
Chorioamnionitis, Inflammatory Mediators and PVL: is there a connection?

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The presenter has no financial or other
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Depending on how you look at it...

- Yes
 - No
 - Maybe
 - Or sometimes....
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Many difficulties figuring this out

- Different definitions
 - Different technologies
 - Changes in therapy over time
 - A multitude of inflammatory mediators
 - Powerful effect of gestational age on outcomes
 - Numerous intervening postnatal events
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What is “PVL” & what causes it?

- Site of injury in periventricular leukomalacia appears to be the pre-oligodendrocyte
 - Studies suggest these cells are prevented from maturing into oligodendrocytes
 - Creating a developmental window of vulnerability
 - Preterm infants uniquely susceptible
 - But term and late preterm infants still vulnerable as myelination processes are not yet complete
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Different histologic definitions

- Cystic – macroscopic necrosis
- Non-cystic – microscopic necrosis with glial scarring
- Diffuse astrogliosis
- “Encephalopathy of prematurity” – multiple abnormalities including neuronal

- Volpe, Pediatrics 2005

▶ Different definitions \Rightarrow different conclusions ◀

For example, on pathologic exam

115 patients, 22 – 41 weeks EGA

(died at 0 days to 10 months)

- 85 (74%) had PVL by neuropathology

- Focal
- Widespread
- Diffuse

- Deguchi et al. Ped Neurology 1999

Type of PVL in relation to gestation

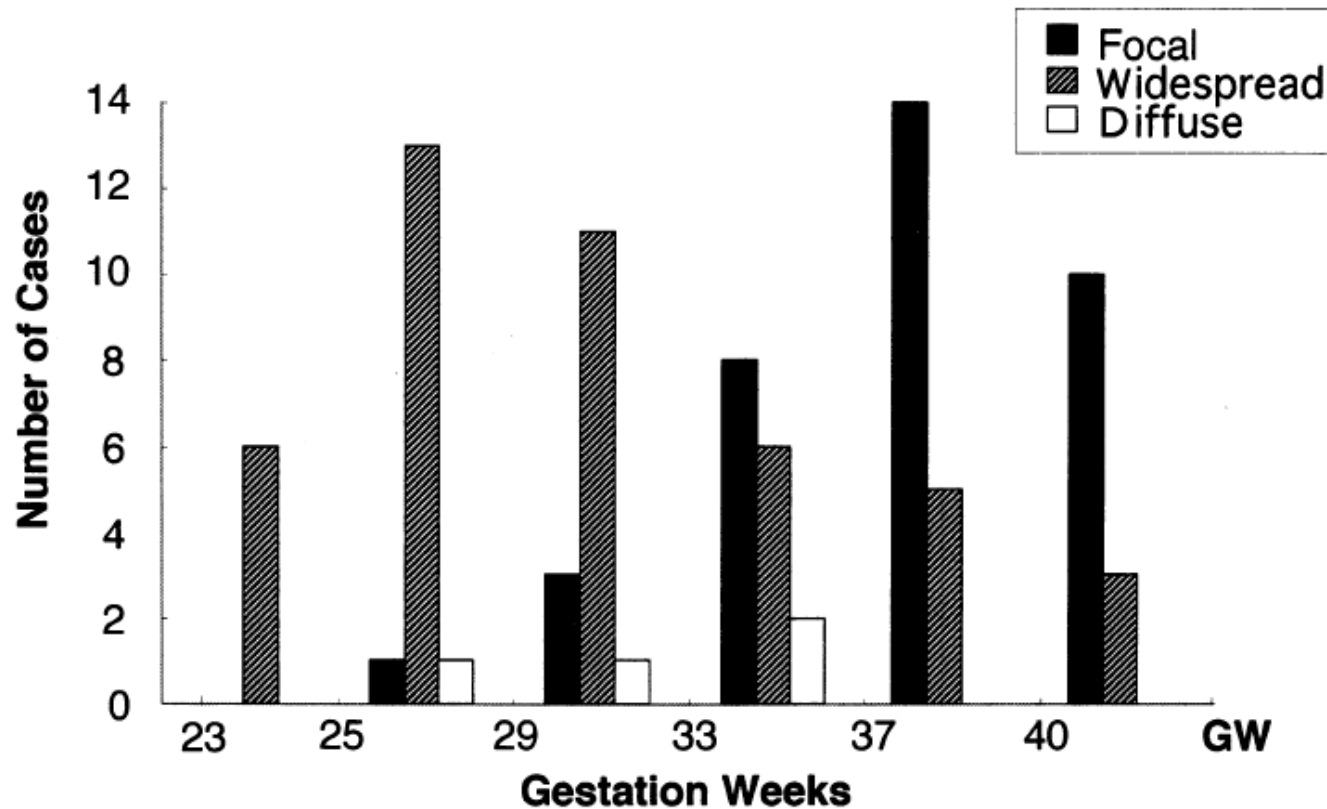


Figure 1. Type of PVL in relation to gestational age.

Different definitions: chorioamnionitis

- Clinical: maternal fever, discharge, abdominal tenderness, ↑ WBC, ↑ FHR
 - Histologic: – placental inflammation
 - Without fetal inflammation
 - With fetal inflammation
 - +/- fetal vascular response
 - ▶ Different definitions ⇒ different conclusions ◀
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For example

- If the link requires \uparrow fetal WBC \pm cytokines, there may only be a connection with the “fetal inflammatory response syndrome”
 - In a prospective study of >1000 VLBW infants
 - Membrane inflammation was not associated with echolucencies on U/S; however,
 - Fetal vasculitis was significantly associated ($\sim\uparrow 10x$) with echolucencies
 - Leviton et al *Pediatr Res* 1999; 46:566
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How are they different?

- Clinical chorioamnionitis
 - Obvious maternal illness
 - Affects a small % of pregnancies
 - And about 20% of women given this clinical dx do NOT have inflammation on histologic exam
 - Histologic chorioamnionitis
 - Not apparent without pathologic exam
 - ↑ with ↓ gestational age
 - Affects > half of deliveries <30 weeks gestation
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Chorioamnionitis in the literature

- Until 1990s, most studies of chorioamnionitis used clinical, not histologic, definition
 - Histologic chorioamnionitis is now more frequently reported; however,
 - Placental histology still not usually available for large cohorts of infants born at term
 - But... if clinical illness reflects \uparrow cytokines, it may be an important factor
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For example

- Meta-analysis of chorioamnionitis as a risk factor for cerebral palsy and cystic PVL
 - Included retrospective & prospective cohorts and case-control studies
 - Positive association of clinical chorioamnionitis
 - With PVL in preterm infants (7 studies)
 - With cerebral palsy in both preterm and term infants (12 studies)

□ Wu & Colford, JAMA 2000

A problem of technique: changing technology, changing information

- Ultrasound – standard for years
 - Very reliable for cystic PVL, macroscopic lesions
 - Significantly limited in non-cystic white matter injury
 - But – cystic PVL is decreasing in frequency
 - Non-cystic WM injury now much more common
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A problem of technique: Changing technology, changing information

- MRI – new techniques, new information
 - Conventional; diffusion-weighted; volumetric
 - Previous data using less optimal technology has given us less optimal information
 - How will future improvements change our already changing view?
- ▶ Different technology \Rightarrow different conclusions ◀
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Example: 'tract-based spatial statistics'

- ❑ Can assess white matter microstructure on a voxel-wise basis
 - ❑ Can evaluate fractional anisotropy (FA) on diffusion tensor imaging data
 - ↓FA indicates white matter injury
 - ❑ MRI data showed that
 - FA ↓ with decreasing gestational age
 - Infants with lung disease had ↓ FA in specific areas after controlling for prematurity
- ❑ Anjari et al, Pediatrics 2009; 124:268
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Confounded by changing therapies

- Antenatal steroid therapy: studies prior to common use of ANS (mid-'90s in USA) generally used
 - Clinical chorioamnionitis definition
 - Ultrasound diagnosis of cystic PVL
 - ANS therapy improved outcomes, ↓ cystic PVL
 - Suggests a link between inflammation and cystic PVL
 - But ANS also improve cardiovascular transition
 - Could the link be ANS → better perfusion → ↓ PVL?
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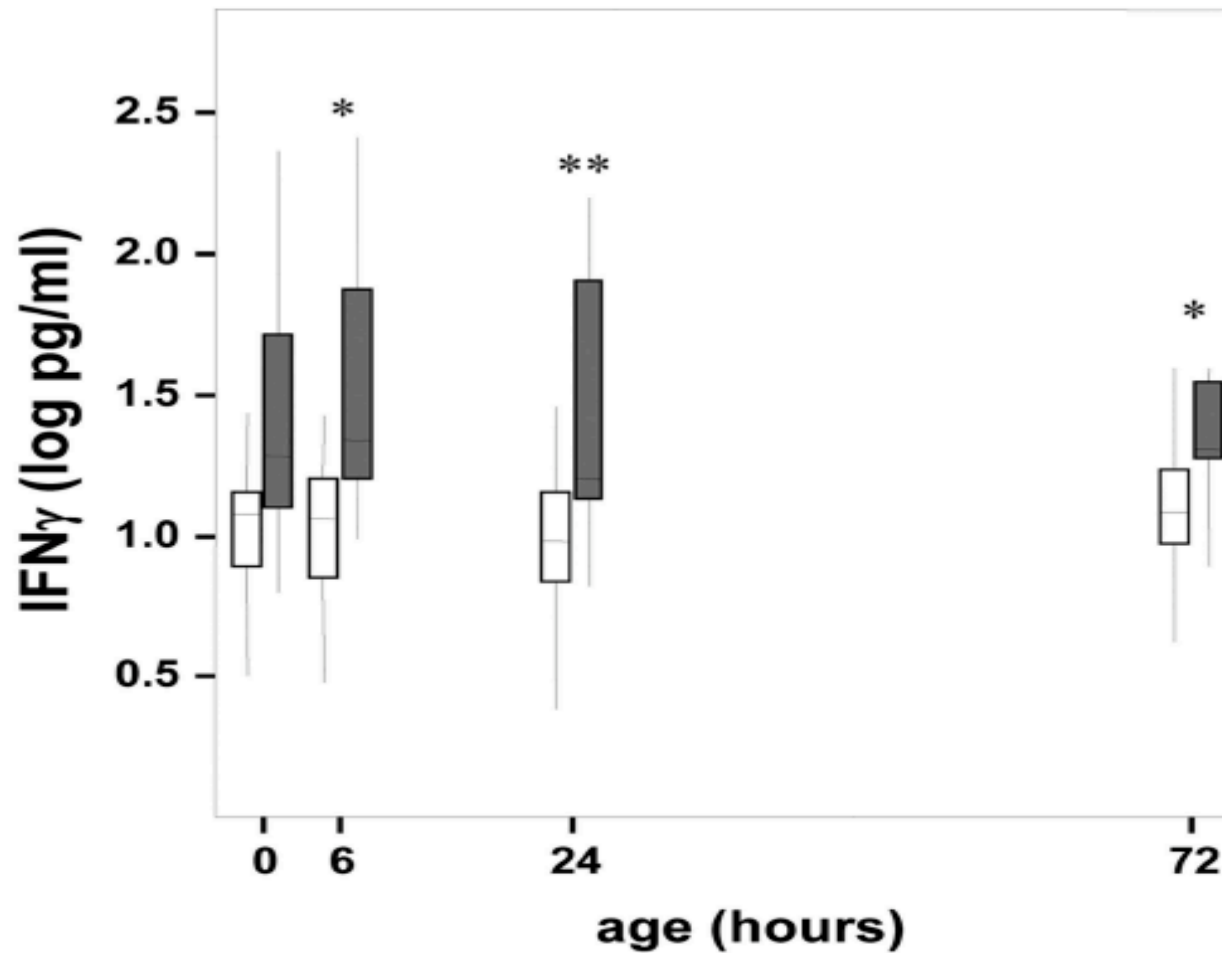
Which mediator(s) to measure?

- ↑ pro-inflammatory cytokines?
 - ↓ anti-inflammatory cytokines?
 - Abnormal balance between the two?
 - Imbalance between cytokine and receptor?
 - How about IL-1, 2, 6, 8, 10 . . .
 - Or TGF-beta, interferon-gamma, RANTES
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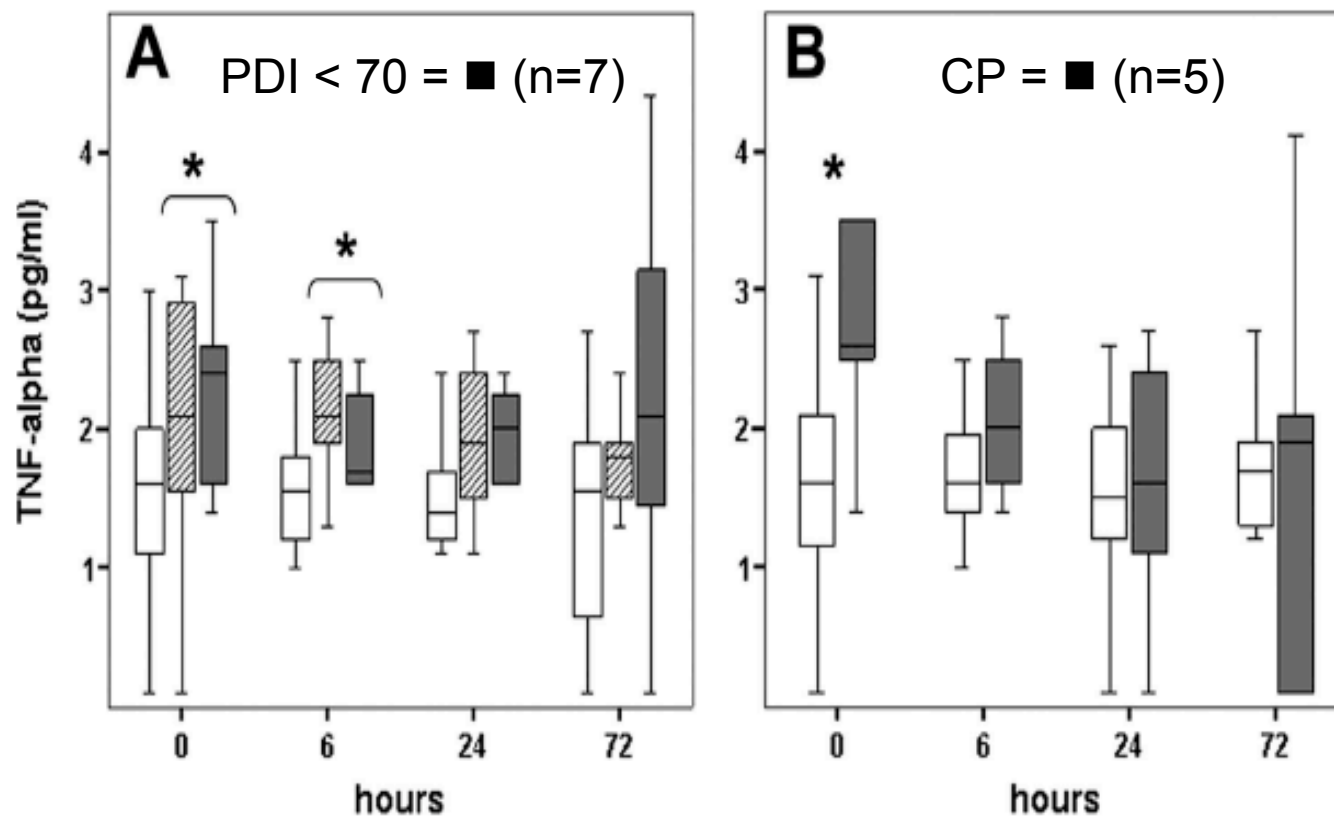
And when to measure it/them?

- Cord blood reflects intra-uterine environment
 - Elevated cytokines represent prenatal inflammation
 - Archived neonatal blood specimens obtained at variable intervals post-delivery
 - Do elevated cytokines reflect intra-uterine environment?
 - Or extra-uterine events?
 - And which one matters most?
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Interferon γ and white matter damage



TNF- α and motor abnormalities at 2 yrs



The problem of how to deal with GA

- ❑ \downarrow GA \rightarrow \uparrow chorioamnionitis and \uparrow vulnerability of brain to PVL (and other insults)
- ❑ “if low GA resulting from maternal infection in itself plays a direct role in the pathogenesis of cerebral palsy, then adjusting for its effect will falsely diminish the observed association”
- ❑ If adjusting for GA eliminates significance, “it is unclear if this is because chorioamnionitis does not contribute independently to CP, or ...because GA lies on the causal pathway”

And sorting out the effects of multiple “hits” for the preterm infant

- Postnatal inflammation (e.g., IMV, sepsis, NEC)
 - Neonatal infections in ELBW infants link to poor neurodevelopmental outcomes (n=6093)
 - Stoll et al JAMA 2004
 - Sepsis/NEC → ↑ white matter abnormalities on MRI and poor psychomotor outcome at (n=192)
 - Shah et al, J Pediatr 2008
 - Episodic or sustained periods of insufficient blood flow
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The problem of imprecise proxies for injury: what outcomes are evaluated?

- In the absence of good CNS imaging
 - Many studies use cerebral palsy as an outcome
 - PVL is a major risk factor for CP, but
 - not the only one
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So, in the face of ...

- Different definitions
 - Changing technology
 - Changes in therapy over time
 - A myriad of cytokines to measure & evaluate
 - Powerful effect of gestational age on outcomes
 - Numerous intervening postnatal events
 - Crude proxies for CNS injury
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- **Where do we go from here?**

Basic science – lots of evidence for CNS injury from inflammation

- Rabbits: E. Coli into amniotic fluid → fetal white matter injury
 - Yoon et al. Am J Obstet Gynecol 1997
 - Sheep: LPS → white matter injury in 50% of preterm and 30% of near-term animals
 - Svedin et al. J Child Neurol 2005
 - Cell culture: IL-1 + TNF α + interferon- γ induced dramatic injury in neuron/glial cultures
 - Jeohn et al. J Neuroimmunol 1998
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Anti-inflammatory measures ↓ injury

- Neutrophil depletion before hypoxic-ischemic insult decreases brain swelling and atrophy
 - Palmer et al, Pediatr Res 2004
 - IL-1 receptor antagonist – same effect
 - Martin et al, Exp Neurology 1994
 - Pentoxifylline pretreatment – ditto
 - Eun et al, Pediatr Res 2000
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Neutrophil depletion affects HI injury

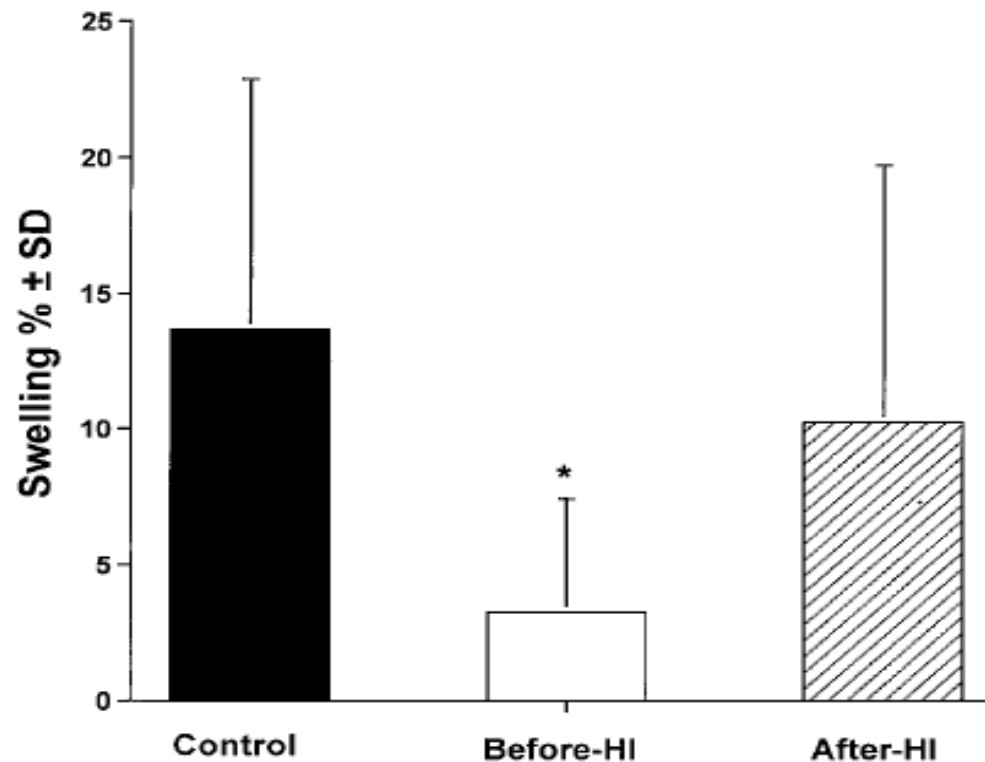
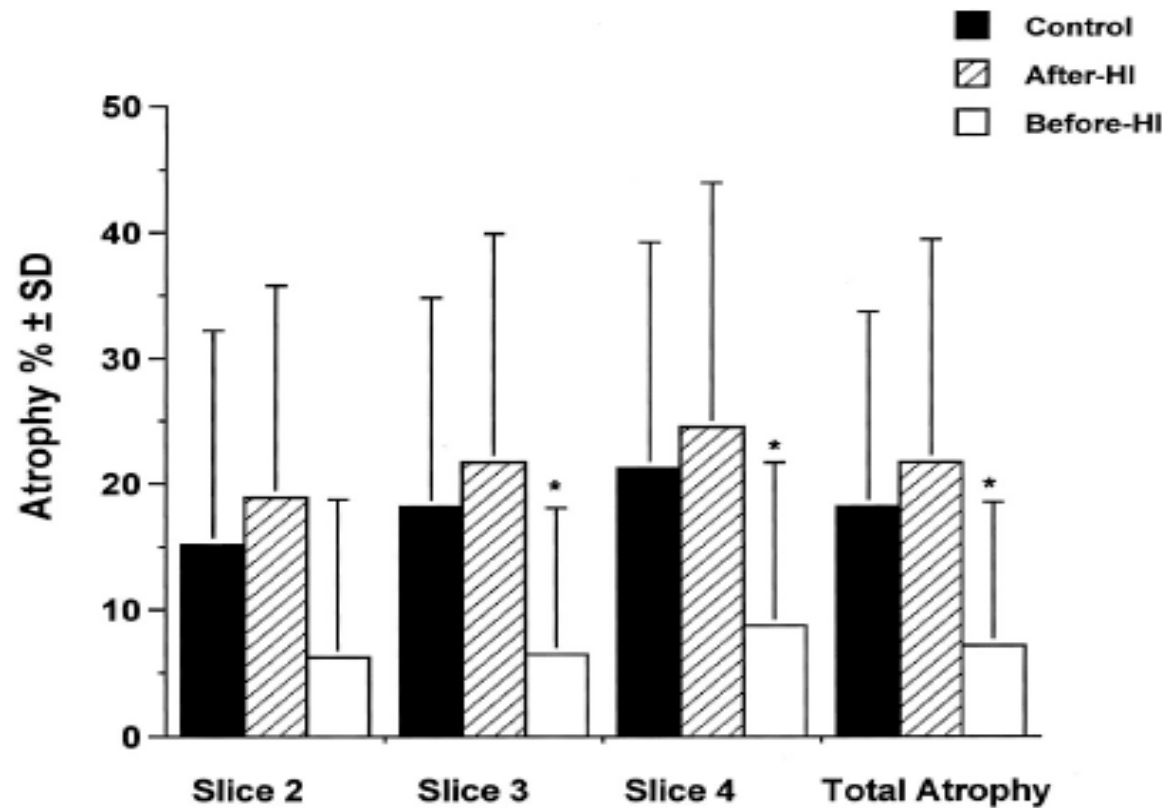


Figure 2. Bar chart showing that brain swelling was reduced in the before-HI group only. (Control group, $n = 25$; before-HI group, $n = 15$; after-HI group, $n = 24$).

Neutrophil depletion affects HI injury



Clinical studies in term infants

- Fewer postnatal inflammatory ‘hits’ than preterm infants
 - Usually no placental histology available
 - But perhaps [cytokines] more important
 - Perhaps maternal illness is an important signal
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Term infants: inflammation and CP

- Maternal infection linked to cerebral palsy (CP)
 - 2 case-control studies from CA (46 & 109 cases)
 - Maternal fever \pm clinical chorio linked to CP
 - Grether & Nelson JAMA 1997, Wu et al JAMA 2003
 - 1 case-control study from Washington state
 - Maternal infection linked to CP
 - Neufeld et al, J Perinatol 2005
 - ↑ Cytokines linked to CP
 - 1 case-control study, blood spots (31 cases)
 - Nelson et al Ann Neurol 1998
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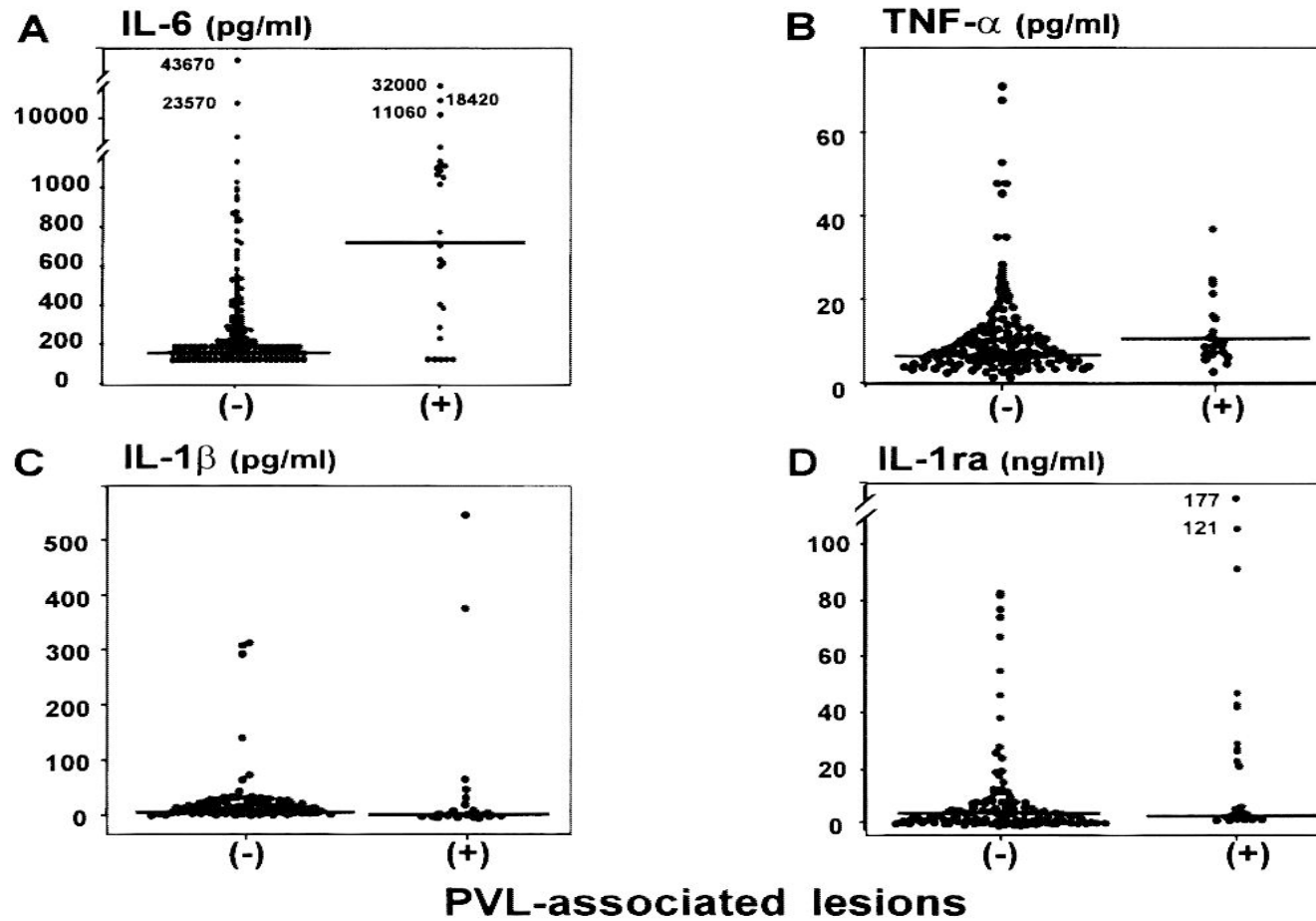
Preterm infants: inflammation and CP

- ❑ Histologic chorioamnionitis (n=515): ↓ survival free of disability, but likely related to ↓BW & GA
 - ❑ Henderson et al, PAS abstract 2007
 - ❑ Histologic chorioamnionitis (n=252): multi-center RCT of HC, no difference in CP (13% vs. 15%)
 - ❑ Watterberg et al, Pediatrics 2007
 - ❑ Cytokines, archived neonatal blood (n=171) – no relationship (did correlate with U/S abnormalities)
 - ❑ Nelson et al, Pediatr Res 2003
 - ❑ Amniotic fluid cytokines: elevated IL6 → ↑CP
 - ❑ Yoon et al Am J Obstet Gynecol 1997; 2000
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Preterm infants: inflammation & PVL

- ↑ IL-6 in umbilical cord plasma associated with cystic PVL on U/S
 - Prospective cohort <32 weeks EGA, n=309
 - Goepfert et al Am J OB Gyn 2004
 - Prospective cohort <36 weeks EGA, n=172
 - Gestation included in the logistic regression as a dichotomous variable, ≤32 or >32 weeks
 - Yoon et al, Am J OB Gyn 1996
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Cord blood cytokines and PVL lesions



Genetics and outcomes

- Intra-uterine infection not risk factor for CP overall, but doubled the risk for white mothers (170 cases)
 - Grether et al, Arch Pediatr Adolesc Med 2003
 - Cytokine polymorphisms ↑ risk of CP in term and preterm infants (443 cases, 883 control)
 - Gibson et al, Am J Obstet Gynecol 2006
 - IL-6 (-174) C/C & C/G associated with mental retardation in infants with cystic PVL (52 infants)
 - Resch et al Arch Dis Child 2009
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So if you don't find a connection, could it be...

- There is no connection? Or....
 - Wrong definition?
 - Wrong technology?
 - Wrong mediator?
 - Wrong timing?
 - Polymorphisms more important than [cytokine]?
 - If there is a connection.....
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Could we intervene?

- *In vitro*, TNF- α & IFN- γ blocked differentiation of pre-OD cells; dexamethasone abolished this effect
 - Mann et al, J Neuroinflamm 2008
 - Critically ill adults: hydrocortisone Rx decreased IL-6
 - Keh et al, Am J Respir Crit Care Med 2003
 - *In utero*: w/o prenatal steroids, chorioamnionitis linked with IVH, parenchymal echodensity and CP (n=62); with steroids, no such link
 - Kent et al J Paediatr Child Health 2005
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What about postnatal interventions?

- Postnatal glucocorticoids?
 - For BPD?
 - For adrenal insufficiency?
 - For hypotension?
 - For sepsis or NEC?
 - Antibiotics?
 - Hypothermia?
 - All unknown....
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In summary, is there a connection between chorioamnionitis and PVL?

- Even with all the problems in teasing it out:
 - Differing definitions for all parts of the equation
 - Variable associations in human clinical studies
 - Variable susceptibility at different gestational ages
 - Multiple postnatal inflammatory insults
 - Changing practice and changing technology
 - It seems likely
 - Causal relationship *in vitro* and in animal studies
 - With evolving technology and better definitions – we can hope for a better understanding
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