HHS Public Access

Author manuscript

Dev Med Child Neurol. Author manuscript; available in PMC 2021 June 03.

Published in final edited form as:

Dev Med Child Neurol. 2021 April ; 63(4): 365–366. doi:10.1111/dmcn.14821.

Altered cytokine responses in children with cerebral palsy: pathogenesis and novel therapies

MARK R SCHLEISS

Department of Pediatrics, Division of Infectious Disease and Immunology, University of Minnesota, Minneapolis, MN, USA.

Cerebral palsy (CP) is very heterogeneous with respect to both etiology and clinical presentation. A common denominator appears to be neuroinflammation, triggered by a variety of mechanisms including fetal and/or maternal infection, stroke, hypoxia, thrombosis, and maternal pre-eclampsia, in addition to potential genetic etiologies.[1] Cytokine dysregulation has been described in both the maternal and the fetal/neonatal compartments. With respect to the maternal cytokine response, increased concentrations of tumor necrosis factor (TNF) alpha, interleukin (IL)-1β, and IL-6 in amniotic fluid have been documented. In the fetus, IL-6 has been shown to play a major role in the pathogenesis of fetal inflammatory response syndrome, which is linked to CP. This process appears to continue after birth in children with CP, giving rise to the 'sustained inflammation hypothesis' according to which prenatal, perinatal, and/or neonatal pro-inflammatory stimuli induce inflammatory responses that contribute to ongoing cytokine dysregulation.[2] Thus, postnatal childhood study of cytokine profiles in CP can reveal key mediators of potential injury, improving our understanding of pathogenesis and offering possible therapeutic interventions, though it is challenging to know whether local findings (e.g. salivary) reflect systemic dysregulation of cytokine reactivity related to the underlying CP diagnosis. In a systematic review of studies that examined the association between peripheral inflammatory molecules and neurological development in children with CP, most studies demonstrated elevations in IL-1β, IL-6, TNFα, and CXCL8/IL-8 in association with abnormal neurological findings.[3]

Against this background, what does the study by Zareen et al. add to our understanding?[4] In this study, 12 children with CP, representing a diverse group, with varying histories of neonatal encephalopathy, stroke, and congenital infection, and 12 age-matched comparisons were recruited. Pro- and anti-inflammatory cytokines (IL-1β, IL-2, IL-6, IL-8, IL-10, IL-18, TNF-α, TNF-β, interferon-γ, granulocyte-macrophage colony-stimulating factor [GM-CSF], vascular endothelial growth factor [VEGF], and IL-1 receptor antagonist) were compared. Responses to in vitro simulation of whole blood with lipopolysaccharide by multiplex cytokine ELISA were compared. Erythropoietin levels, both at baseline and after lipopolysaccharide stimulation, were also measured. There was a strong response to lipopolysaccharide for IL-8, VEGF, TNF-α, and GM-CSF in both children with CP and the comparison group, but perhaps unexpectedly there was significant lipopolysaccharide

This commentary is on the original article by Zareen et al. To view this paper visit https://doi.org/10.1111/dmcn.

hyporesponsiveness in children with CP compared with the comparison group for IL-1α, IL-1β, IL-2, and IL-6 responses. The authors also observed significantly higher erythropoietin levels at baseline in children with CP compared with the control group.

These results of decreased lipopolysaccharide responsiveness of some cytokines may seem inconsistent with the observations of the important role of enhanced cytokine responses, particularly IL-6, noted by other groups in their studies of the pathogenesis of CP. However, the authors suggest that dampened responsiveness to lipopolysaccharide for some cytokines may reflect a more generalizable cytokine hyporesponsiveness, and that the decreased capacity to produce pro-inflammatory cytokines in response to lipopolysaccharide stimulation may be a biomarker related to CP. There data indicate that there is a response to lipopolysaccharide, but this response is decreased, at least for some cytokines, in CP versus control leukocytes. It is unclear how long such hyporesponsiveness would last. If it persists into childhood, it could have important implications for how children with CP respond to infections, vaccinations, and other immunological stimuli. This could have wide-ranging implication for the overall health of these children, and this observation deserves further investigation.

Another important experimental observation that merits future study is the finding of significantly higher levels of erythropoietin found at baseline and after lipopolysaccharide stimulation in children with CP compared with controls. As the authors note, significantly increased levels of erythropoietin have been associated with neonatal encephalopathy, microcephaly, CP, and atypical development. On the other hand, there is evidence suggesting a neuroprotective effect for erythropoietin therapy, including protection against CP. A recent Cochrane Review showed promising but conflicting results related to the neuroprotective effect of erythropoietin.[5] If the neuromodulatory effect of erythropoietin can be clarified, future studies of its role in both the short- and long-term pathogenesis of CP can potentially lead to novel therapeutic intervention.

FINANCIAL SUPPORT

NIH HD079918, HD098866, and the University of South Carolina Disability Research and Dissemination Center (DRDC) through its cooperative agreement (6U19DD001218) with CDC.

REFERENCES

1. Korzeniewski SJ, Slaughter J, Lenski M, Haak P, Paneth N. The complex aetiology of cerebral palsy. Nat Rev Neurol 2018; 14: 528–43. [PubMed: 30104744]
2. Gotsch F, Romero R, Kusanovic JP, et al. The fetal inflammatory response syndrome. Clin Obstet Gynecol 2007; 50: 652–83. [PubMed: 17762416]
3. Magalhães RC, Moreira JM, Lauar AO, et al. Inflammatory biomarkers in children with cerebral palsy: A systematic review. Res Dev Disabil 2019; 95: 103508. [PubMed: 31683246]
4. Zareen Z, Strickland T, Fallah L, et al. Cytokine dysregulation in children with cerebral palsy. Dev Med Child Neurol 2021. 10.1111/dmcn.14724.
5. Ohlsson A, Aher SM. Early erythropoiesis-stimulating agents in preterm or low birth weight infants. Cochrane Database Syst Rev 2020; 2: CD004863. [PubMed: 32048730]