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Elevated cytokines in pneumococcal meningitis: Chicken or egg?*

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Are the elevated cytokines seen in pneumococcal meningitis brain-derived or plasma-derived? In this issue of *Critical Care Medicine*, Dr. Møller and colleagues (1) attempt to answer the question whether intrathecally produced cytokines migrate into the bloodstream, or whether circulating cytokines cross into the cerebrospinal fluid (CSF) in pneumococcal meningitis.

In the host response to infection, there is bidirectional interaction between the nervous system and the immune system via neurotransmitters released by the sympathetic nervous system (2, 3) and hormones involved in the stress responses. This process is essential for maintaining homeostasis. The cytokines that act directly on the central nervous system either originate from peripheral immune organs and cross the blood-brain barrier or are produced locally by neuronal cells within the central nervous system (4).

Pneumococcal meningitis is a cause of significant morbidity and mortality, particularly in the developing world, where mortality rates in children are up to 50% (5, 6). Additionally, the increasing antibiotic resistance of *Streptococcus pneumoniae* presents a particular challenge to the critical care practitioner in the clinical management of pneumococcal meningitis. Improved understanding of the pathogenesis of pneumococcal meningitis may help contribute to the identification of new therapeutic targets.

Dr. Møller and colleagues (1) studied seven adults with pneumococcal meningitis, contrasting these with seven healthy volunteers using Kety-Schmidt-estimated cerebral blood flow. As well as this, paired arterial and jugular venous samples were drawn for tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , and IL-6 determination to calculate global cerebral flux. In pneumococcal meningitis, the authors found an increase over the cerebral vascular bed in plasma concentrations of TNF- α and IL-6 but not of IL-1 β . The healthy volunteers, on the other hand, demonstrated a slight but significant cerebral influx of IL-6, a finding that the authors were unable to explain. The authors speculate that the release of cytokines from brain to blood may contribute to the evolution of the systemic features of sepsis during pneumococcal meningitis.

*See also p. 979.

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These interesting findings are difficult to interpret, for several reasons. First, the meningitis and control groups were physiologically very different. Patients in the meningitis group were older, were septic, had higher core temperatures, and were sedated and mechanically ventilated. Second, the sample size is too small to exclude both type I and type II statistical errors. Third, the samples were drawn approximately 24 hrs after antibiotic therapy was commenced, which in itself will influence the inflammatory response. These limitations are discussed in the article.

The investigators provide valuable information on cerebral flux of three cytokines in pneumococcal meningitis, but it would have been interesting to compare this with concentrations of these cytokines in the CSF and also to measure concentrations of other mediators, including chemokines, such as CXCL1 (GRO- α), CXCL5 (ENA-78), CXCL8 (IL-8), CCL2 (MCP-1), CCL3 (MIP-1 α), and CCL4 (MIP-1 β) in both plasma and CSF. These chemokines are present in the CSF of patients with bacterial meningitis and also contribute to the chemotactic activity of leukocytes (7, 8).

In pneumococcal meningitis, the host defenses contribute to the damage resulting from meningeal inflammation and yet do not succeed in eliminating the pathogens. In addition to antibiotics, therapies for pneumococcal meningitis should include adjunctive therapies directed at immunologic mediators that play a crucial role in the induction and amplification of the host response (9). Steroids are the intervention with the most evidence of benefit in meningitis, particularly in pneumococcal meningitis (10, 11). Steroids are more effective when given before or with the first dose of antibiotic. As antibiotic resistance is an increasing problem with pneumococci, a concern is that steroids will increase the risk of relapse of meningitis. This concern is not borne out by the results of the most recent trial (10), where the impressive feature was a reduction in the number of deaths and an increase in the number who survived without neurologic deficit. A better knowledge of the inflammatory response may allow the development of improved adjunctive treatments.

TNF- α , IL-1 β , and IL-6 are released sequentially and early (12) in the inflammatory response, triggering a series of other inflammatory mediators including pro- and anti-inflammatory cytokines, chemokines, reactive oxygen species such as superoxide, and reactive nitrogen intermediates such as nitric oxide (13). In a rat model of pneumococcal meningitis, slightly increased IL-1 β and TNF- α expression was seen in brain tissue at 2 hrs postinoculation, which peaked at 8 hrs and declined at 18 hrs. IL-6 expression remained low throughout and was unchanged from controls. IL-12 and interferon (IFN)- γ expression was significantly increased at 2 hrs and increased further at 8 hrs, peaking at 8 hrs for IL-12 and 18 hrs for IFN- γ . TNF- β expression was increased at all time points, with maximum levels at 8 hrs. IL-10 and transforming growth factor- β were elevated at 8 hrs and 18 hrs, peaking at 8 hrs (14). By contrast, in Hib-inoculated rats, there was marked messenger RNA expression of IL-1 β , IL-6, TNF- α , IL-12, and IFN- γ . The rapid induction of IL-1 β and TNF- α messenger RNA suggests that these cytokines are produced by intrinsic brain cells, in response to pneumococcal infection.

The source of the cytokines within the brain is unclear. Within the literature, several cell types within the central nervous system are described as being capable of producing TNF- α , IL-1 β , and IL-6. These include astrocytes, microglial cells, and cerebral vascular endothelial cells (4). Human astrocytes stimulated in culture by IL-1 β and TNF- α have been shown to produce CXCL8, IL-6, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor, but TNF- α was a less potent stimulus than IL-1 β (15).

So in essence, the study by Dr. Møller and colleagues (1) suggests that cerebral output may contribute to the elevated levels of plasma cytokines seen in sepsis, but this is by no means

conclusive. The mechanism by which mediators produced in different compartments control the host response to pneumococcal infection is probably far more complex than the discussion suggests. Cytokines originating either systemically or within the central nervous system act on various different cell types and are themselves subject to counterregulation by other cytokines. Furthermore, neurotransmitters, co-transmitters, and other mediators may fine tune cytokine production both in the central nervous system and in the peripheral immune cells (4). At issue, therefore, is not, “Which came first, the chicken or the egg?” but rather, “What are the exact mechanisms involved in the relationship between chicken and egg?”

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