

## REVIEW

# Can polyclonal intravenous immunoglobulin limit cytokine mediated cerebral damage and chronic lung disease in preterm infants?

P V Mohan, W Tarnow-Mordi, B Stenson, P Brocklehurst, K Haque, V Cavendish, A Cust

Recent evidence suggests that inflammatory cytokines may play an important role in cerebral and pulmonary injury, especially in preterm infants. Immunomodulatory agents may help to limit such injury by reducing inflammation. Immunoglobulin has multiple anti-inflammatory properties and can modulate the inflammatory cytokine response. New evidence is required to test the hypotheses that prophylaxis or treatment with intravenous immunoglobulin may limit such inflammatory damage.

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development of cerebral palsy.<sup>5</sup> Cerebral palsy was strongly associated with antenatal exposure to intra-amniotic inflammation, as evidenced by increased IL6, IL8, and white cells in the amniotic fluid and a systemic fetal inflammatory response, indicated by funisitis.<sup>6</sup> In autopsy specimens, local expression of proinflammatory cytokines is increased in brains with periventricular leucomalacia<sup>7,8</sup> and is mainly detected in hypertrophic astrocytes and microglial cells. Cytokine release is also observed after hypoxia-ischaemia and trauma, which are important contributors to perinatal brain damage.<sup>9,10</sup> In a prospective study of 50 infants born before 30 weeks gestation, 36% had cerebral lesions on magnetic resonance imaging that were associated with an inflammatory response to prenatal infection, as evidenced by increased umbilical cord blood cytokines, T cell activation, raised maternal C reactive protein, and preterm prolonged rupture of membranes.<sup>11</sup>

Furthermore, the idea that neonates have a reduced ability to produce proinflammatory cytokines<sup>12</sup> has been challenged by recent studies. A higher percentage of monocytes positive for the cytokines IL6 and IL8 has been reported in term and preterm infants than in adults, and, in very low birthweight infants with proven infection, the frequency of cytokine positive cells was substantially greater than in infants without infection.<sup>13</sup> Preliminary data indicate that preterm fetuses can produce substantial quantities of proinflammatory cytokines. The preterm fetal inflammatory response may play a greater role in the pathogenesis of cerebral lesions than previously suspected.<sup>14</sup>

## PERINATAL INFECTION AND ADVERSE NEONATAL OUTCOME

Chorioamnionitis and prolonged rupture of membranes increase the risk of cerebral palsy in preterm infants.<sup>1</sup> In a meta-analysis of 26 studies in preterm infants, clinical chorioamnionitis trebled the risk of cystic periventricular leucomalacia and doubled the risk of cerebral palsy, even when the analysis was adjusted for gestational age. In a meta-analysis in term infants, clinical chorioamnionitis increased cerebral palsy nearly fivefold.<sup>2</sup> In one study, infants born at term after chorioamnionitis had 9 times greater risk of cerebral palsy.<sup>3</sup> In another, neonatal sepsis increased the risk of cerebral palsy fourfold, after adjustment for gestational age.<sup>4</sup>

## THE INFLAMMATORY CYTOKINE RESPONSE

Infection initiates a complex immune process, which includes antigen detection, T cell activation and proliferation, and release of cytokines. Cytokines are low molecular mass proteins, which mediate cell growth, inflammation, immunity, differentiation, migration, and repair. They regulate the amplitude and the duration of the inflammatory response and include interleukins (IL), interferons, colony stimulating factors, tumour necrosis factor (TNF) $\alpha$  among others.

## INFLAMMATORY CYTOKINES AND LUNG INJURY

There is increasing evidence that proinflammatory cytokines may be a common pathway in lung inflammation, which can result in chronic lung disease (CLD).<sup>15</sup> Intrauterine inflammation, as evidenced by increased amniotic fluid IL6, TNF $\alpha$ , IL1, and IL8<sup>16</sup> and increased umbilical cord blood IL6,<sup>17</sup> can predict the development of CLD. Inflammatory cytokines, especially IL1, are increased in the tracheal lavage fluid after

## INFLAMMATORY CYTOKINES AND BRAIN INJURY

Elevated cytokine levels in blood spots collected in the newborn period can predict the later

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**Abbreviations:** CLD, chronic lung disease; IL, interleukin; IVIG, intravenous immunoglobulin; TNF, tumour necrosis factor

chorioamnionitis on the first day after birth in those who develop CLD,<sup>18</sup> suggesting the importance of intrauterine inflammation, perhaps initiated by uteroplacental infection.<sup>19</sup> Postnatal infection or colonisation of the airways may also cause an inflammatory response, which could contribute to CLD.<sup>20</sup>

### CYTOKINES AND TISSUE INJURY: CAUSE OR EFFECT?

Animal models have shown that cytokines can do cause brain damage.<sup>21–23</sup> Blocking the effect of cytokines by IL1 receptor antagonism, platelet activating factor antagonism, or neutrophil depletion can limit brain damage.<sup>21</sup> The association cannot be dismissed as an epiphenomenon, and the evidence suggests that inflammatory cytokines lead to tissue injury in humans.

However, the mechanisms of tissue damage associated with elevated cytokine levels are unclear. This may be a direct effect, or caused by stimulation of other immune mechanisms—for example, complement activation or migration and degranulation of neutrophils with release of matrix metalloproteinases. Evidence of a direct effect comes from elegant observations in transgenic mice that overexpressed IL6 from birth. These animals did not develop a blood-brain barrier and at 6 months had evidence of severe injury to the central nervous system.<sup>23</sup> In humans, IL6 genotypes may increase the risk of septicaemia in preterm neonates,<sup>24</sup> and genetic polymorphisms can affect the development of CLD.<sup>25</sup>

### IMMUNOMODULATORY AGENTS

Whatever the mechanism of cerebral and pulmonary injury, the apparent importance of inflammation in their pathogenesis makes immunomodulatory therapy an attractive proposition. Dammann and Leviton<sup>26</sup> have proposed a model of perinatal cerebral damage with a balance between developmental insult and protective components. They postulated the existence of developmentally regulated endogenous neuroprotective agents, which they have named “oligotrophins”. There is considerable evidence that immunoglobulin may fulfil similar functions, as it has important immunomodulatory effects that modify inflammatory disease processes in man.

### CLINICAL EVIDENCE FOR HIGH DOSE POLYCLONAL INTRAVENOUS IMMUNOGLOBULIN (IVIG) AS AN IMMUNOMODULATORY AGENT

High dose polyclonal IVIG is effective in the treatment of inflammatory disorders of the nervous system in adults. In randomised trials, IVIG reduced clinical disability in Guillain-Barre syndrome,<sup>27</sup> chronic inflammatory demyelinating polyneuropathy,<sup>28</sup> and multifocal motor neuropathy.<sup>29</sup> A systematic review of trials in multiple sclerosis suggests that IVIG reduced the relative risk of relapses by 21–28% (relative risk (RR) 0.79, 95% confidence interval (CI) 0.49 to 0.92; RR 0.72, 95% CI 0.54 to 0.97).<sup>30–32</sup> In randomised controlled trials evaluating serial magnetic resonance imaging in multiple sclerosis, brain lesions decreased in size and number after IVIG treatment.<sup>33–34</sup> These studies suggest that IVIG can reduce cerebral inflammation and ameliorate pre-existing cerebral lesions.

In a systematic review of 11 randomised controlled trials with 492 patients of all ages with sepsis or septic shock, polyclonal IVIG reduced mortality by 36%, with a narrow confidence interval (RR 0.64, 95% CI 0.51 to 0.80).<sup>35</sup> This highly significant result may also, in part, reflect its multifactorial anti-inflammatory effects.

### POTENTIAL MECHANISMS OF POLYCLONAL IMMUNOGLOBULIN AS AN IMMUNOMODULATORY AGENT

IVIG modulates cytokine production *in vitro*<sup>36</sup> and *in vivo*, and downregulates the IL1 system.<sup>37</sup> IVIG contains antibodies directed against IL1, IL6, and interferons  $\alpha$ ,  $\beta$ , and  $\gamma$ , which modulate the cytokine cascade.<sup>38</sup> IVIG has a cytoprotective effect on TNF $\alpha$  induced cell death in fibroblasts.<sup>39</sup> IVIG regulates B cell differentiation and immunoglobulin production<sup>40</sup> and can regulate CD8 mediated suppressor or cytotoxic T cell function.<sup>41</sup> IVIG causes degranulation and impairment of migration and reduces infiltration of neutrophils in inflamed tissues.<sup>42</sup> IgG also stimulates inactivation of C3b-containing complexes thereby reducing C3 activation<sup>43</sup> and complement mediated inflammation.

IVIG may play an important role in local central nervous system inflammatory processes and has been shown to increase nitric oxide production by cultured rat microglia.<sup>44</sup> Microglial phagocytosis is inhibited by IVIG, which can protect oligodendroglia from antibody mediated complement injury.<sup>45</sup> Monoclonal antibodies directed against certain surface antigens on the oligodendroglia can enhance remyelination in virus mediated demyelination. These antibodies may be a component of the normal repertoire of endogenous immunoglobulin (and IVIG preparations).<sup>46</sup>

### PRETERM INFANTS AND IMMUNOGLOBULINS

Transport of immunoglobulin from the mother to the fetus across the placenta occurs after 32 weeks, and significant endogenous synthesis does not occur until after 24 weeks after birth.<sup>47</sup> If the mother does not have antibody to specific pathogens, then pathogen specific antibodies are also deficient in the newborn.<sup>48</sup> Therefore preterm infants, especially those born before 32 weeks, could be quantitatively and qualitatively deficient in immunoglobulins. Preterm infants are at high risk for infection, with subsequent inflammatory damage to the brain and the lungs. Therefore a physiological basis exists for the use of intravenous immunoglobulins in preterm infants for prevention or treatment of neonatal infections. IVIG, being a broad spectrum immunomodulating agent, may help to reduce the inflammatory response and limit organ damage. However, there is currently little evidence from controlled trials to support the hypothesis that IVIG limits neonatal inflammatory damage. In the Cochrane reviews of trials using IVIG for prophylaxis in preterm and/or low birthweight infants and for treatment of clinical or proven sepsis, there are no data on periventricular leucomalacia and very little on CLD or neurodevelopmental outcome.<sup>49–50</sup> Furthermore the doses of IVIG used were lower than in adult studies, which typically start with 2 g/kg, followed by repeat doses of 400 mg/kg at one or two month intervals. An ideal randomised controlled trial to test the hypothesis that IVIG can reduce inflammatory damage should randomise neonates at high risk of central nervous system or pulmonary injury to prophylactic, repeated high dose IVIG or placebo. It should include short term outcomes of serial cytokine response, T cell activation, magnetic resonance imaging of the brain, oxygen dependency, and long term outcomes of neurodevelopmental and cognitive impairment.

INIS, the international neonatal immunotherapy study, is a large randomised placebo controlled trial (<http://www.npeu.ox.ac.uk/INIS.htm>) of IVIG, in a cumulative dose of 1 g/kg, as an adjunct to antibiotic treatment in proven or suspected neonatal sepsis. It does not therefore fulfil the criteria for an ideal test of these hypotheses. However, it may provide preliminary insights, particularly in specific subgroups. These include infants born after chorioamnionitis, prolonged rupture of membranes, or increased maternal C

reactive protein, who are at high risk of cerebral inflammatory damage.<sup>1 2 11 51 52</sup>

## OTHER IMMUNOMODULATORY AGENTS

Pentoxifylline, a methylxanthine and a phosphodiesterase inhibitor, inhibits the production of TNF $\alpha$  and has been shown to have beneficial biological effects in sepsis.<sup>53</sup> It was found to reduce neonatal mortality when used as an adjunct in neonatal sepsis,<sup>54</sup> and in a nebulised form may be useful in CLD.<sup>55</sup> In animal models, antagonism of platelet activating factor, neutrophil depletion, and IL1 receptor antagonism have all been effective in limiting brain damage<sup>21</sup> and so have inhibitors of matrix metalloproteinases.<sup>56</sup> These immunomodulatory agents have a narrow spectrum of activity and involve inhibitory effects of one or a few cytokines in the inflammatory cascade. They may therefore not be fully effective in improving outcomes in clinical trials.

Antenatal steroid prophylaxis for preterm birth reduces neonatal mortality (odds ratio (OR) 0.60, 95% CI 0.48 to 0.75) and nearly halves the incidence of respiratory distress syndrome (OR 0.53, 95% CI 0.44 to 0.63).<sup>57</sup> The use of antenatal steroids has been associated with a reduction in the incidence of cerebral white matter lesions in very low birthweight neonates<sup>58</sup> and a reduction in cerebral palsy by more than half.<sup>59</sup> Steroids have a broad spectrum anti-inflammatory effect, and the reduction in brain damage may in part be due to an anti-inflammatory effect. However, the use of postnatal steroids for CLD when the brain is still immature has been associated with an adverse neurological outcome.<sup>60</sup> Unlike steroids, IVIG has a broad spectrum anti-inflammatory effect which so far seems to be free of serious side effects and is hence very promising.

## CONCLUSIONS

There is consistent evidence linking perinatal infection and adverse neonatal outcome. Infection leads to an inflammatory response that may be responsible for initiating and prolonging tissue injury. Modulation of inflammation is a relatively new strategy for preventing or treating such injury. New evidence is needed to evaluate the role of IVIG as a non-steroidal anti-inflammatory agent that may reduce neonatal mortality and morbidity.

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