PRETERM HYPOXIC ISCHAEMIC ENCEPHALOPATHY (HIE)

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SAPA webinar

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OVERVIEW

- Definition
- Risk factors
- Pathophysiology
- Neuropathology
- Differences between preterm and term HIE
- Clinicopathological syndromes
- Management
- Outcomes

INTRODUCTION

- Preterm births and the survival is inversely proportional to the wealth of the country (GDP)

- Preterm births accounts for 35% of all neonatal deaths worldwide
- Second commonest cause of death

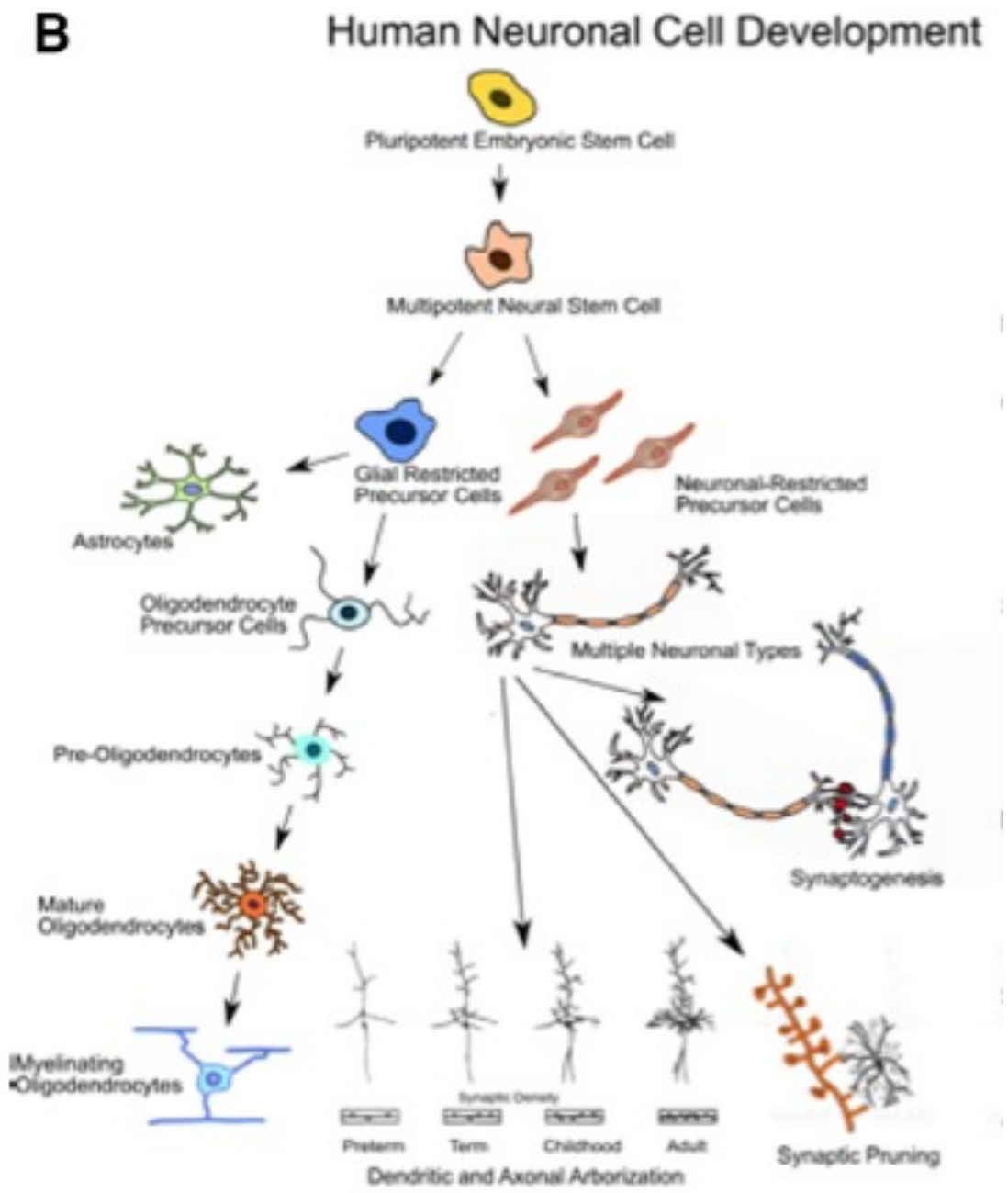
- With advances in neonatal care smaller babies are surviving
- Limits of viability in some countries are decreasing

- Thus, there is an increase in morbidity and neurodevelopmental impairment (NDI)

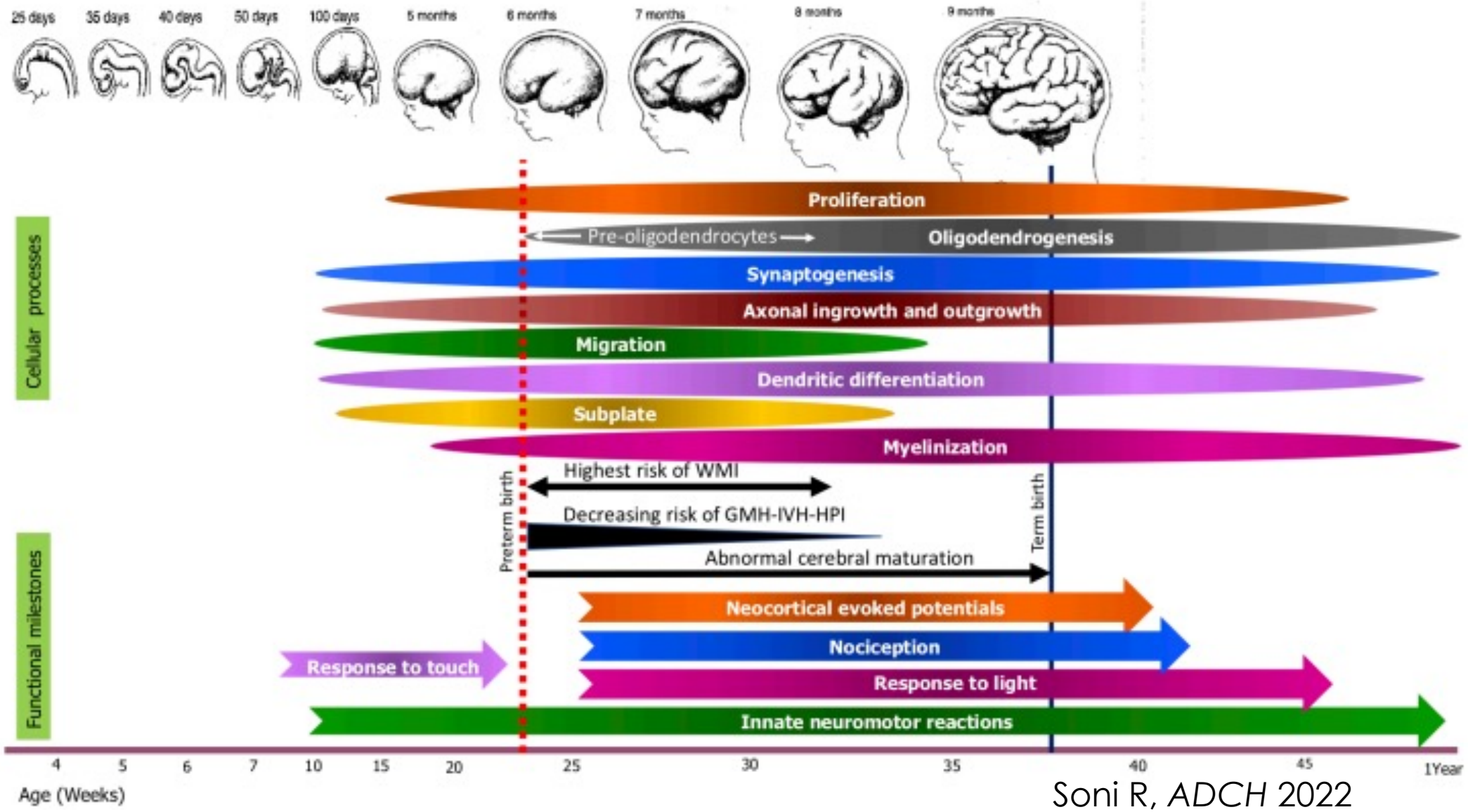
BRAIN DEVELOPMENT

- At 25 – 40 weeks – tripling of brain volume surface area
- Continued ‘birth’ and migration of neurons to the subventricular zone (SVZ) and ganglionic eminence (GE)
  - These migrate to the thalamus (T), basal ganglia (BG), and deeper cortical layers
- Growth of axons in the periventricular regions
- Development of oligodendrocytes (OL), astrocytes and microglia
- Synaptogenesis
- Myelination
- Pruning

Human neuronal cell development over a lifetime



BRAIN DEVELOPMENT



Soni R, *ADCH* 2022

HYPOXIC ISCHAEMIA IN PRETERM POPULATION

- Hypoxia Ischaemia in preterm infants is complex
- Severity, timing, selective vulnerability and immaturity of the brain

- Vascular fragility
  - Underdeveloped distal network
  - Immature cerebral autoregulation
  - Lack of collateral vessels in the peripheral arteries
  - Limited vasodilator function
- Blood – brain barrier function
  - Altered function and increased permeability of the BBB

NEURONAL CELL TYPES

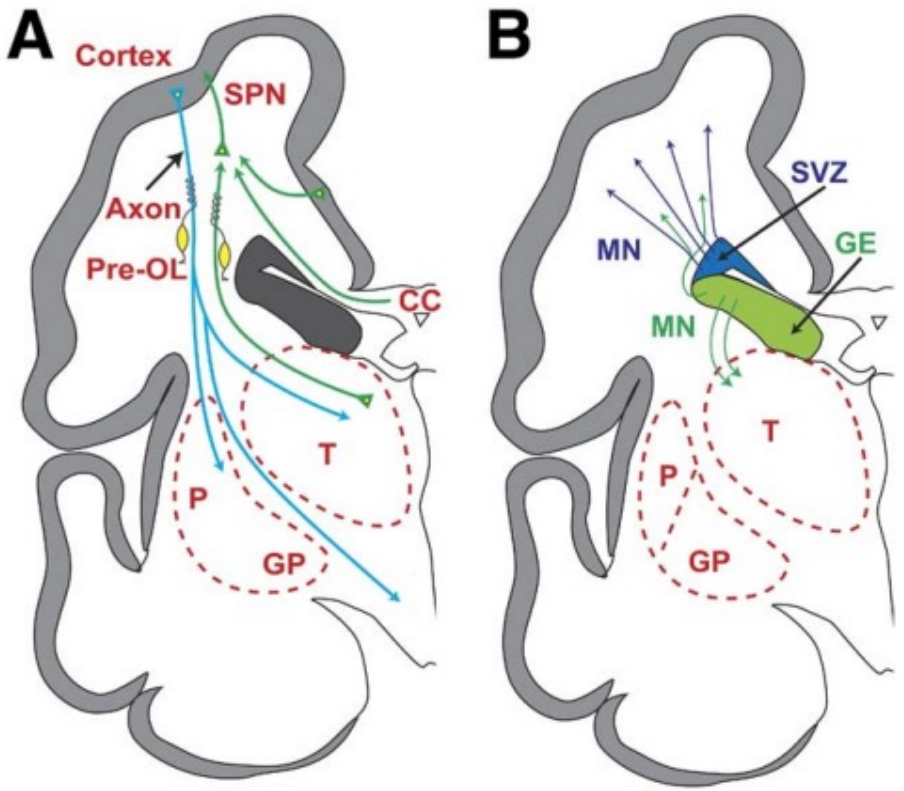
- Oligodendrocytes – myelinating cells in the brain
  - Crucial role in myelination of the white matter (WM)
  - Mature between 24 – 32 weeks
  - Vulnerable to injury during this period - caused by glutamate, free radicals, and inflammation
  - Injury to oligodendrocyte progenitor cells (OPC) and preoligodendrocytes (preOL) leads to an increase in OPCs
    - They fail to mature and
    - There is a block in maturation – axonal injury and white matter injury (WMI)
- Astrocytes
  - Scavenge the high levels of excitatory neurotransmitters
  - Neuroprotective – promotes erythropoeisis

NEURONAL CELL TYPES (2)

- Microglial cells – important for synaptogenesis, pruning, inflammation and tissue repair
  - Peak abundance in 3rd trimester
  - Activated in areas of OL injury

- Subplate neurons (SPN) – transient population of excitatory neurons
  - Prominent in 24 – 32 weeks of gestation
  - Role in establishment of cortical lamination and thalamocortical connectivity
  - At 33 weeks and once thalamocortical synapses have been established – APOPTOSIS
  - Damage to SPN – disrupts thalamocortical axons, and cortical neuronal connectivity
  - Thus, long-term motor and cognitive deficits

SCHEMATIC REPRESENTATION OF NECROSIS AND DYSMATURATION



Volpe JJ et al Seminars in Paediatric Neurology 2009

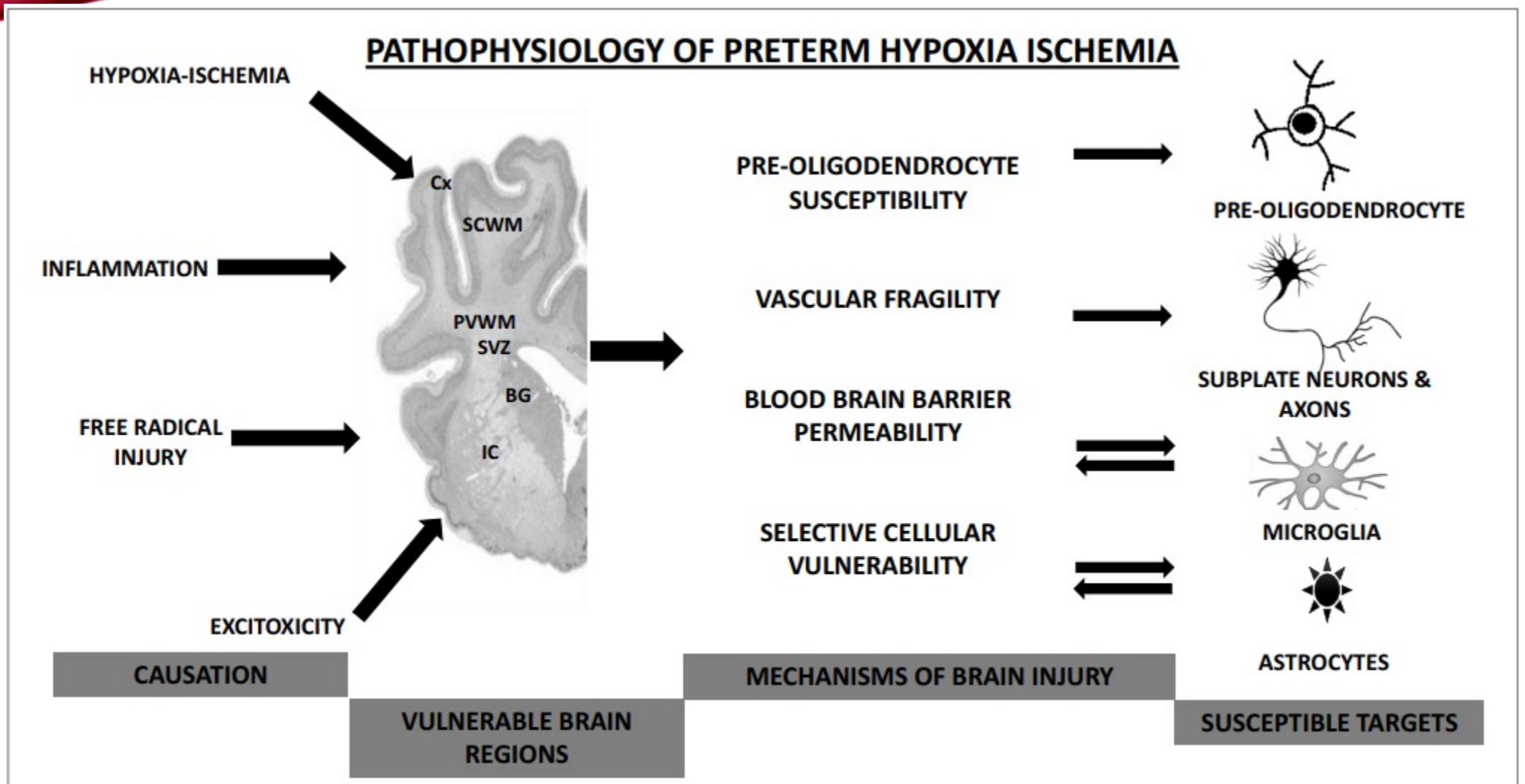
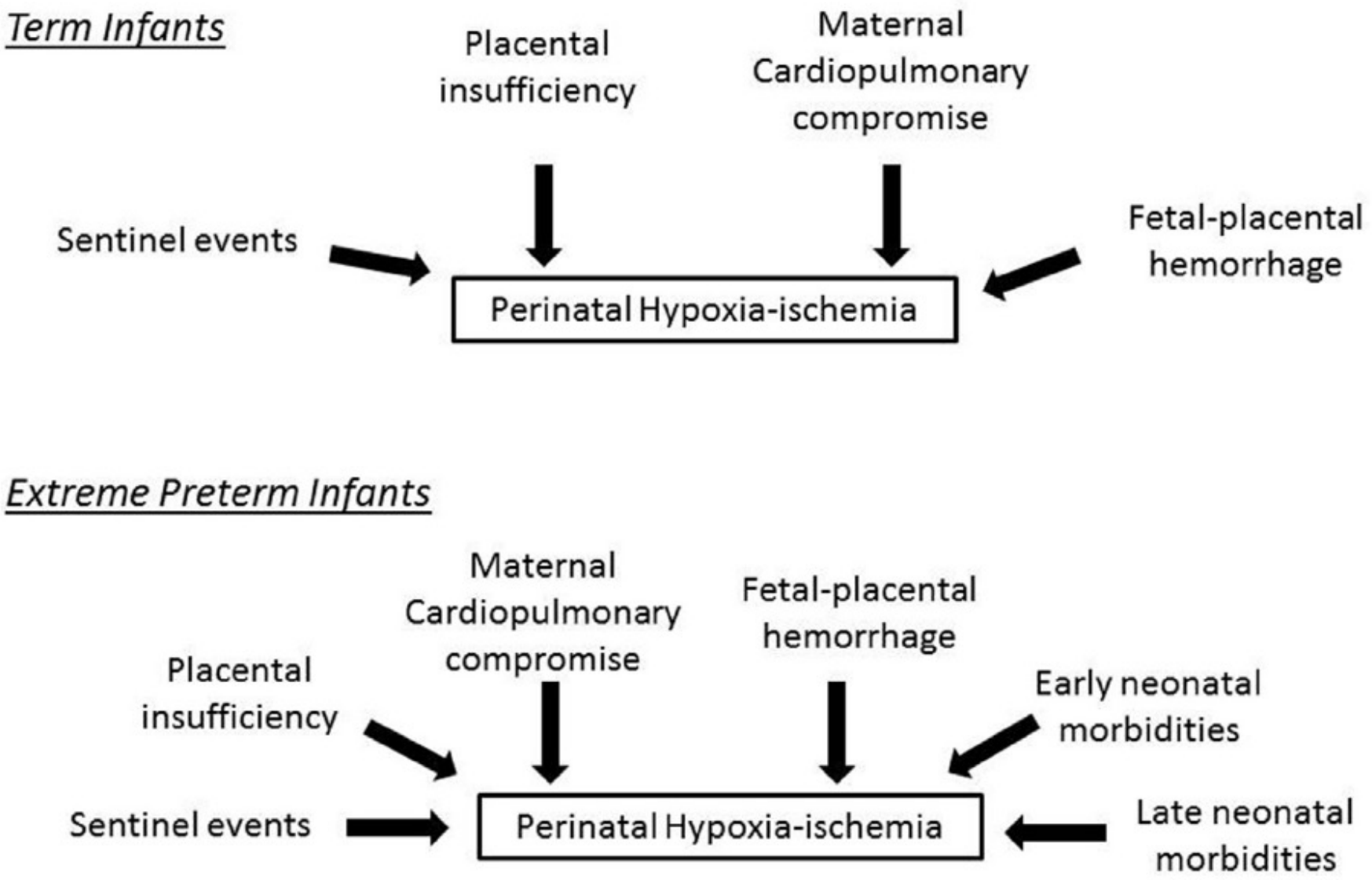


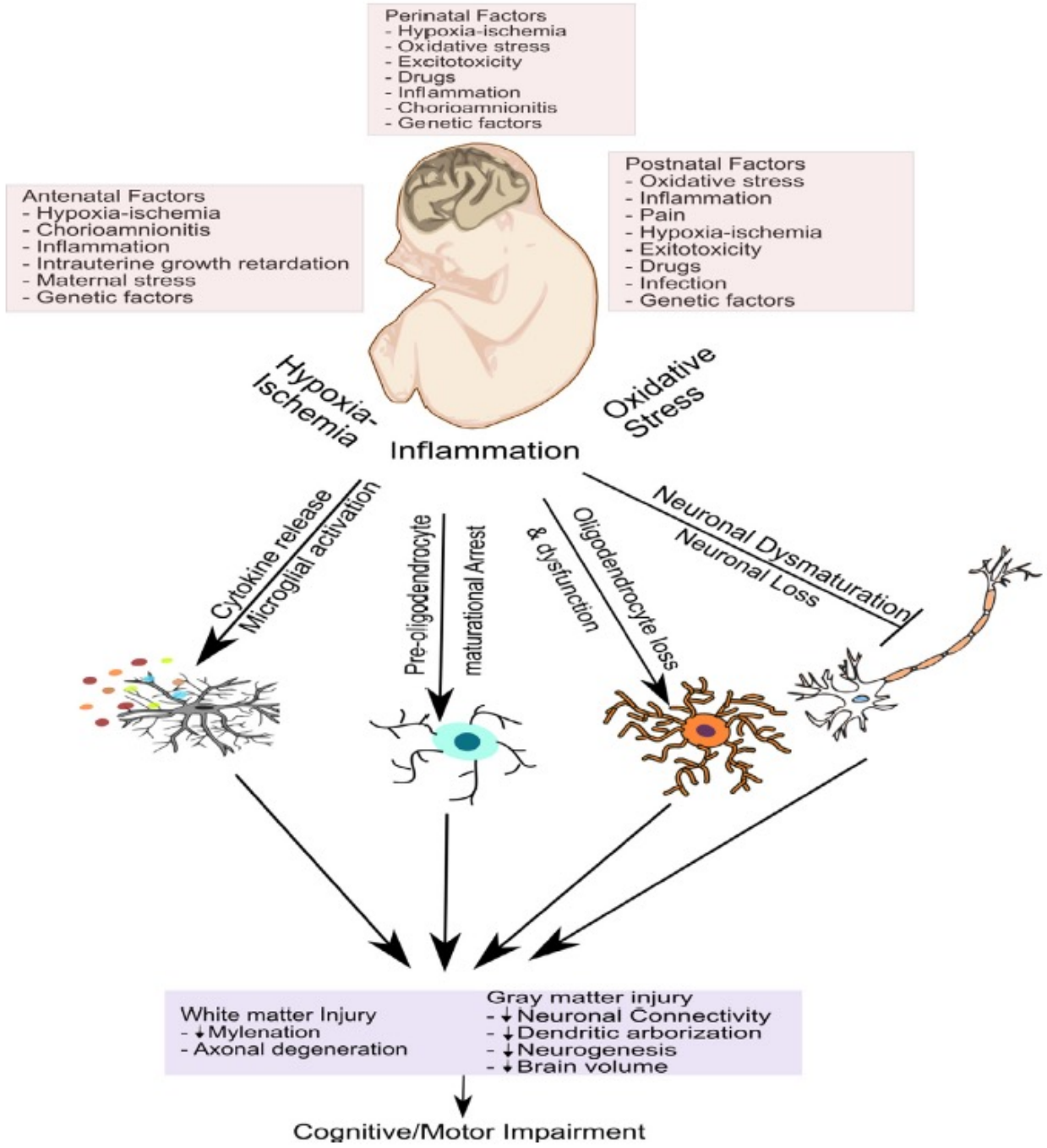
FIGURE 1 | Pathophysiological mechanisms involved in preterm hypoxic–ischemic encephalopathy. Cx, cortex; SCWM, subcortical white matter; PVWM, periventricular white matter; BG, basal ganglia; IC, internal capsule.

EVENTS THAT LEAD TO HYPOXIA ISCHAEMIA IN TERM AND PRETERM INFANTS



Laptook AR Clinics Perinatology (43) 2016; 529 -545

RISK FACTORS AND UNDERLYING MECHANISMS OF PRETERM ENCEPHALOPATHY



RISK FACTORS ASSOCIATED WITH PRETERM HIE

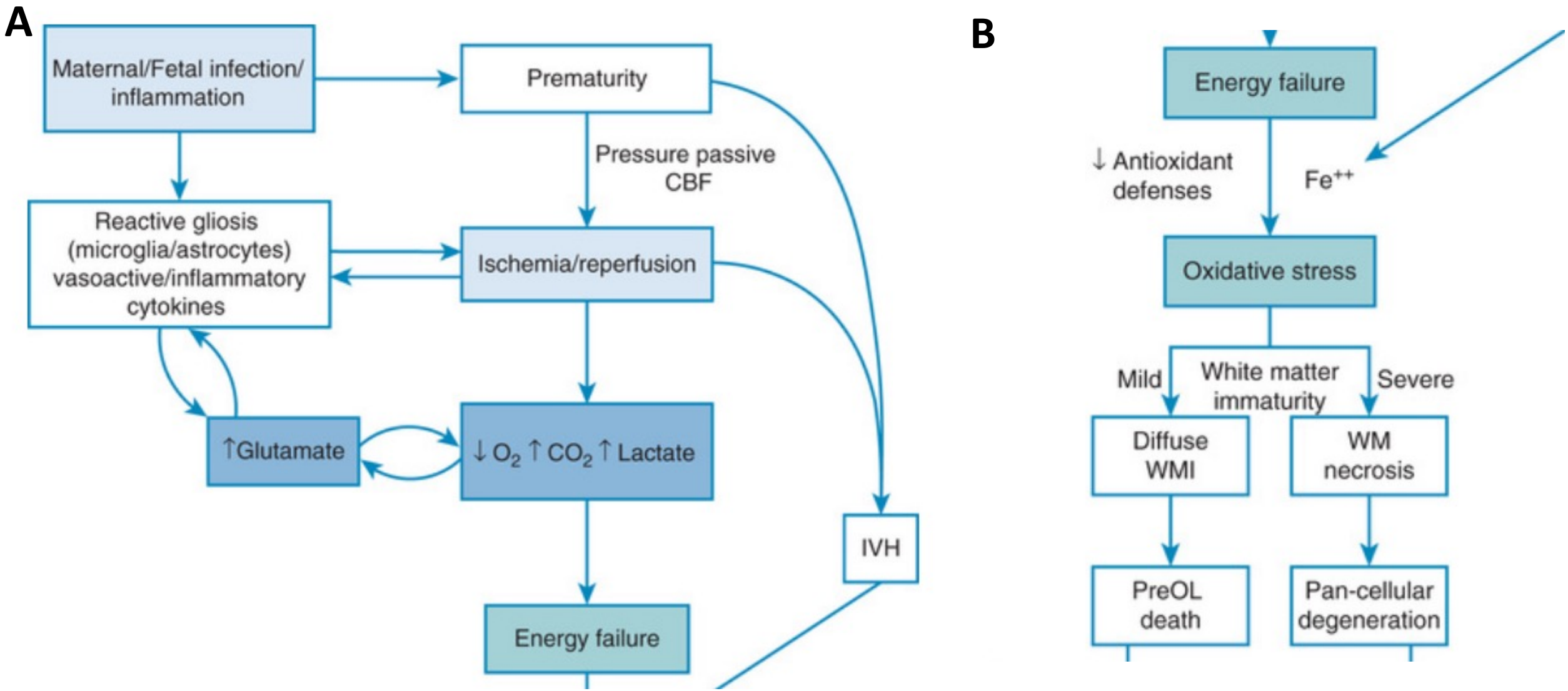
Primarily HIE

- Fetal metabolic acidosis
- Respiratory insufficiency associated with RDS
- Cardiac insufficiency/hypotension
  - Severe RDS
  - Recurrent apnoeic spells
  - Large PDA
  - Congenital heart disease
  - Sepsis

Primarily Systemic infection

- Maternal intrauterine infection
- Neonatal Sepsis
- Necrotising enterocolitis

PATHOPHYSIOLOGY OF PRETERM HIE



PATHOPHYSIOLOGY OF PRETERM HIE

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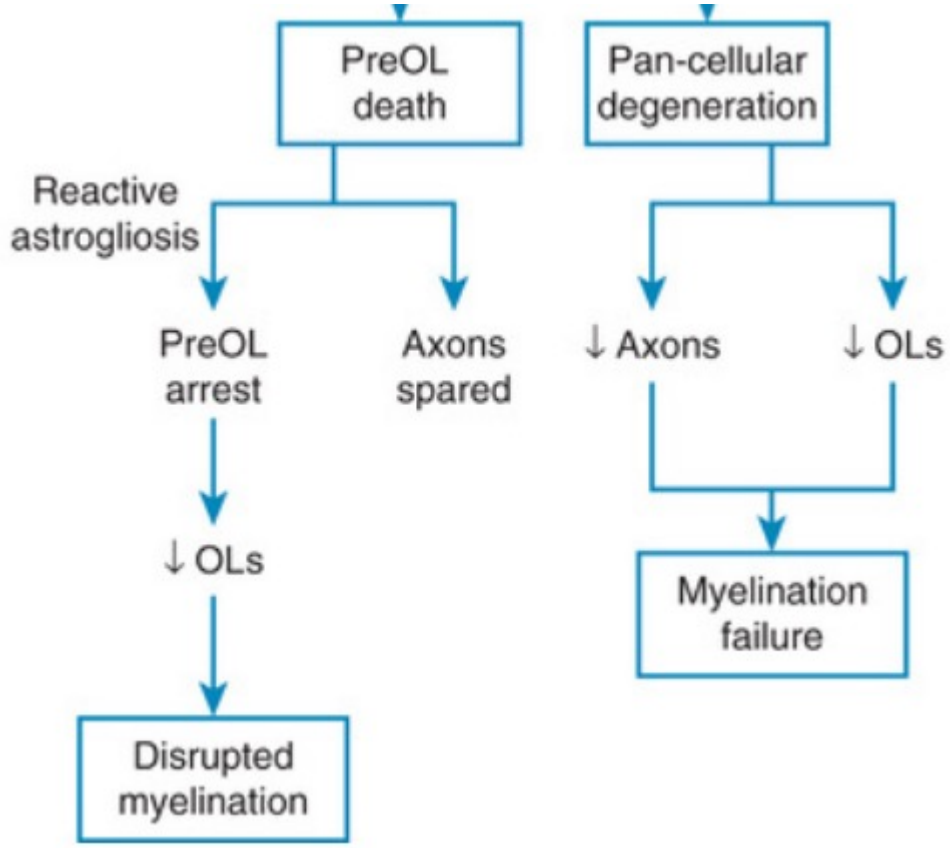


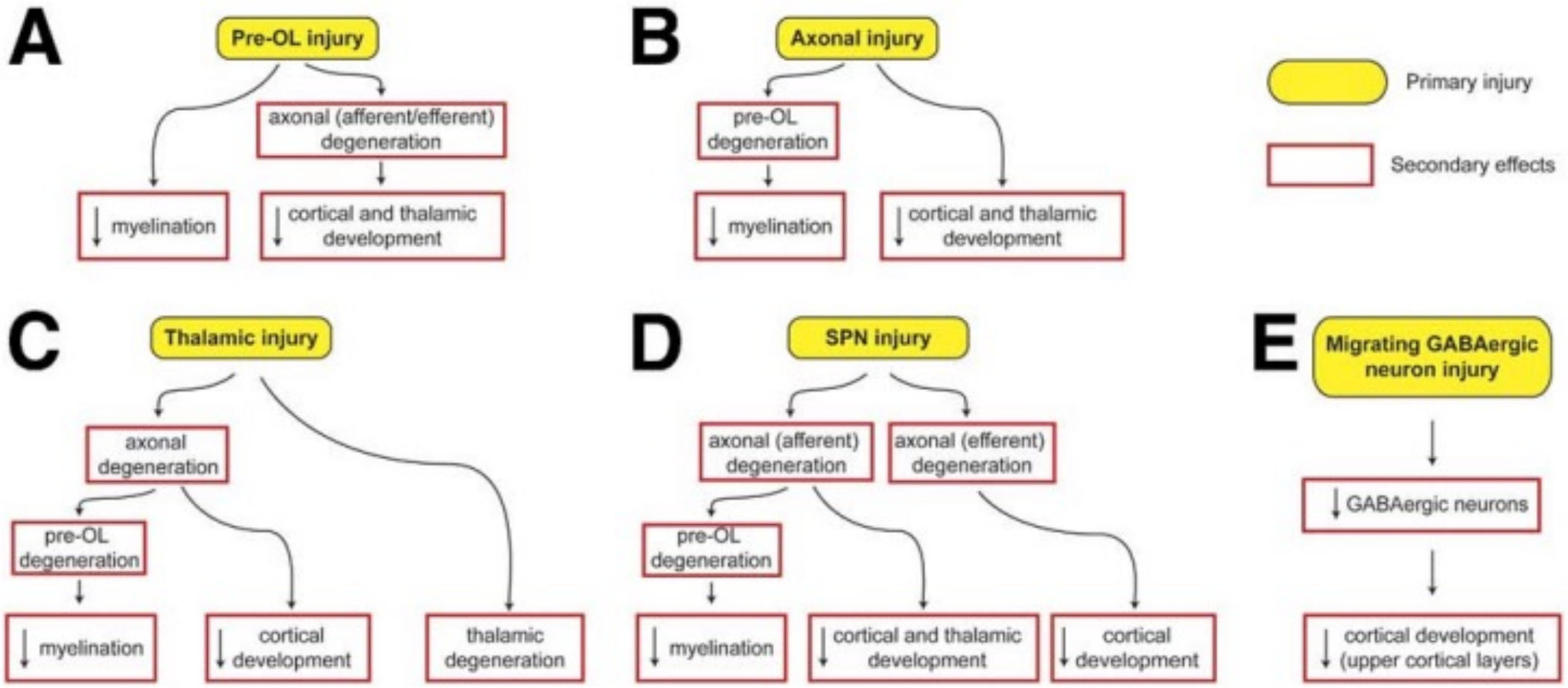
MECHANISM OF PRETERM ENCEPHALOPATHY

- White matter injury (WMI)
  - Hallmark of preterm brain injury
  - Focal cystic necrosis, focal macroscopic necrosis, diffuse non-necrotic lesions
  - Diffuse microcystic WMI is more common
  - Axonal degeneration occurs in focal injury but spared in diffuse injury
  - Factors associated with this injury
    - Hypoxia-ischaemia
    - Hypoxia, hyperoxia, hypocarbia, hypo- and hyperglycaemia
    - Perinatal haemodynamic instability
    - Inflammation

MECHANISM OF PRETERM ENCEPHALOPATHY

- Gray matter injury
  - Abnormal cortical folding
  - Decrease in gyral complexity
  - Increased ventricular volume
  - Altered arborization
- Vulnerability is dependent on
  - Type of neuron,
  - The degree of prematurity,
  - Severity of the insult
  - Severity of the WMI
- The dysmaturation and maturational arrest – key factors in preterm encephalopathy

POTENTIAL SEQUENCE OF EVENTS IN ENCEPHALOPATHY OF PREMATURITY



Volpe JJ et al Seminars in Paediatric Neurology 2009

Criteria used to define Preterm HIE

- Vague, variable and not well studied
- Difficulties due to developmental immaturity
- Most studies use pH <7.2 and persistent or delayed resolution of metabolic acidosis
- No studies in < 32 weeks gestation

Study (reference, type, number of patients)	Gestational age (weeks)	Criteria for HIE	Clinical features	Outcomes
Barkovich and Sargent 1995 (63), retrospective case series, *n* = 5	27–32	Profound hypoxia at birth	None mentioned	Pattern of injury on MRI
Salhab and Perlman 2005 (60), retrospective cohort, *n* = 61	31–36	Fetal acidemia (cord arterial pH <7)	Abnormal neurological examination based on Sarnat staging Abnormal neurological outcome seen in those with low 1 and 5 min Apgar, need for CPR, mechanical ventilation	3 out of 8 babies died No mention on long-term neurological outcome
Logitharajah et al. 2009 (58), retrospective cohort, *n* = 55	26–36	Apgar scores <5 at 1 and <7 at 5 min Major resuscitation (intubation/cardiopulmonary resuscitation/adrenaline) at birth Brain MRI within 6 postnatal week Additional inclusion criteria: abnormal intrapartum CTG, sentinel event, meconium staining, cord pH <7, neonatal seizures, and multiorgan failure	Longer duration of assisted ventilation and seizures was associated with severe outcome/death	Mainly focused on imaging pattern in preterm HI insult and long-term neurological outcome associated with imaging abnormality
Schmidt and Walsh 2010 (59), retrospective cohort, *n* = 12	32–36	5-min Apgar score <6 Cord or initial patient blood pH <7, or base deficit >15 mmol/L Evidence of encephalopathy at or shortly after birth (seizures, hypotonia) History of a sentinel event at the time of delivery	Incidence 0.9%, significant acidosis, poor tone, seizures	25% of study population died. 44% had long-term neurological adverse outcome
Chalak et al. 2012 (57), retrospective cohort, *n* = 9	33–35	pH <7 and base deficit >16 mmol/L Sentinel event 10-min Apgar score <5, requiring assisted ventilation at birth	Incidence 5/1000 live births Graded according to Sarnat staging HIE 1 – brief ventilation, mild elevation of liver enzymes, creatinine, normal neurological examination HIE 2 – multiple organ injury resolved by 7 h. Normal neuro examination at discharge. One had seizure HIE 3 – severe multiorgan dysfunction, DIC, status epilepticus, prolonged ventilation, persistent abnormal neurological exam	Stages 1 and 2 had normal neurological outcomes

Gopagondanahalli et al. Frontiers in Paediatrics 2016

DIFFERENCES BETWEEN TERM AND PRETERM HIE

- Criteria used to diagnose HIE as in term neonates not applicable to preterm HIE
- Impaired placental gas exchange may be affected by morbidities of prematurity
- Low Apgar scores, need for resuscitation and/or intubation may be due to prematurity and not necessarily HIE
- Apgar scores may be lower in preterm neonates – hypotonia, depressed reflexes irritability and difficulty in initiating effective respirations
- Need for intubation and mechanical ventilation may be as a result of preterm disease processes or morbidities of prematurity
- aEEG – has maturational changes – may not be useful to identify neonates for intervention

PRETERM VS TERM HIE

- Preterm brain is particularly vulnerable due to maturational changes
- Pattern of injury is different
  - Term neonates have more gray matter injury and to a lesser extent WMI
  - Preterm - follow ischaemic necrosis in a vascular distribution affects the cerebral WM – lesions are periventricular leukomalacia (PVL) as well as gray matter lesions
- The term ‘Encephalopathy of Prematurity’ has been coined
  - Involves both cortical, thalamus basal ganglia and white matter injury (WMI)
- Timing is important – preterm HIE may reflect intrapartum events as well as early and late neonatal morbidities
- Thus there will be a spectrum of brain injury

NEUROPATHOLOGY OF HIE

Gestational age	Primary Cell Type Affected	Common Patterns of Injury	Affected Regions
Extreme Preterm	Pre-oligodendrocyte (preOL) (arrested lineage)	Periventricular ± remote gray matter	Diffuse white matter ± thalamus, basal ganglia, hippocampus, cerebellum and brain stem
Term	Neuron (selective necrosis)	Basal ganglia, thalamic Watershed Diffuse hemispheric	Basal ganglia Thalamus PLIC Intervascular white matter Cortical gray/white

Laptook AR Clinics Perinatology (43) 2016; 529 -545

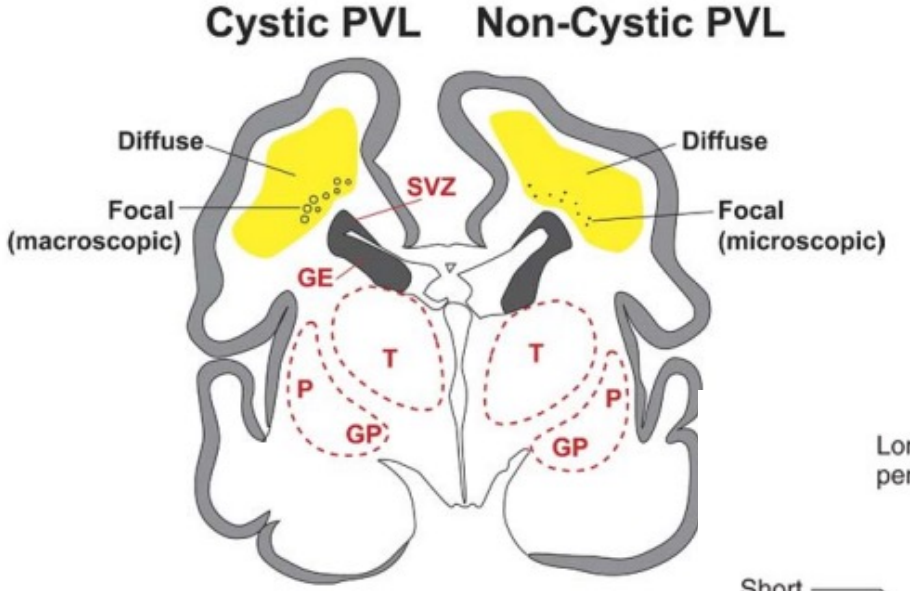
NEUROPATHOLOGY – ENCEPHALOPATHY OF PREMATURITY

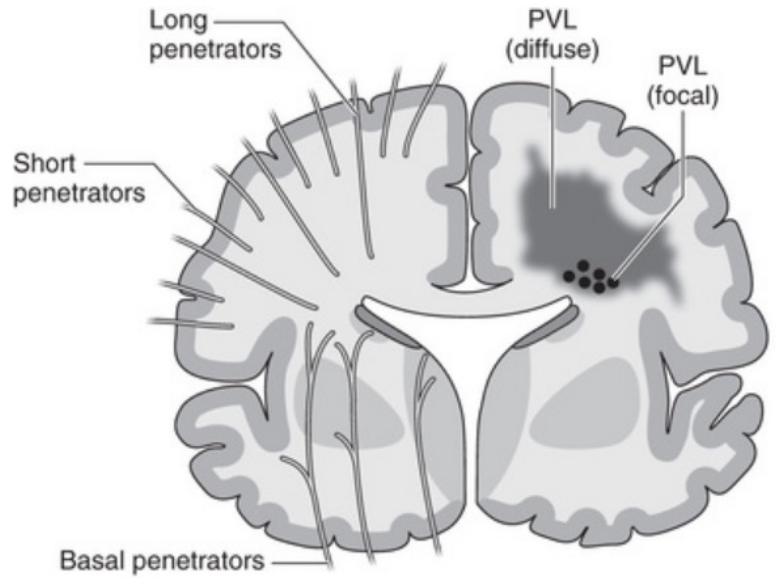
Focal

- Deep in the white matter
- Loss of all cellular elements
- Evolve into cysts if macroscopic
- Microscopic – glial scars

Diffuse

- Central cerebral white matter
- Injury to pre-OL
- Marked astrocytosis and microgliosis
- Cell death and hypomyelination





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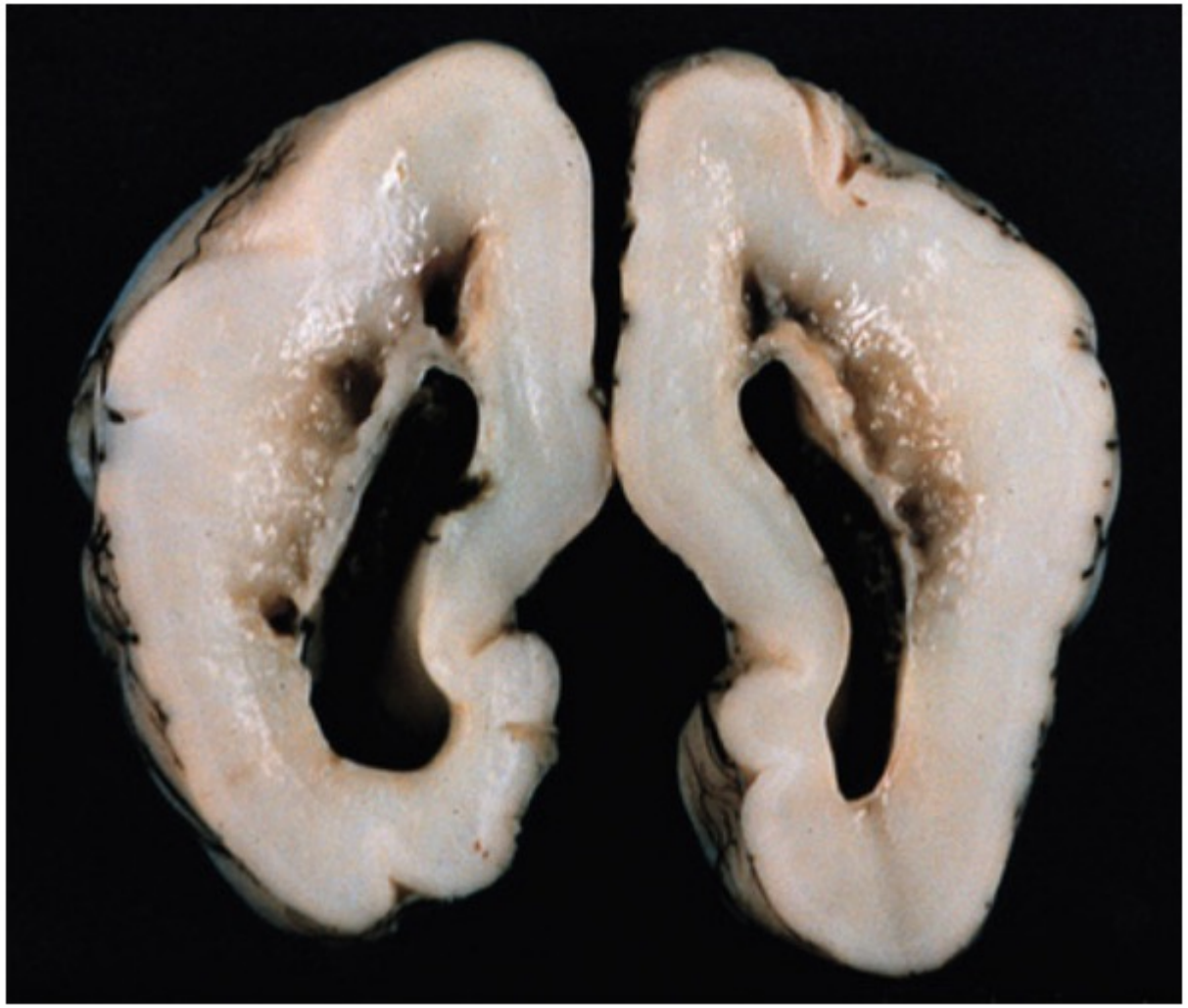
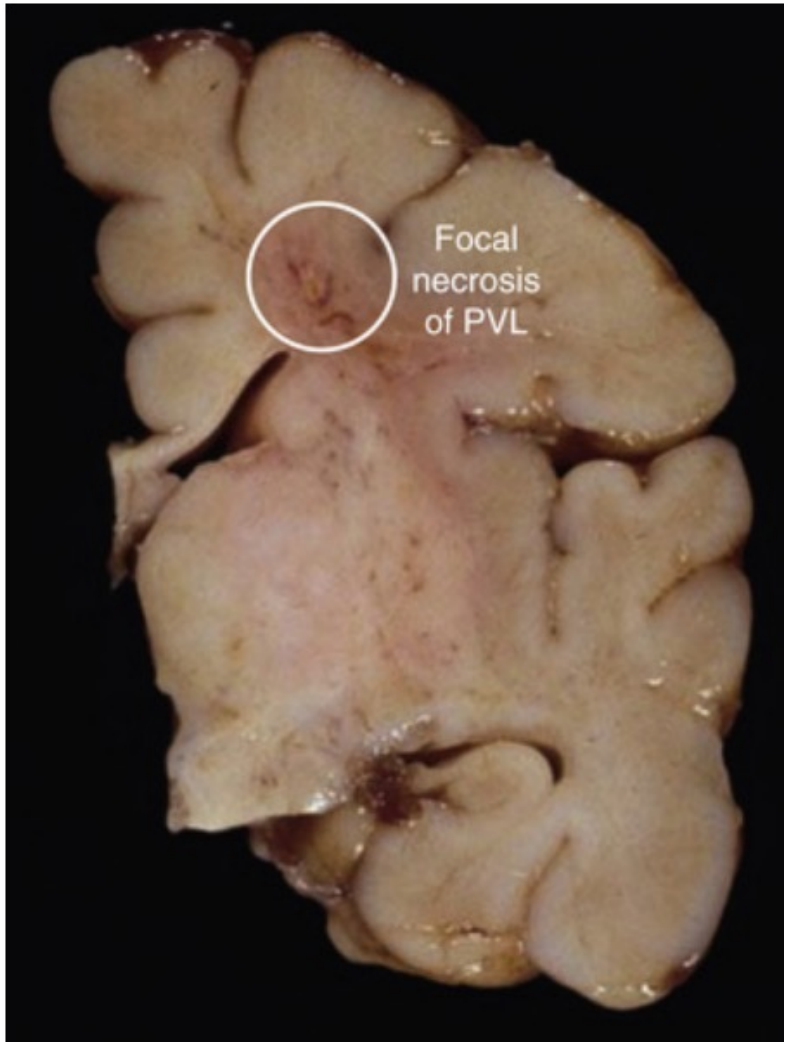
GROSS ANATOMY OF PVL LESIONS





NEUROLOGICAL SYNDROMES IN PRETERM HIE

- Difficult to identify neonatal neurological syndrome associated with preterm HIE and PVL
- Normal neurological characteristics of a growing preterm makes it difficult
- Acute neurological correlation – large cystic lesions may lead to lower limb weakness
- Associated with focal periventricular white matter injury (WMI)
- Even in the presence of relatively large lesions
- Non-cystic PVL – it is difficult to identify specific motor deficits
- Visual perception and visual fields affected if optic radiations are affected
- Seizures may be seen in preterm neonates, associated with WMI – associated with early language delay

CRANIAL ULTRASOUND IN PRETERM ENCEPHALOPATHY

ULTRASONOGRAPHIC APPEARANCE	TEMPORAL FEATURES	NEUROPATHOLOGICAL CORRELATION
Echogenic foci, bilateral, posterior > anterior	First week	Necrosis with congestion and/or hemorrhage, (size > 1 cm)
Echolucent foci ("cysts")	1–3 weeks	Cyst formation secondary to tissue dissolution (size > 3 mm)
Ventricular enlargement, often with disappearance of "cysts"	≥2–3 months	Deficient myelin formation; gliosis, often with collapse of cyst

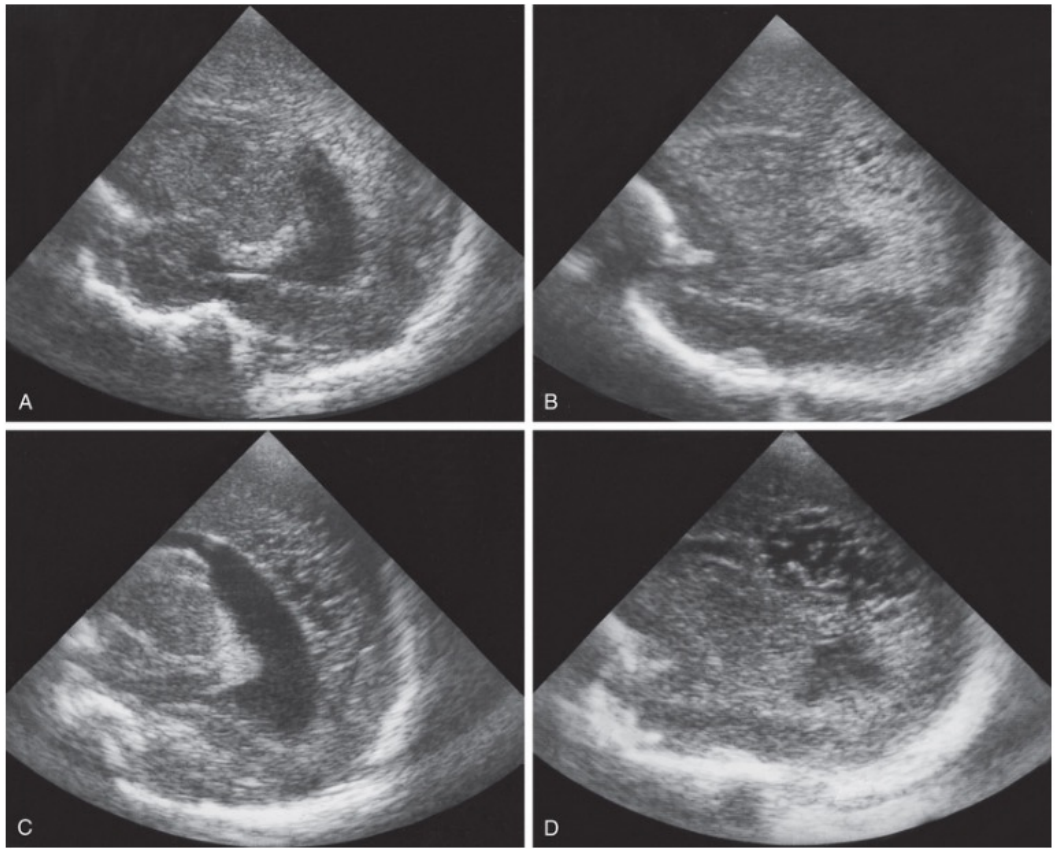
Volpe JJ, Neurology of the Newborn

IMAGING IN PVL

FORM OF PVL	FOCAL PERIVENTRICULAR INJURY	DEGREE OF DIFFUSE WHITE MATTER INJURY[a]	IMAGING CORRELATE[a]	APPROXIMATE INCIDENCE (%)
Severe ("cystic")	Large areas of macroscopic necrosis, evolving to cysts	Severe	Periventricular cysts	5
Moderate ("noncystic")	Smaller areas of macroscopic necrosis, evolving to gliotic scarring	Intermediate	Periventricular signal abnormality on CUS and punctate white matter lesions on MRI	25
Mild	Microscopic areas of necrosis	Mild	No periventricular signal abnormality	? 25–35

Volpe JJ, Neurology of the Newborn

CRANIAL ULTRASOUND OVER TIME



Parasagittal ultrasound scans of periventricular leukomalacia obtained from a premature infant at (A) 2, (B) 13, (C) 17, and (D) 26 days of age.

Volpe's Neurology of the Newborn 6th Edition

CUS WITH GLIOSIS

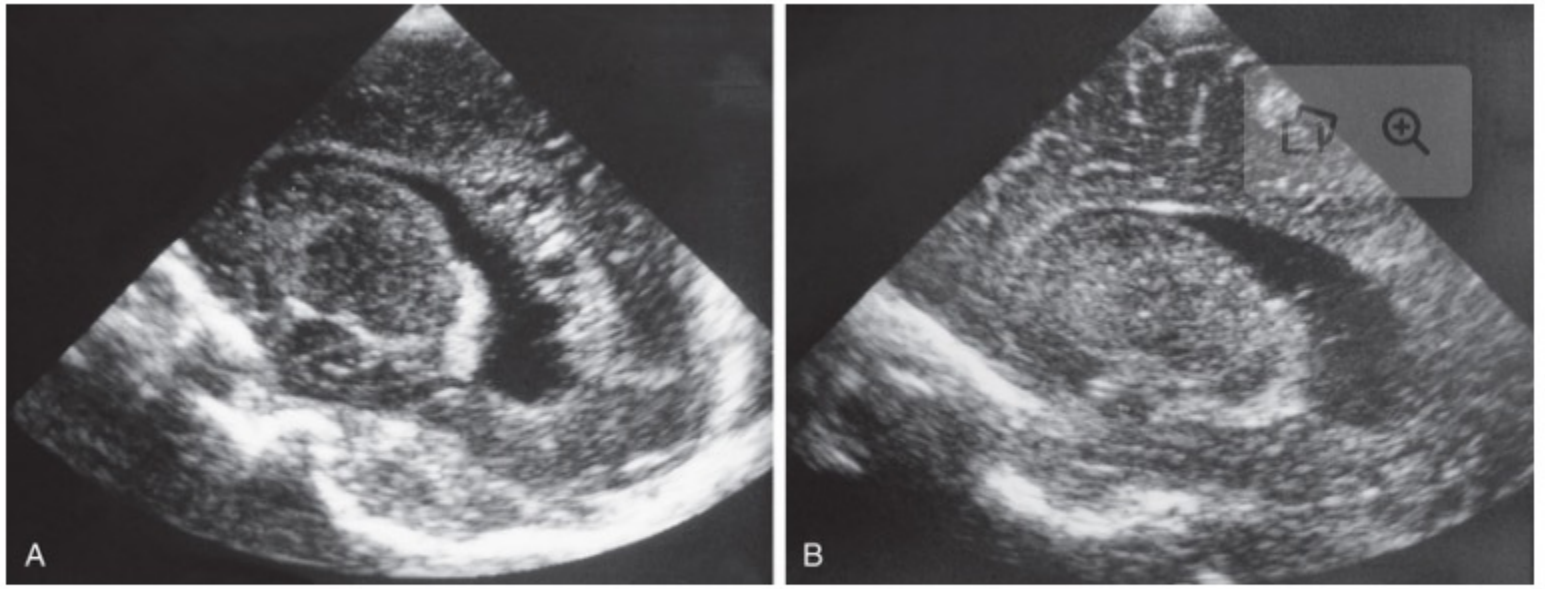


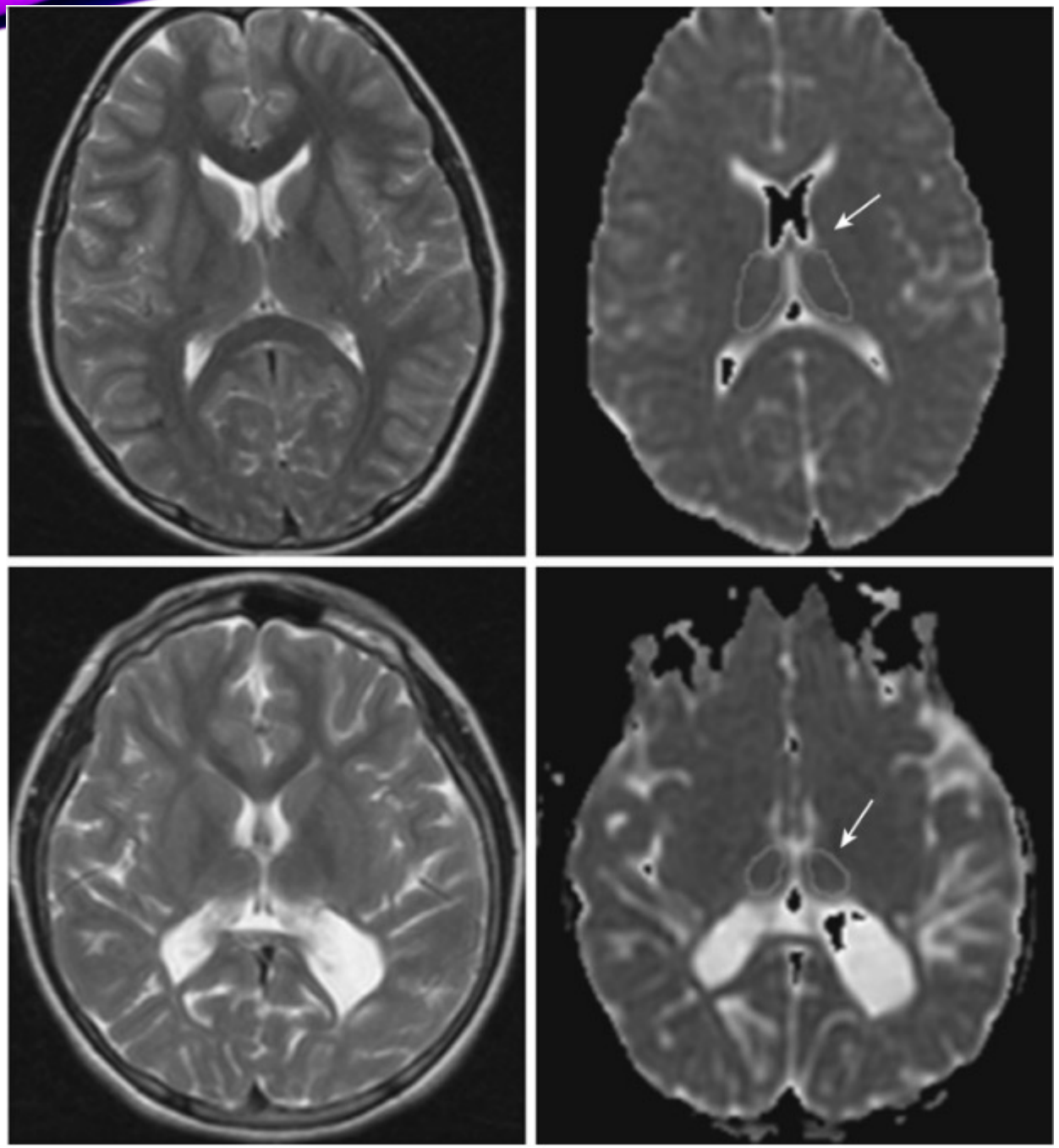
FIGURE 16.7 Parasagittal ultrasound scans obtained from a premature infant at (A) 24 and (B) 93 days of age. Note that the echolucent cysts apparent at 24 days have disappeared by 93 days of age. The trigonal region of the lateral ventricle at 93 days is dilated because of loss of periventricular white matter and failure of early myelination.

Volpe's Neurology of the Newborn 6th Edition

Normal

MRI WITH THALAMIC VOLUMETRIC LOSS

PVL -Abnormal



LONG-TERM SEQUELAE

- Spastic diplegia
- Motor deficits (without spastic diplegia)
- Spastic quadriplegic
- Cognitive deficits
- Visual deficits
- Behavioural deficits
- Attention deficits
- Social deficits

INTELLECTUAL FUNCTION

INTELLECTUAL FUNCTION	SPASTIC DIPLEGIA[a] (*n* = 81) (%)	SPASTIC QUADRIPLEGIA[a] (*n* = 56) (%)
Normal or IQ ≥70	68	14
Moderate mental retardation	15	21
Severe mental retardation	17	54

[a]Spastic diplegia—lower extremities affected more than upper extremities; spastic quadriplegia—lower and upper extremities equally affected.

Pharoah et al. *Arch Dis Child* 1987

MRI ABNORMALITIES

OUTCOME MEASURE	WHITE MATTER ABNORMALITY AT TERM[a]				
	NONE (n = 47)	MILD (n = 85)	MODERATE (n = 29)	SEVERE (n = 6)	P
MDI cognitive score	92	85	80	70	<.001
PDI psychomotor score	95	91	80	56	.008
Severe motor delay (%)	4	5	26	67	<.001
Cerebral palsy (%)	2	6	24	67	<.001
Neurosensory impairment (%)	4	9	21	50	.003

[a]Severity of white matter abnormality graded according to a numerical scale based on nature and extent of white matter signal abnormality, white matter volume loss, cystic abnormalities, ventricular dilation, and thinning of the corpus callosum.

MDI, Mental Development Index; *PDI,* Psychomotor Development Index.

Woodward et. Al NEJM 2006

THERAPEUTIC HYPOTHERMIA IN PRETERM HIE

- May be offered to moderate to late preterm neonates (33 – 35 weeks gestational age)
- Hypothermia shifts oxygen-dissociation curve to the left and decreases oxygen availability – impairs oxygen among preterm neonates with respiratory morbidities
- Serum drug levels may be elevated in the care of critically ill neonates
- Hypothermia causes immune suppression – greater risk for nosocomial infections
- More immature neonates are at risk of intracranial bleeding – hypothermia has effects on coagulation cascade and platelet function – increase intracranial bleeding
- Study by Herrera et al. (2018) – increased complications:

  coagulopathy (50%), early clinical seizures (43%), arterial hypotension (40%), persistent metabolic acidosis (37%) and thrombocytopaenia (20%), 4/30 (18.2%) died.
- TH not recommended for neonates < 32 weeks – need for other neuroprotective strategies

MANAGEMENT

Antenatal therapies

- Decosahexaenoic acid (DHA)
- Choline
- Antenatal corticosteroids
- Magnesium sulphate

Perinatal therapies

- Delayed cord clamping (DCC)

MANAGEMENT

Postnatal therapies
- Breastmilk
- Caffeine
- Family centered developmental care
- Erythropoeitin

Future therapies
- Stem cells
- Melatonin

Preclinical therapies
- Exosomes
- Polyphenols
  - Reserveratrol
  - Curcumin

PROPOSED DEFINITION OF PRETERM HYPOXIC–ISCHEMIC ENCEPHALOPATHY

Definite pHIE (Both Criteria Needed)

- pH ≤7 and base deficit ≥12 mmol/L in fetal/cord/first neonatal blood sample (within 1 h of birth).
- Neonatal encephalopathy – Sarnat staging [staged according to all criteria (except EEG) for infants between 33 and 35 weeks of gestation],
- significant changes in neurological examination and/or seizures
- (for infants less than 33 weeks of gestation).

Probable pHIE (Any Two Criteria)

- pH 7.01–7.2 in fetal/cord/first neonatal blood sample.
- Early (less than 48 h) multisystem involvement, e.g., renal, liver, cardiac dysfunction.
- Preceding identifiable sentinel event (e.g., placental abruption, uterine rupture, cord prolapse) with cardiotocograph abnormalities with previously normal pattern.
- Prolonged (more than 72 h) need for assisted ventilation in absence of respiratory illness/neuromuscular disorder.
- Delayed (more than 24 h) resolution of metabolic acidosis.
- Specific region injury (predominant WM and basal ganglia injury, relative sparing of cortex) on MRI brain performed within the first week of life.

Gopagondanahalli et al. Frontiers in Paediatrics 2016

TAKE HOME MESSAGE

- No consensus in criteria to diagnose preterm HIE
- Preterm HIE is complex, heterogenous with a wide spectrum of clinical manifestations
- Not many studies on therapeutic hypothermia in moderate to late preterms with HIE
- ‘Encephalopathy of Prematurity includes injury to both white and gray matter
- Combination of degeneration and dysmaturation
- Challenging to recognize, evaluate and prognosticate
- Aim for a neurocritical care bundle as a management strategy

QUESTIONS

Thank you