Antenatal causes of cerebral palsy and adverse pregnancy outcomes: Investigating associations between inherited thrombophilia, cytokine polymorphisms and viral infections

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Abstract

Objective: The objective of this thesis was to investigate three potential antenatal risk factors – inherited thrombophilic polymorphisms, cytokine polymorphisms and exposure to viral infections – and their possible association with the development of cerebral palsy (CP) and other adverse pregnancy outcomes (APO), including intrauterine growth restriction, pregnancy-induced hypertensive disorders, antepartum haemorrhage and preterm birth.

Methods: Newborn screening cards from 1,326 babies (443 CP cases and 883 non-CP controls for the CP study; 717 APO cases and 609 non-APO controls for the APO study) were tested for inherited thrombophilic polymorphisms, cytokine polymorphisms and exposure to viral infections using polymerase chain reaction technology in the largest study of its kind worldwide. The four inherited thrombophilic polymorphisms tested were: Factor V Leiden (FVL G1691A), Prothrombin gene mutation (PGM G20210A) and Methylenetetrahydrofolate reductase gene (MTHFR) C677T and MTHFR A1298C. Five cytokine polymorphisms were genotyped: Tumour necrosis factor alpha -308 (TNF-α -308), Mannose binding lectin -221, (MBL -221) and three polymorphisms in Exon 1 of the MBL gene at codons 52, 54 and 57. The newborn screening cards were also tested for viral nucleic acids from enteroviruses and herpesviruses.

Results: Inherited thrombophilic polymorphisms may play a role in the development of CP and adverse pregnancy outcomes, as suggested by previous small studies. This thesis determined that the MTHFR C677T thrombophilic polymorphism approximately doubled the risk of CP in preterm infants, and a combination of homozygous MTHFR C677T and heterozygous PGM increased the risk of quadriplegic CP five-fold at all gestational ages. The results also suggested that some fetal thrombophilia, in particular PGM, may be related to such adverse pregnancy outcomes as intrauterine growth restriction.

The role of the TNF-α -308 polymorphism and four polymorphisms within the MBL gene had not previously been described for the subsequent development of CP. Carriage of polymorphisms in the TNF-α and MBL genes were associated significantly with an increased risk of CP. The TNF-α -308 polymorphism was also found to be associated with intrauterine growth restriction, pregnancy-induced hypertensive disorders, antepartum haemorrhage and preterm birth, and the MBL polymorphisms were associated with antepartum haemorrhage, pregnancy-induced hypertensive disorders and preterm birth.

Viral nucleic acid sequences were detected from newborn screening cards in 46.1% of cases, compared with 39.8% of controls (OR 1.30, 95% CI 1.00-1.67). This study was the first to demonstrate that evidence of direct infection with herpesviruses is associated with CP. In particular, detection of herpes group B viruses were associated with the development of CP (OR 1.68, 95% CI 1.09-2.59). These viral nucleic acid sequences were also found to be associated with adverse pregnancy outcomes, in particular preterm birth and pregnancy-induced hypertensive disorders.

Multivariable analysis demonstrated no significant interactions between the three main outcome measures listed above and the development of CP. Bivariable analyses showed increased risks of CP. The combination of Herpes group B viruses and carriage of any cytokine polymorphism was associated with an increased risk of CP (OR 2.47, 95% CI 1.43-4.27). This relationship was linear and showed no significant synergistic relationship between the two outcome measures in the causation of CP.

Conclusions: This research has shown that thrombophilic polymorphisms, cytokine polymorphisms and viral infections are all independently associated with the subsequent development of CP. These three factors do not interact to further increase the risk of CP, and this may reflect different pathological pathways to the brain white matter damage and periventricular leukomalacia that ultimately leads to CP. Together, their potential attributable risk is 15% of cerebral palsy cases, but further studies of new polymorphisms and infections are likely to increase this attributable risk. This data set has also shown that these same inherited thrombophilic and cytokine polymorphisms and viral infections are associated with adverse pregnancy outcomes such as intrauterine growth restriction, pregnancy-induced hypertensive disorders, antepartum haemorrhage and prematurity. These associations suggest interaction between genes and environmental risk factors.

Implications: Future research should investigate interactions between genes and the environment. Possible preventative strategies should be explored, such as vaccination programmes against the neurotropic viruses identified in this thesis as being associated with CP. This research also has medico-legal and political implications. The possible causal pathways for most CP outcomes currently cannot be influenced by obstetric practice. Their detection in retrospect may lead to prospective testing and research into the antenatal causes of cerebral palsy and its eventual prevention, saving hundreds of millions of dollars annually.