Hypothesis

Is some white matter damage in preterm neonates induced by a human pestivirus?

We offer the hypothesis that some forms of cerebral white matter damage (WMD) in preterm neonates might be caused by transplacental viral infection of the fetus during the first or second trimester of pregnancy. Potts and colleagues speculated on the possible role of a human pestivirus (PV) in the aetiology of congenital microcephaly. We suggest PV might be a candidate virus for some form of WMD. We further offer our view that a virus induced cytokine cascade might place the fetus at double jeopardy—that is, disturb white matter development and lead to preterm birth.

Virus related WMD

White matter damage is the most important predictor of childhood neuromotor disability among those born preterm. About 50% of infants who have echolucent zones in the periventricular white matter or ventriculomegaly on preterm.About50%ofinfantswhohaveecholucentzones in the periventricular white matter or ventriculomegaly on preterm cranial ultrasound scans subsequently develop childhood neuromotor disability among those born preterm. Virus related WMD.7 Maternal infection with pestiviruses led to dysmyelination of their brains.8 Hypomyelination is a symptom of some diffuse forms of WMD.3 Infection with the pestivirus BDV leads to necroses and cysts in the periventricular white matter and enlarged ventricles in lamb fetuses.9 All of these are expressions of WMD in preterm human babies.4, 10

Infection with BDV is accompanied by a decrease in thyroid hormone activity in lambs.3 Low thyroid hormone values are also an important predictor of maldevelopment among preterm infants.22–24 After adjustment for gestational age, Reuss and colleagues found an 11-fold increased risk of disabling cerebral palsy among preterm infants with severe hypothyroxinaemia. What is still unclear is whether low thyroid hormone values are the cause of the brain damage or merely an indicator of illness severity and/or immaturity related vulnerability, which conveys risk information above and beyond that given by gestational age information.

Does a virus induced cytokine cascade cause both preterm birth and WMD?

A common antecedent of both preterm birth and WMD could serve as a likely explanation for why WMD is more common among preterm than term infants.22 A transplacental virus infection early in pregnancy potentially fulfills the criteria of such a common antecedent (fig 1).

One in four women with asymptomatic shedding of herpes simplex virus at the onset of labour gave birth before the completion of 37 weeks of gestation; this percentage was only 12% among unaffected controls.17 In two other studies not involving uninfected newborns for comparison,
41%²⁶ and 48%²⁷ of infants with neonatal herpes simplex infection were born before term. Herpesviridae stimulate the production of cytokines such as IL-1β and TNFα by peripheral blood mononuclear cells.²⁸ In contrast, the fetal brain undergoes significant changes in the brain after crossing the placenta and blood–brain barrier, at various levels of the materno-fetal unit (placenta, fetal membranes, umbilical vessels)³⁰ and blood-brain barrier,³¹ which can be mediated by cytokines.³²,³³ Moreover, infection by herpesviridae can lead to fetal death,³⁴ congenital anomalies,²³³⁵³⁶ and cerebellar hypoplasia,³⁷³⁸³⁹ abnormality in the perinatal period,³⁸³⁹ and periventricular leukomalacia.⁴⁰

Intrauterine infection with WNV can result in preterm labour and delivery,³⁴³⁶⁴⁵⁴⁶ in 3% of cases.³⁴³⁶³⁷³⁸ The present study investigated the role of cytokines, cytokine interactions, and their effects on the development of preterm labour in infants with periventricular leukomalacia.³⁴³⁶³⁷³⁸

Testing the hypothesis

Our hypothesis is that a transplacental human herpesvirus infection might be involved in the aetiology of WMD in preterm neonates is difficult to test. We consider the epide- miological approach, and in particular a case–control study design to be most rewarding. If a human herpesvirus-like infection is indeed related to WMD, then characteristics of such an infection should be found significantly more often among infants born with WMD than among non-affected controls, while adjusting for potential confounders such as gestational age. Despite the necessity to conduct a large scale, multicentre study to obtain a sufficient number of WMD cases, we believe that the opportunity to identify a possible preventable antecedent of WMD in the preterm neonate would be worth the effort.

This work was supported by National Institute for Neurologic Disorders and Stroke Grant NS 27306 and United Cerebral Palsy Research and Educational Foundation Grant R-712-96.

OLAF DAMMANN
ALAN LEVITON

Neuroepidemiology Department, University of Pennsylvania, Children’s Hospital and Harvard Medical School, Boston, MA 02115, USA
E-mail dammannon@a1.tch.harvard.edu


8 Macfarlane DW, Boyd RD, Dodrill CB, Tufts E. Intranufactureleibul marrow in preterm neonates with cerebral palsy and subsequent intelligence quotient (IQ) at 8 year follow up. BMJ 1996; 312:53-7.


11 Dammann O, Leviton A. The role of perinatal brain damage in preterm neonates is difficult to test. We consider the epide- miological approach, and in particular a case–control study design to be most rewarding. If a human herpesvirus-like infection is indeed related to WMD, then characteristics of such an infection should be found significantly more often among infants born with WMD than among non-affected controls, while adjusting for potential confounders such as gestational age. Despite the necessity to conduct a large scale, multicentre study to obtain a sufficient number of WMD cases, we believe that the opportunity to identify a possible preventable antecedent of WMD in the preterm neonate would be worth the effort.

This work was supported by National Institute for Neurologic Disorders and Stroke Grant NS 27306 and United Cerebral Palsy Research and Educational Foundation Grant R-712-96.

OLAF DAMMANN
ALAN LEVITON

Neuroepidemiology Department, University of Pennsylvania, Children’s Hospital and Harvard Medical School, Boston, MA 02115, USA
E-mail dammannon@a1.tch.harvard.edu


8 Macfarlane DW, Boyd RD, Dodrill CB, Tufts E. Intranufactureleibul marrow in preterm neonates with cerebral palsy and subsequent intelligence quotient (IQ) at 8 year follow up. BMJ 1996; 312:53-7.


11 Dammann O, Leviton A. The role of perinatal brain damage in preterm neonates is difficult to test. We consider the epide- miological approach, and in particular a case–control study design to be most rewarding. If a human herpesvirus-like infection is indeed related to WMD, then characteristics of such an infection should be found significantly more often among infants born with WMD than among non-affected controls, while adjusting for potential confounders such as gestational age. Despite the necessity to conduct a large scale, multicentre study to obtain a sufficient number of WMD cases, we believe that the opportunity to identify a possible preventable antecedent of WMD in the preterm neonate would be worth the effort.

This work was supported by National Institute for Neurologic Disorders and Stroke Grant NS 27306 and United Cerebral Palsy Research and Educational Foundation Grant R-712-96.

OLAF DAMMANN
ALAN LEVITON

Neuroepidemiology Department, University of Pennsylvania, Children’s Hospital and Harvard Medical School, Boston, MA 02115, USA
E-mail dammannon@a1.tch.harvard.edu