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Chilled to the marrow: Neonatal brain injury, hypothermia and the immune system

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Both systemic and local inflammatory responses are major players in determining neurological outcomes after brain injury (1-3). The complex and intricate interactions between the innate and adaptive immune systems appear to play a role not only in the acute response to neurologic injury but also the long term responses related to reperfusion, repair and regeneration after the initial insult. Neuroinflammation is mediated by microglia in the brain, and by infiltrating peripheral macrophages, T, natural killer and dendritic cells, involving modulation of cytokines, chemokines and complement in the brain and blood circulation. Although all of these components may play dual roles in perpetuating the injury and in neuroprotection, the timing when the switch happens and the factors in the injured host that drive the response towards worsening injury vs. neuroprotection and repair are not clearly known.

Th1, Th2 and Th17 responses have been shown to be activated following brain injury in animal models. Recent studies have shown that in a mouse model of stroke, the effects of ischemia are attenuated in mice lacking T cells and that treatment with an IL-17A blocking antibody attenuated the injury (2,4). Infiltration of T cells in the brain have been demonstrated in animal models of TBI and in humans with stroke (5,6). However, interactions between the injured developing brain and the immature immune system is even less defined or understood. Since the innate immune system is immature in neonates, the responses to injury and/or therapeutic interventions may be different from that seen in adults (7). The pro-inflammatory cytokine responses to an inflammatory insult in neonates are typically attenuated (IL-12, IL-23, TNF- and IL1), while the anti-inflammatory responses (IL10 and TGF) are greater, when compared to later in life (7,8). Hence the effect of CNS injury on the developing immune system may be different from that on the mature immune system.

Perinatal asphyxia resulting in hypoxic ischemic encephalopathy (HIE), can cause as many as a million deaths per year worldwide with a large proportion of survivors developing

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neurological disabilities (9). As of now, the only possible therapeutic option for hypoxic ischemic injury that can be offered in the clinical setting, and has shown effectiveness in the neonatal population is hypothermia (10). The use of therapeutic hypothermia not only reduces the risk of death but also the possibility of long-term disability for infants who survive birth asphyxia (11). The neuroprotective mechanisms of therapeutic hypothermia seem to be related to attenuating oxidative injury, and preventing apoptosis and necrosis in neurons (9). However, hypothermia can affect the immune response resulting in immunosuppression when used for longer periods of time. The developmental differences in innate immunity in neonates make them a particularly vulnerable population, and evaluating and understanding the effect of therapeutic hypothermia on the brain and peripheral immune response in this population would be crucial for further advancement in the field.

In this issue of Pediatric Critical Care Medicine, Jenkins et al have addressed this important question by studying the effect of therapeutic hypothermia in modulating the peripheral immune response in neonates following a hypoxic ischemic insult (12). They have demonstrated that neonates with HIE that were treated with hypothermia had lower WBC counts, lower ANC and lymphocytes when compared to patients that were treated with normothermia and that there was a strong treatment-time interaction in the counts. However, 24 hrs after re-warming there was a rebound increase in the ANC in patients that were treated with hypothermia. Interestingly, neonates who had the worst outcomes (death or severe neurodevelopmental scores at 12 months) had much lower WBC counts at later time points.

The interaction between brain injury and the immune system may be bidirectional. Severe brain injury can result in suppression of the immune system with leukopenia, decreased cytokines and splenic involution (13). In this study by Jenkins et al, the authors demonstrate that in the hypothermia group, those patients that did not have a recovery of the WBC count after re-warming, had a poor outcome while those that had recovery of WBC counts had better long term outcome (12). They speculate that this may indicate immune dysregulation or immune paralysis. It is possible that this immune dysregulation may be mediated by the extent of CNS injury. The authors have tried to address this by comparing the initial injury severity with the WBC counts over time and did not find an association, but they also indicate that further studies would be required to evaluate this in more detail. In one of their previous studies the authors showed that therapeutic hypothermia resulted in altered IL-6, IL-8, IL-10 and MCP-1 serum levels, with worse outcomes being associated with an increase in IL-8 and IL-10 (14). This may correlate with the low leukocyte counts noted in patients with poor outcomes in this study. In the same study, they also report that poor outcomes were associated with increased IL12 and increased MIP1, cytokines that can promote a Th1 type response, at the time of re-warming and persisting up to 72 hrs, (14). Hence it appears that suppression of WBC counts as seen in the hypothermia group may be beneficial, but too much suppression or persistent suppression leading to immune dysregulation would be harmful.

As with all thought-provoking and interesting studies, this study by Jenkins et al., leaves us with several more questions that will need to be addressed in future studies. A better understanding of the temporal progression of the innate and adaptive immune response over a prolonged period following neonatal HIE, and the role of other factors that may influence the immune system such as neonatal sepsis and exposure to maternal infection/inflammation, would be crucial for optimally manipulating the immune response to achieve the desired effects of neuroprotection with therapeutic hypothermia.

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