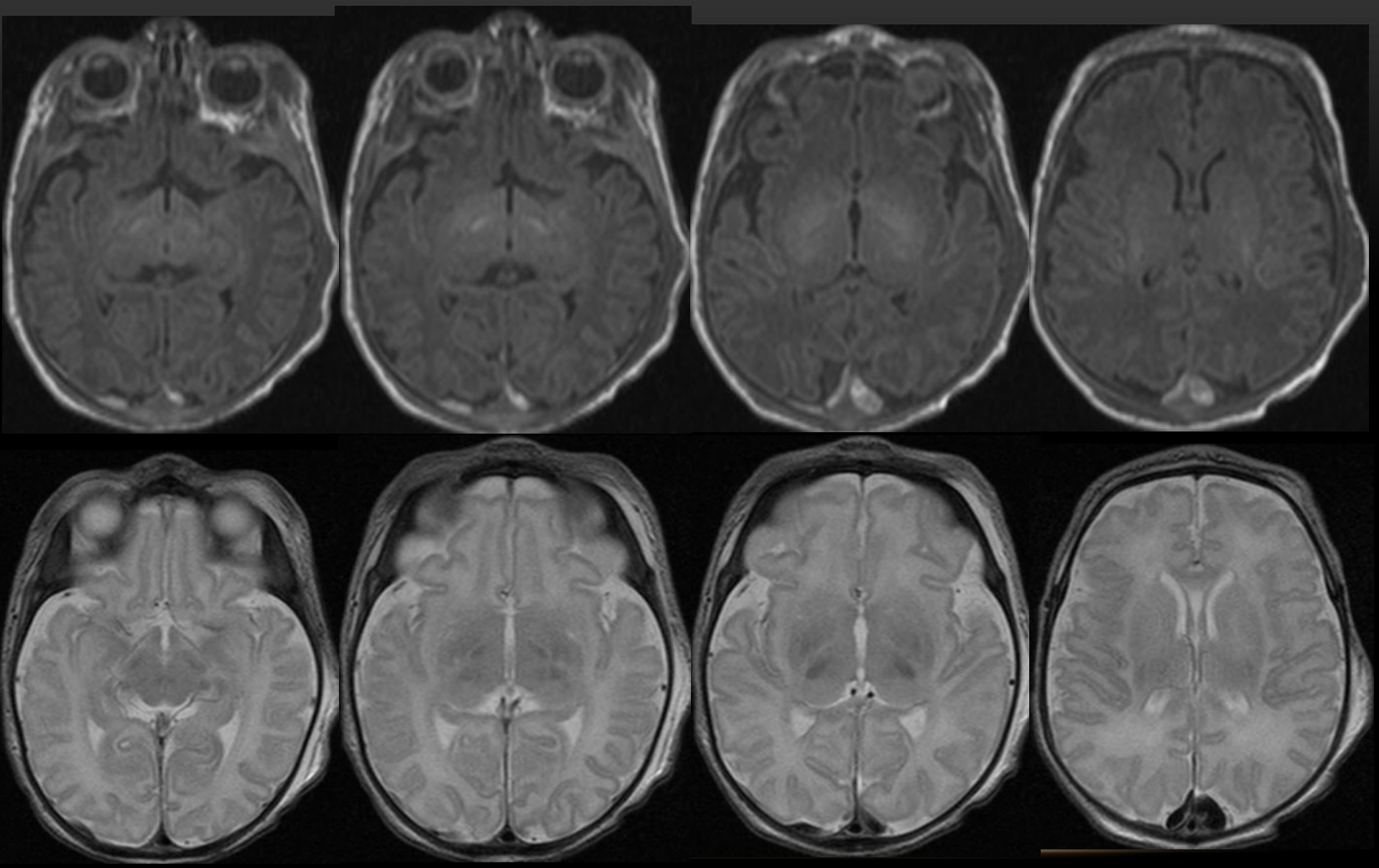
Reduction of leukotriene production

Inhibition of apoptosis

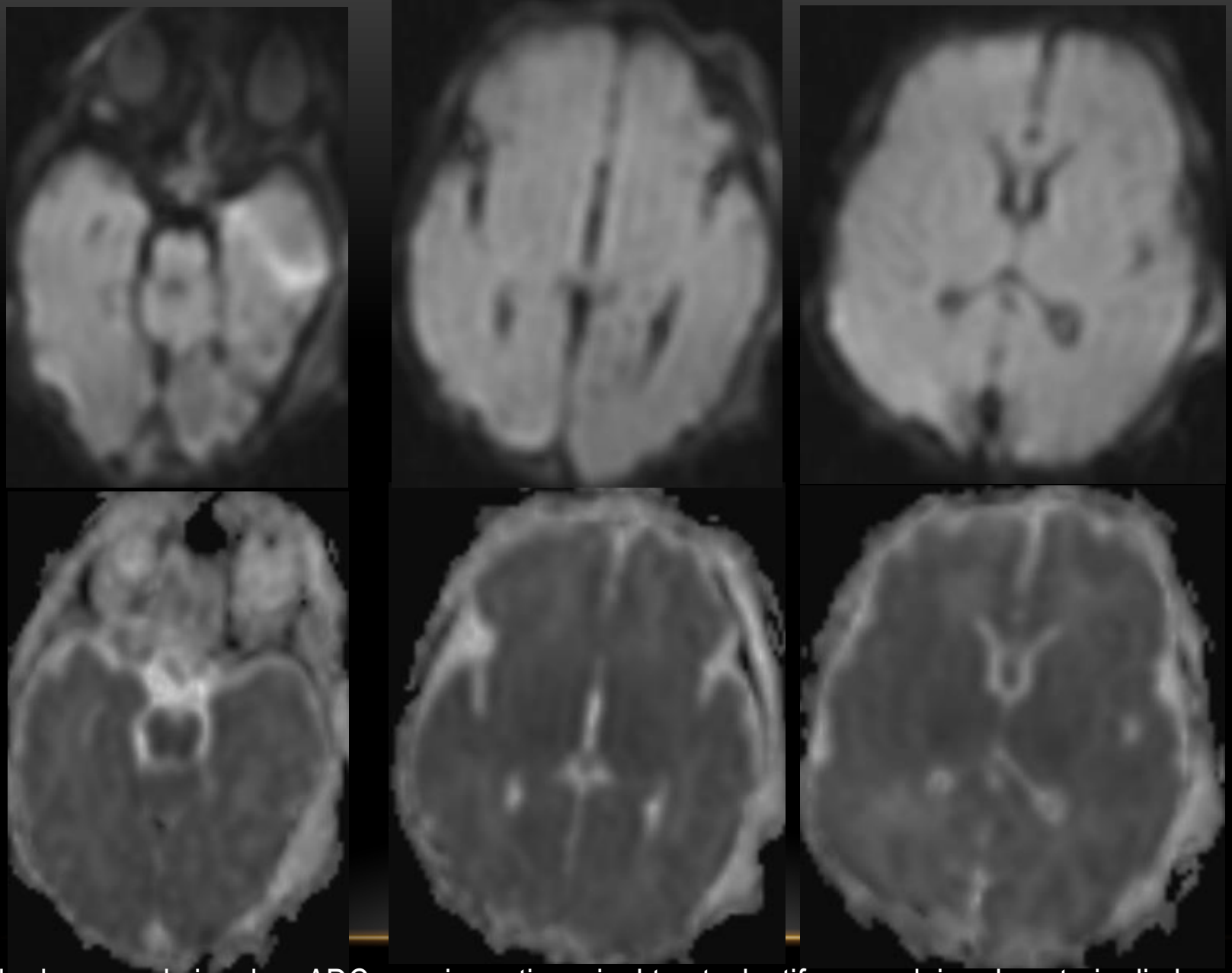
Reduction in cerebral metabolism

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

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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.