Pestivirus as a cause of white matter damage – down but not out

There is now substantial evidence to suggest that the presence of inflammatory molecules within the fetal circulation and brain is associated with damage to vulnerable oligodendrocyte precursor cells before 32 weeks' gestation and long-term white matter damage (WMD); however, the nature of the inflammatory stimulus remains unclear. The common association between ascending bacterial infection from the vagina, haematogenous spread of periodontal organisms, chorioamnionitis, preterm delivery, and neonatal brain injury provides indirect clinical evidence supporting an important role for bacteria.[1] Animal experiments in which live bacteria, or endotoxins, lead to the classical focal necrotic lesions of periventricular leukomalacia add further support to this concept.[2] The isolation of bacteria-specific DNA from only a small proportion of cases where there is evidence of histological chorioamnionitis, suggests that there may be non-bacterial causes of fetal inflammation. Viruses make attractive alternative candidates; they are a common cause of maternal pyrexia, can cross the placenta (e.g. cytomegalovirus and rubella), are known to cause WMD and microcephaly, and are difficult to isolate. A recent study of viral DNA in stored neonatal blood spot specimens suggested a possible link between viral exposure and later cerebral palsy, particularly in preterm babies.[3] Dammann and Leviton[4] have been even more specific, identifying maternal pestivirus (PV) infection as a hypothetical cause of WMD in preterm neonates.

In this issue Dammann[5] reports a study designed to address his original hypothesis. Immunohistochemistry using a monoclonal mouse antibody to bovine virus diarrhoea virus (BVDV), an important pestivirus strain, failed to show any BVDV antigen in the forebrains or cerebellum of 22 fetuses/neonates, 11 of which had periventricular leukomalacia. These data suggest that WMD was not caused by a BVDV encephalitis, although this would need to be confirmed by PCR studies to detect viral DNA. However, as the authors point out in the discussion, this study does not preclude the possibility of direct cerebral transfection with other viruses or viral stimulation of systemic fetal inflammation as causes of WMD. Similar conclusions can be derived from another study in which maternal infection with influenza virus during pregnancy in mice, did not result in presence of viral antigen in fetal brain; again, the authors invoke an indirect, inflammation-mediated mechanism for the brain injury.[6]

There are several ways in which maternal viral infection could contribute to fetal brain injury, apart from transplacental passage of virus and direct cerebral transfection. Proinflammatory cytokines could be produced from various sites at the materno–fetal interface, cross the blood brain barrier, and lead to glial activation, as well as having a direct neurotoxic action. In addition, it is possible that activation of fetal inflammatory pathways could sensitize the brain and lower the threshold at which a subsequent hypoxic-ischaemic insult would lead to neural cell death.[7] Such a synergistic interaction has been demonstrated between hypoxic-ischaemia and bacterial endotoxin in neonatal rats.[8] Maternal pyrexia may also make the fetal brain more vulnerable to both hypoxic and inflammatory challenges; there is a link between maternal pyrexia during labour and neonatal seizures.[9] These data do not prove the case that maternal viral illness leads to WMD. Further animal studies are required to link antenatal exposure to a variety of common viruses with histological and functional evidence of brain injury. Parallel clinical studies will also be needed to determine whether markers of viral infection in maternal blood or membranes are more common in preterm infants who develop WMD.

Before such a link is established it would be premature to alarm women with suggestions that any viral illness might lead to fetal brain injury, or to alter the mode of delivery in pregnancies where the mother has a pyrexia or evidence of a recent infection. Common sense obstetric interventions, however, such as use of antipyretics and efforts to reduce maternal pyrexia during labour, are unlikely to cause harm and may be neuroprotective. Dammann's study does not support a direct role for pestivirus in the causation of neonatal white matter injury; however, it does not close the door on this intriguing story.

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