UNIVERSITY OF TORONTO

Troubled Waters
Hydrocephalus and the Preterm Infant

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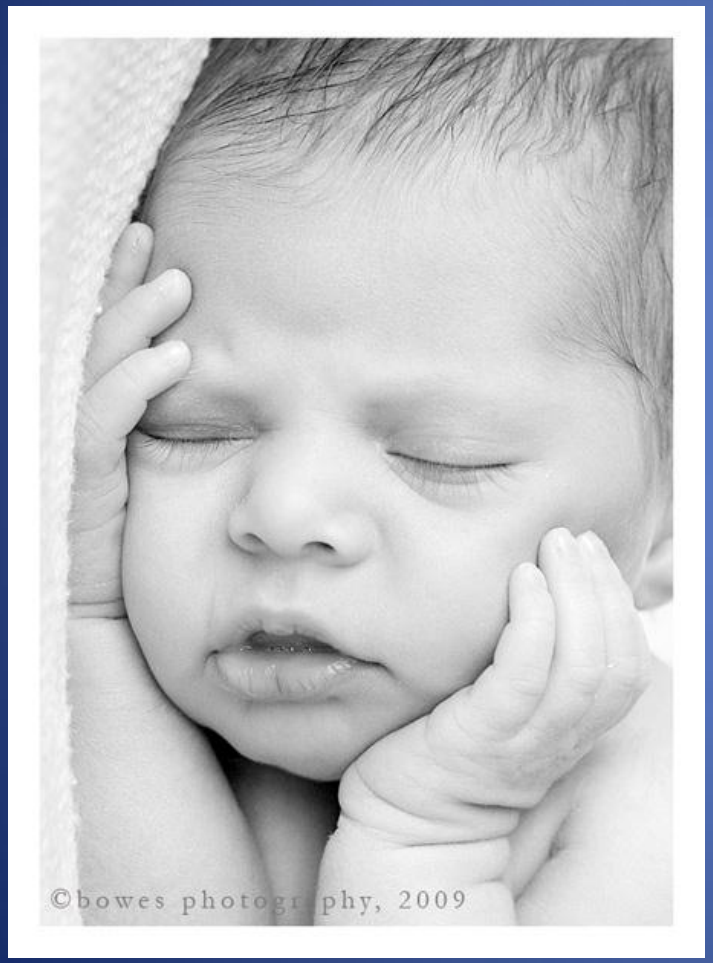
Disclosure

- I have no actual or potential conflict of interest in relation to this program.
- I also assume responsibility for ensuring the scientific validity, objectivity, and completeness of the content of my presentation

Objectives



- Review Post Hemorrhagic Hydrocephalus as it relates to:
  - Preterm neurodevelopment/behavioral phenotype
  - Interventions & timing of interventions
  - Potentiation of initial injury
  - Future directions

Introduction

- " Who you are inside is what helps you make and do everything in life." Fred Rogers

Introduction

- IVH devastating consequence of prematurity
- PHVD develops in ¼ as complication of IVH
  - Spontaneous arrest 2/3
  - Progression in 1/3*
  - Severe IVH (Grades III, PVHI) more likely

  - Bassan H. Intracranial Hemorrhage in the Preterm Infant: Understanding It, Preventing It. Clinics in Perinatology 2009;36:737-62.

Case

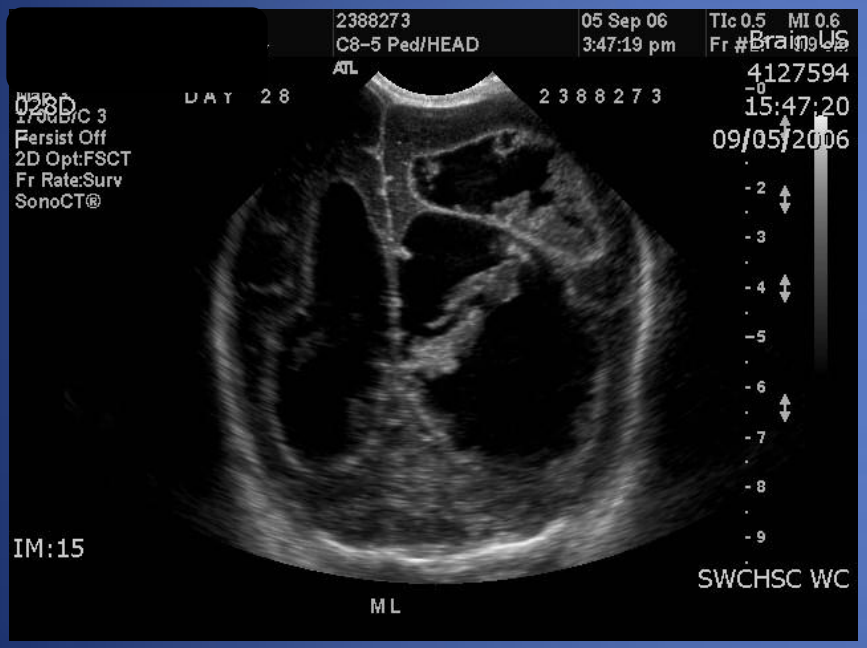
- Case 1
- 29 weeks gestation
- Singleton
- PVHI with PHVD
- HUS with left fronto-parieto-occipital venous infarct

Case 2

- 26 weeks
- Twin gestation
- PVHI with PHVD
- HUS with right fronto-parieto-occipital venous infarct

Case

- Case 1



Case 2

PHVD-Management Options

- Diuretics→NOT recommended
  - Whitelaw A, Brion LP, Kennedy CR, Odd D. Diuretic therapy for newborn infants with posthemorrhagic ventricular dilatation. Cochrane Database of Systematic Reviews 2001.
- Fibrinolytic therapy→NOT recommended
  - Whitelaw A, Odd D, Brion LP, Kennedy CR. Intraventricular streptokinase after intraventricular hemorrhage in newborn infants. Cochrane Database of Systematic Reviews 2007.
- Serial tapping→NOT recommended*
  - Whitelaw A. Repeated lumbar or ventricular punctures in newborns with intraventricular hemorrhage. Cochrane Database of Systematic Reviews 2001.
- Ventriculoperitoneal shunts???

Outcome: Literature Review

Neurodevelopmental Outcome of Extremely Low Birth Weight Infants With Posthemorrhagic Hydrocephalus Requiring Shunt Insertion

Ira Adams-Chapman, Nellie I. Hansen, Barbara J. Stoll, Rose Higgins and for the NICHD Research Network

Pediatrics 2008;121;e1167-e1177; originally published online Apr 7, 2008; DOI: 10.1542/peds.2007-0423

TABLE 4 Neurodevelopmental Outcomes at 18 to 22 Months' Corrected Age: Univariate Analyses

Outcome[a]	Group				
	No IVH/No Shunt (N = 5163)	IVH 3/No Shunt (N = 459)	IVH 3/Shunt (N = 103)[b]	IVH 4/No Shunt (N = 311)	IVH 4/Shunt (N = 125)[c]
MDI score					
Mean (SE)	80.6 (0.25)	74.1 (0.91)	66.2 (1.72)[d]	71.5 (1.09)	60.3 (1.57)[d]
Median	82	75	61	72	50
MDI < 70, n (%)	1318/4807 (27)	183/424 (43)	59/99 (60)[e]	143/295 (48)	87/115 (76)[d]
MDI = 49, n (%)	294/4805 (6)	70/424 (17)	32/99 (32)[d]	60/295 (20)	55/115 (48)[d]
PDI score					
Mean (SE)	84.7 (0.25)	77.4 (0.97)	64.1 (1.88)[d]	73.2 (1.17)	55.2 (1.24)[d]
Median	87	82	51	75	49
PDI < 70, n (%)	810/4741 (17)	140/417 (34)	65/100 (65)[d]	123/294 (42)	98/114 (86)[d]
PDI = 49, n (%)	313/4738 (7)	73/417 (18)	39/100 (39)[d]	76/294 (26)	74/114 (65)[d]
CP, n (%)	492/5125 (10)	103/457 (23)	58/102 (57)[d]	114/310 (37)	100/125 (80)[d]
Vision impairment, n (%)	465/5115 (9)	77/453 (17)	24/100 (24)	64/307 (21)	41/123 (33)[e]
Hearing impairment, n (%)	73/5091 (1)	25/446 (6)	2/101 (2)	12/304 (4)	6/119 (5)
NDI, n (%)	1690/4764 (35)	234/426 (55)	79/101 (78)[d]	189/299 (63)	114/124 (92)[d]

[a] Information was missing for MDI (421), PDI (495), CP (42); vision impairment (63), hearing impairment (100), and NDI (447).

[b] Statistically significant comparisons between IVH 3/shunt versus IVH 3/no shunt are shown. Comparisons between IVH 3/shunt versus no IVH/no shunt were statistically significant for all outcomes ($P < .001$) except hearing impairment ($P = .6$).

[c] Statistically significant comparisons between IVH 4/shunt versus IVH 4/no shunt are shown. Comparisons between IVH 4/shunt versus no IVH/no shunt were statistically significant for all outcomes ($P < .001$ for all, except hearing impairment $P < .01$).

[d] $P \leq .001$, [e] $P \leq .01$ for IVH 3/shunt versus IVH 3/no shunt or for IVH 4/shunt versus IVH 4/no shunt by the χ^2 or Wilcoxon test.

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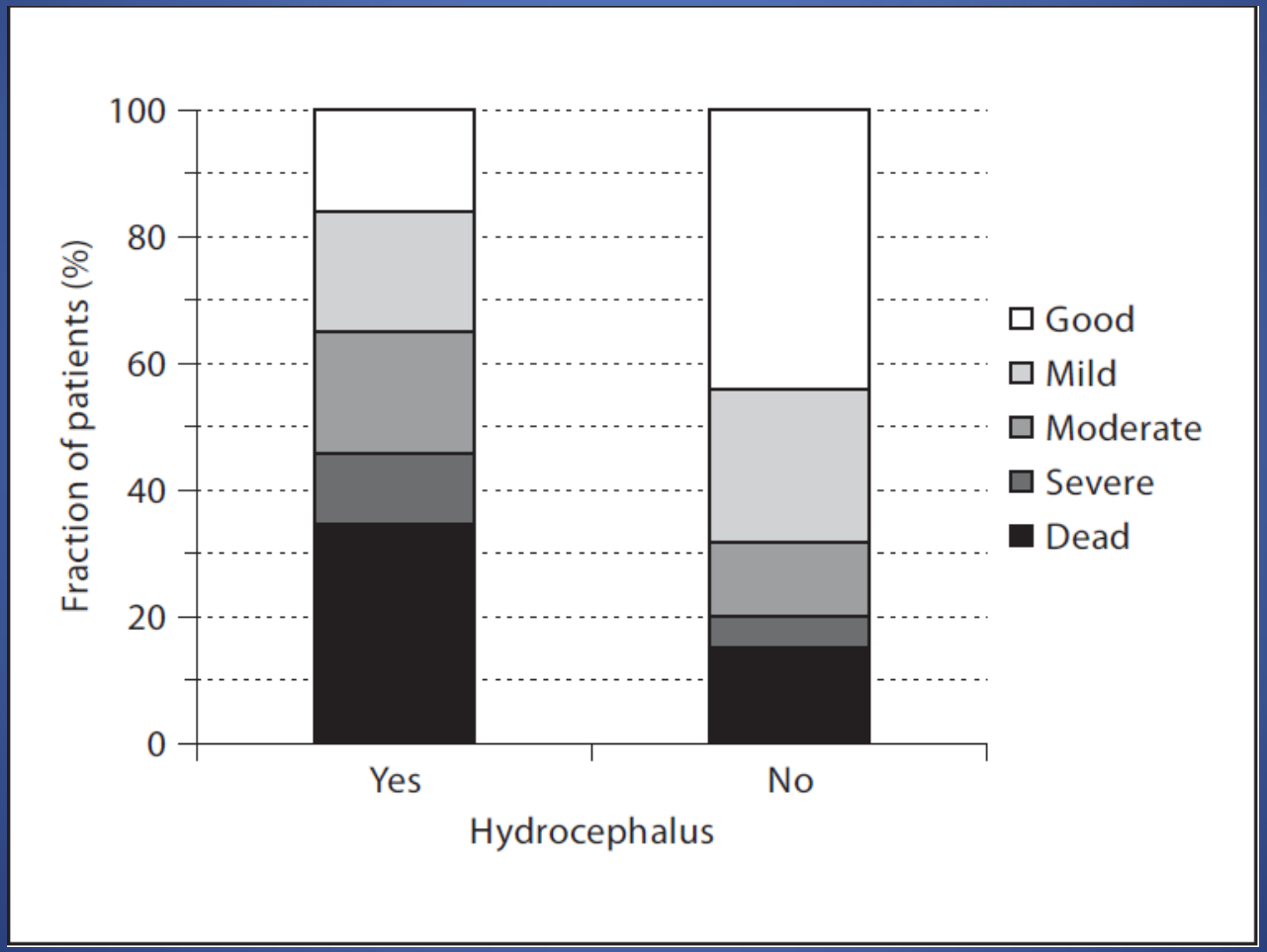
Outcome: Literature Review

Vassilyadi M, Tataryn Z, Shamji MF, Ventureyra ECG. Fundtional Outcomes among Premature Infants with Intraventricular Hemorrhage. Pediatr Neurosurg 2009;45:247-55.



Church 2012

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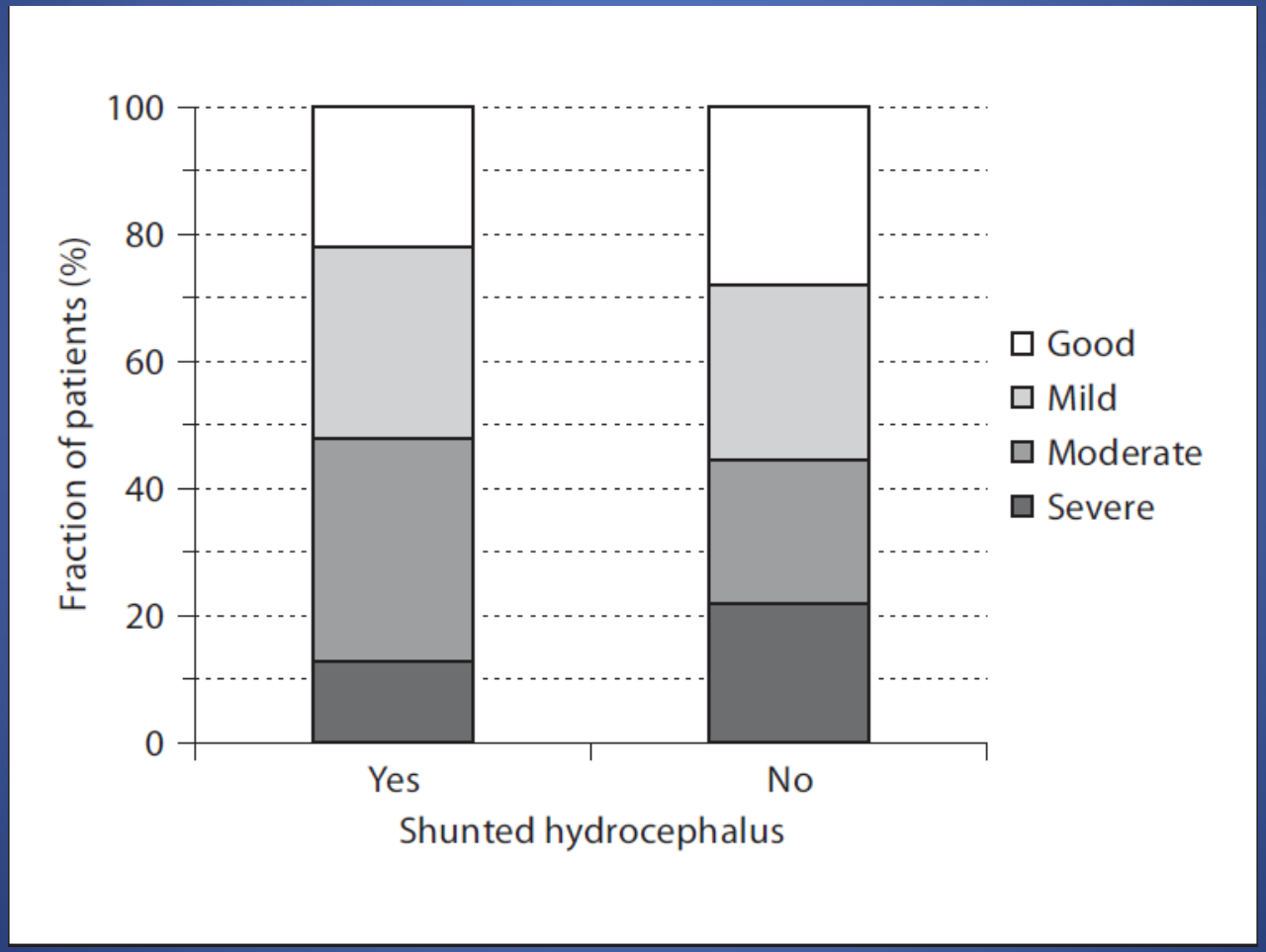
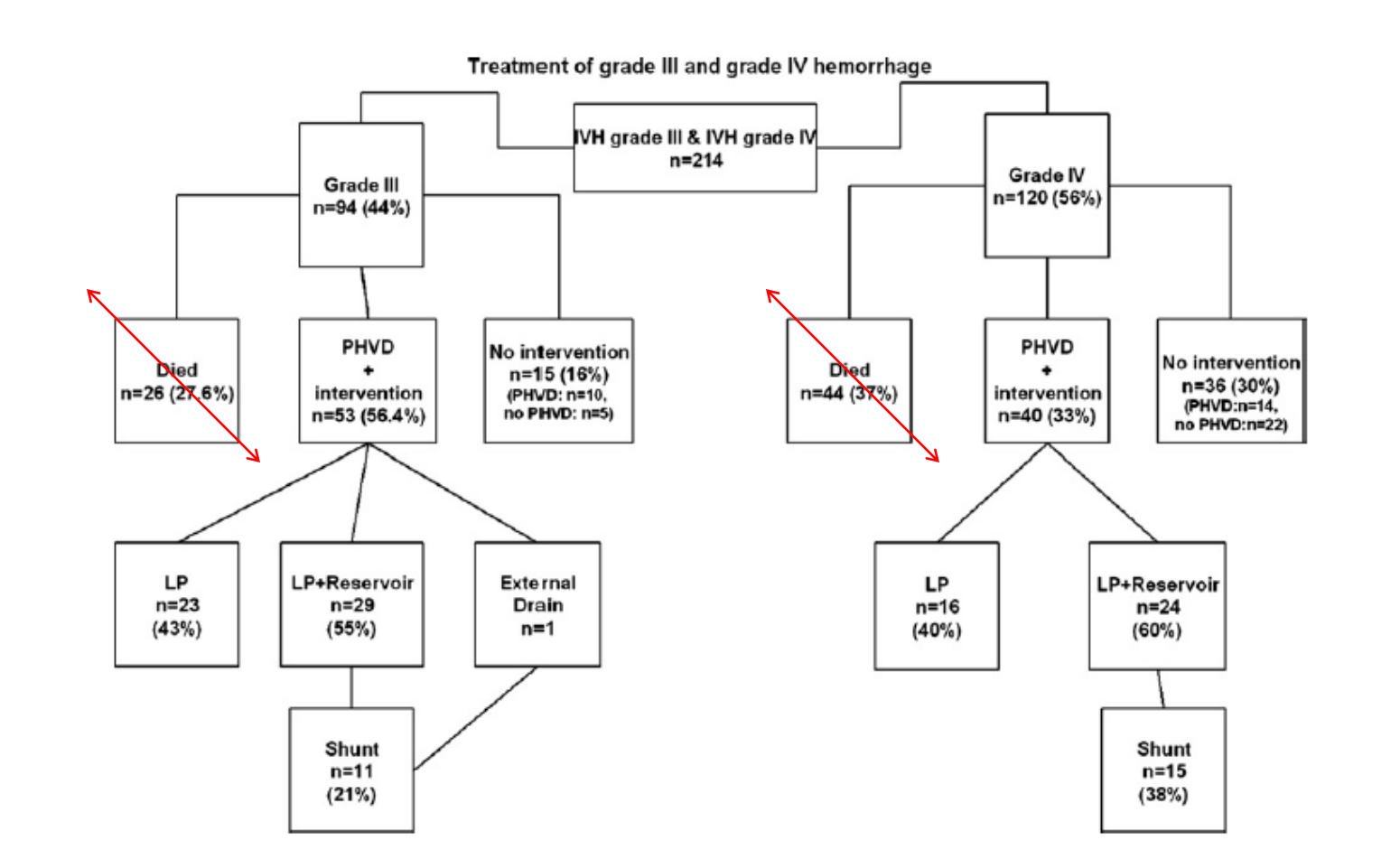


Church 2012

Outcome: Literature Review

Brouwer A, Groenendaal F, van Haastert IL, Rademaker K, Hanlo P, deVries L. Neurodevelopmental Outcome of Preterm Infants with Severe Intraventricular Hemorrhage and Therapy for Post-Hemorrhagic Ventricular Dilatation. J Pediatr 2008;152:648-54.



Church 2012

Outcome: Literature Review

Brouwer A, Groenendaal F, van Haastert IL, Rademaker K, Hanlo P, deVries L. Neurodevelopmental Outcome of Preterm Infants with Severe Intraventricular Hemorrhage and Therapy for Post-Hemorrhagic Ventricular Dilatation. J Pediatr 2008;152:648-54.

- Timing of intervention significant
- Developmental Quotient > 85:
  - 94.6% of those not reaching 97%+4 mm
  - 70% of those treated after reaching 97%+4mm
- VPS requirement
  - 27% Early intervention
  - 72% Late intervention

Outcome: Literature Review

Brouwer AJ, van Stam C, Uniken Venema M, Koopman C, Groenendaal F, deVries LS. Cognitive and Neurological Outcome at the Age of 5-8 years of Preterm Infants with Post-Hemorrhagic Ventricular Dilatation Requiring Neurosurgical Intervention. Neonatology 2012;101:210-16.

Table 3. Cognition (mean ± SD)

Group	N	IQ	IQ >85 n (%)
IVH III and IV	32	93 ± 16[a]	22 (71%)[a]
IVH III	17	96 ± 15	13 (76.5%)
IVH IV	15	91 ± 10[a]	9 (64.3%)[a]
IVH III <p97+4 mm	11	99 ± 17	9 (82%)
IVH III >p97+4 mm	6	90 ± 10	4 (66.6%)
IVH IV <p97+4 mm	6	95 ± 22[a]	3 (60%)[a]
IVH IV >p97+4 mm	8	89 ± 15	6 (75%)
IVH <30 weeks	23	92 ± 17	15 (65.2%)
Controls	23	98 ± 15	17 (74%)
IVH III no VP shunt	9	101 ± 9	9 (100%)
IVH III + VP shunt	8	90 ± 19	4 (50%)
IVH IV no VP shunt	10	91 ± 19	6 (60%)
IVH IV + VP shunt	4	90 ± 13	3 (75%)

[a] One child could not be tested.

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Outcome: Literature Review

Shankaran S, Pappas A, Bajaj M, Natarajan G. Management of Post-hemorrhagic Ventricular Dilatation: Impact of Early vs. Late Intervention, a Single Center Observational Study. Platform presentation, PAS annual meeting 2012.

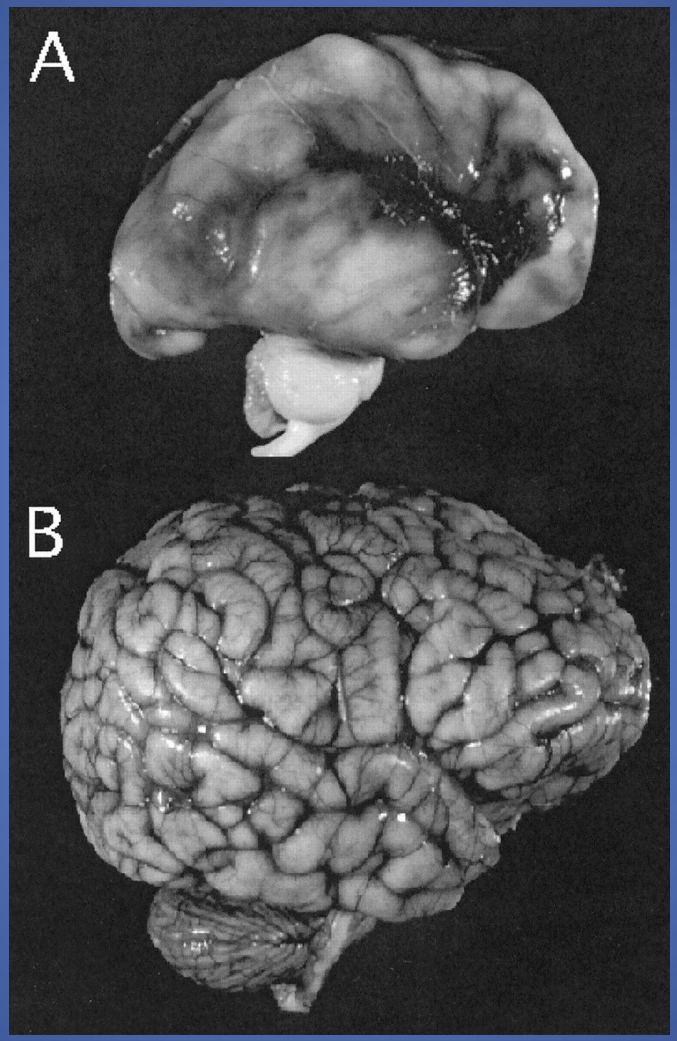
- Early Intervention: less than 3 weeks of age
- 28 infants (13 early, 15 late)
- Less VPS dependence with early (61% vs. 93%)
- BSID II outcomes same (MDI 63)
- BSID III outcome:
  - Cognition 73 for early vs. 59 for late
  - Language 75 for early vs. 56 for late

Conundrum

- Outcomes more likely linked to:
  - Initial injury
  - Gestational age at time of injury
  - Timing of intervention

- Potential of PHH to exacerbate initial injury

Comparison of the preterm brain at 28 weeks' gestational age (A) and the term brain (B) demonstrates increasing cortical development during the third trimester of gestation.



Ment L R Neoreviews 2000;1:e53-e57

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Pathogenesis
Interrupted Neuro-development

- Architectural changes to neuron

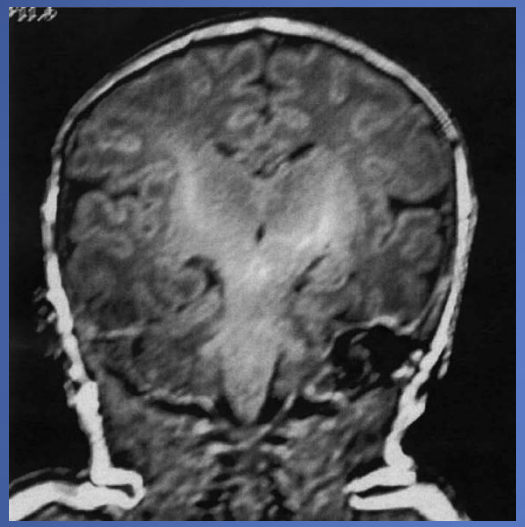
- Loss of subplate neurons, interneurons
- Arrest of OPC's-->WM loss

- Neuronal loss
  - Thalamus
  - Basal ganglia
  - Cortical (parieto-occipital, sensorimotor, premotor, temporal, hippocampal)
  - External granule cells in cerebellum

- Gliosis

- Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol 2009;8:110-24.

Pathogenesis
Interrupted neuro-development



- 3-4% with abnormality on HUS
- 20-65% with abnormality on MRI

- Inder TE, Wells SJ, Mogridge NB, Spencer C, Volpe JJ. Defining the Nature of the Cerebral Abnormalities in the Premature Infant: A Qualitative Magnetic Resonance Imaging Study. J Pediatr 2003; 143: 171-179.
- Del Bigio MR. Neuropathology and Structural Changes in Hydrocephalus. Dev Disabil Res Rev 2010;16:16-22.

“Tertiary” Brain Damage

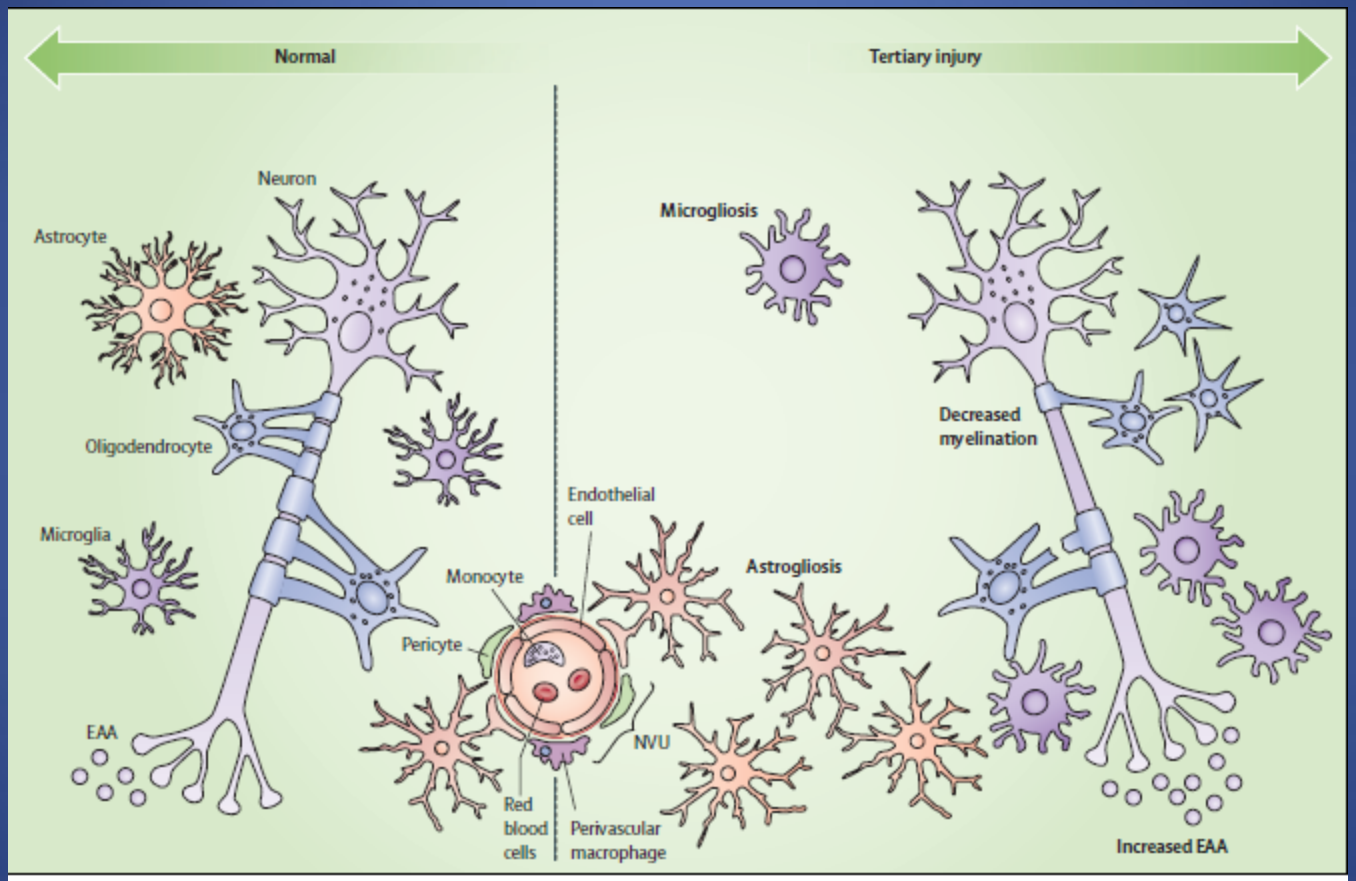


Figure 2: **Schematic representation of tertiary phase damage**
Changes in oligodendrocytes, maturational blockade, and the production of glial scar products leading to decreased myelination, changes to glia, astrogliosis and microgliosis, and possible changes in EAA bioavailability are shown. Also shown is the NVU, a possible target for novel therapeutics because of its ability to mediate transmigration of inflammatory mediators. EAA= excitatory aminoacid. NVU= neurovascular unit.

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Tertiary mechanisms of brain damage: a new hope for treatment of cerebral palsy?

Bobbi Fleiss, Pierre Gressens

Encephalopathy of the Preterm

- End result is:
  - Gray matter architecture distorted
  - White matter connectivity altered
  - Cerebellum under-developed

- PHH potentially:
  - Exacerbates initial injury
  - Exaggerates altered neural development

- Volpe JJ. Brain injury in preterm infants: a complex amalgam of destructive and developmental disturbances. J Lancet 2009; 8: 110-124.
- Alyward GP. Neurodevelopmental Outcomes of Infants Born Prematurely. J Dev Behav Pediatr 2005; 26: 427-440.

Behavioral Phenotype

- Describes a constellation of behavioral, cognitive, motor, and social difficulties observed in a population with a common biological disorder

– Hodapp RM, Fidler DJ. Special Education and Genetics: Connections for the 21st Century. The J Spec Educ 1999; 33: 130-137.

- Premature survivors have a phenotype
  – Common biological disorder = brain injury

– Church PT, Luther M, Asztalos EA. The Perfect Storm: the High Prevalence Low Severity Outcomes of the Preterm Survivor. Curr Paediatr Rev 2012;8:00.

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Behavioral Phenotype

- 50-70% in very preterm infants will have non-disabling ("minor") morbidities
- Isolated 'minor' morbidity is rare
  - Cluster of conditions more common

- Alyward GP. Neurodevelopmental Outcomes of Infants Born Prematurely. J Dev Behav Pediatr 2005; 26: 427-440.

Behavioral Phenotype

- Challenges to early identification
  - BSID not predictive of IQ
  - Discrete assessments needed
  - Sleeper effect

- Challenges may also contribute to difficulty assessing impact of PHH and intervention

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Behavioral Phenotype

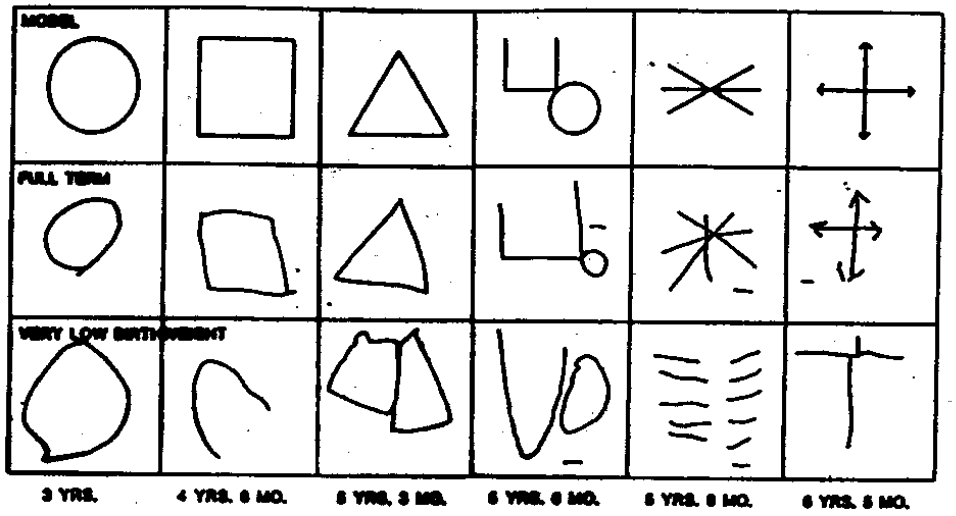
- Preterm with:
  - Lower IQ than term
  - More likely to have borderline IQ
- Socially labile, anxious
  - Internalizing
- Preterms with greater:
  - Executive dysfunction
  - Hyperactivity, inattention
  - ADHD/ADD

Anderson PJ, Doyle LW, and Victorian Infant Collaborative Study Group. Executive Functioning in School-Aged Children Who Were Born Very Preterm or With Extremely Low Birth Weight in the 1990's. Pediatrics 2004; 114: 50-57.

Spittle AJ, Treyvaud K, Doyle LW, *et al*. Early Emergence of Behavior and Social-Emotional Problems in the Very Preterm Infants. J. Am Acad Child Adolesc Psychiatry 2009; 48: 909-918.

Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJS. Cognitive and Behavioral Outcomes of School-Aged Children Who Were Born Preterm: A Meta-Analysis. JAMA. 2002; 288: 728-737.

Behavioral Phenotype



Preschool Performance of Children with Normal Intelligence Who Were Very Low-Birth-Weight Infants

Nancy Klein, Maureen Hack, John Gallagher and Avroy A. Fanaroff

Pediatrics 1985;75;531

Case

- Case 1
- Shunted at 6 weeks
- CP GMFCS I
  - Right hemiplegia
- Strabismus
- Development appropriate
- BSID III 100

Case 2

- Not shunted
- CP GMFCS IV
  - Left hemiplegia
- Optic nerve hypoplasia
- Seizures
- Developmental delay
- BSID III 70-80

Conclusion

- Intervention thus far linked to major outcomes
  - Crude measures of ‘outcome’
- Functional outcomes essential
- No clear literature to guide management

Conclusions

- Cohorts
  - Canadian Neonatal Network
  - Neonatal Research Network
  - VT Oxford Network

- Research focus to shift
  - Early markers of dysfunction (EEG, biomarkers, MRI, neurologic exams)

Conclusion

- "Mom, on the way home tonight, can we go to the store to get a more comfortable crown for me?" Summer's Blog (4.5y)

Thank You!

- Sunnybrook Health Sciences Centre
- Neonatal Follow Up Clinic
  - Marion DeLand, RN
  - Maureen Luther, PT
  - Denise Hohn, OT
  - Pat Maddalena, PNP
  - Laura Cooper, OT
  - Rudaina Banihani, MD (neo/developmental fellow) and Jessie VanDyk, MD (neonatal fellow)
  - Vanessa Warsh, administrator
  - Carol Grenade, administrator