Should We Add Corticosteroids to the Treatment of Acute Bacterial Meningitis?

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Before the introduction of antibiotic therapy, acute bacterial meningitis was invariably fatal. Even with the development of new and highly bactericidal antibiotics, the disease continues to carry a significant morbidity and mortality. Recent research suggests a key role for the inflammatory response in the pathogenesis of acute bacterial meningitis, implying that the addition of inflammation-modifying agents to the antibiotic treatment may help to achieve a significantly better outcome [1]. However, present results should be carefully evaluated before such a recommendation can be made.

A correlation between the intensity of inflammation in the subarachnoid space and the outcome of acute bacterial meningitis was noted long ago [2]. The defence systems within the cerebrospinal fluid (CSF) are quite limited and the inflammatory response is largely recruited from the serum through disruption of the blood–brain barrier [3]. Cells within the central nervous system, including astrocytes, microglia, vascular endothelium, and macrophages, may also contribute to this response [4]. This cellular inflammatory response is not necessarily dependent on the presence of live bacteria in the subarachnoid space. Conversely, inflammation may increase following induction of massive bacterial lysis by a β-lactam or other antibiotic, due to the release of Gram-positive cell wall constituents or Gram-negative endotoxin [5]. The major mediators of inflammation in the CSF are cytokines, whose production is induced by bacterial components. Tumour necrosis factor-α and interleukin-1 are particularly important, and interact to create synergistic and self-potentiating inflammatory cascades resulting in CSF pleocytosis and brain oedema [5, 6]. Elevated levels of these cytokines in plasma and CSF are correlated with seizures, severity of disease and even survival [7, 8].

The biological basis of these observations is quite firm. Both cytokines have a profound proinflammatory activity, produced by varied mechanisms [9]. Tumour necrosis factor-α, for example, enhances chemotaxis and activation of macrophages and polymorphonuclear cells, increases endothelial permeability and expression of class I and II MHC molecules, has a pyrogenic and procoagulant effect, and induces the synthesis and release of hepatic acute-phase proteins and many additional inflammatory mediators such as interleukin-1 and -6, prostaglandins, leukotrienes and platelet-activating factor. Tumour necrosis

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factor-α-mediated necrosis of myelin and oligodendrocytes in vitro has also been recently demonstrated [10]. Many of these properties of tumour necrosis factor-α are shared by interleukin-1 [9]. Intracisternal administration of recombinant tumour necrosis factor-α or interleukin-1β produced a significant inflammatory response in the cerebrospinal fluid which could be abrogated by monoclonal antibodies to the cytokines [4]. When experimental meningitis in rabbits was induced by either viable bacteria or lipopolysaccharide, tumour necrosis factor appeared in the central nervous system within minutes (much earlier than interleukin-1 or -6), preceding pleocytosis and other inflammatory changes, which again could be blocked by antibodies to tumour necrosis factor or interleukin-1 [4–6]. Similar observations were reported in humans with acute bacterial meningitis, in whom increased levels of cytokines in the cerebrospinal fluid correlated with endotoxin levels, variables of cerebrospinal fluid inflammation, and seizures. Moreover, the appearance of cytokines in the plasma was strongly associated with a fatal outcome [6–8].

These extensive data suggest an inflammatory basis for the persistently high mortality and morbidity of acute bacterial meningitis, and a new therapeutic approach, which not only eliminates bacteria but also counteracts the excessive synthesis of inflammatory mediators by the host, therefore appears to be indicated. Of several alternative methods [1], the use of corticosteroids, whose pleiotropic effects in suppressing inflammation are well recognized, is the best studied so far. Steroids inhibit the synthesis or release of many substances, notably interleukin-1 and tumour necrosis factor, especially when given early, preferably before initiation of transcription [9]. Dexamethasone has been used most frequently in animal experiments, and consistently produced a marked inhibition of cytokines and inflammation in the cerebrospinal fluid [5, 11]. This led to a trial of dexamethasone in four double-blind placebo-controlled studies of children with acute bacterial meningitis [12, 13]. All studies provided evidence that the addition of intravenous dexamethasone (0.15 mg/kg every 6 hours for the first 4 days) to a second or third-generation cephalosporin produced a more favourable course than antibiotics and placebo. All indices of cerebrospinal fluid inflammation and cerebral perfusion improved in the treatment group, but deteriorated in the placebo group, and the improvement was paralleled by a dramatic decrease in tumour necrosis factor-α and platelet activating factors levels in the cerebrospinal fluid. The febrile period was shorter and fewer patients had seizures (4 per cent vs. 15), brain CAT scan abnormalities (14 per cent vs. 29 per cent), neurological sequelae (10 per cent vs. 31 per cent) and hearing loss. A study from Egypt found the addition of dexamethasone to be effective in adults as well, even when less bacteriolytic agents (ampicillin + chloramphenicol) were used; overall mortality was decreased almost by half [14]. As suggested by the experimental data, the timing of dexamethasone administration appears to be critical and should ideally precede the first antibiotic dose by 15–20 minutes [13], or the two therapies should be given concurrently. The rate of dexamethasone-related complications during therapy was remarkably low: two patients with gastrointestinal tract bleeding requiring transfusions constitute all reported serious complications of the short-term dexamethasone therapy employed in over 360 patients with acute bacterial meningitis [12–14].

In conclusion, the deleterious role of cytokines released into the subarachnoid space during acute bacterial meningitis, in particular following successful and lytic antibiotic therapy, is well established. Tumour necrosis factor-α and interleukin-1-β are the primary mediators, and their pharmacological suppression or neutralization by monoclonal antibodies in experimental models has consistently ameliorated meningeal inflammation and brain oedema. Novel methods of intervention, using monoclonal antibodies or derivatives of naturally occurring inhibitors such as the interleukin-1 receptor antagonist or soluble tumour necrosis factor receptors are being developed [4, 9], and hold promise in the
future treatment of diseases where these cytokines play an important role in the pathogenesis. Non-steroidal anti-inflammatory drugs and pentoxifylline may also useful [15, 16]. In the meantime, notwithstanding that more patients should be enrolled in controlled studies, one clear fact emerges after a careful evaluation. The convincing biological and experimental basis, taken together with the initial impressive clinical results on one hand, and the lack of evidence so far for any significant adverse effects on the other hand, single out the addition of dexamethasone to the antibiotic treatment as a new and exciting development in the treatment of acute bacterial meningitis, which should be adopted and further studied at the same time.

REFERENCES