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Brain Edema and Increased Intracranial Pressure in the Pathophysiology of Bacterial Meningitis

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A number of advances in our understanding of the pathophysiology of bacterial meningitis have been made in recent years. In vivo studies have shown that bacterial cell wall fragments and endotoxins are highly active components, independent of the presence of viable bacteria in the subarachnoid space. Their presence in the cerebrospinal fluid is associated with the induction of inflammation and with the development of brain edema and increased intracranial pressure. Antimicrobial therapy may cause an additional increase of harmful bacterial products in the cerebrospinal fluid and thereby potentiate these pathophysiological alterations. These changes may contribute to the development of brain damage during meningitis. Some promising experimental work has been directed toward counteracting the above phenomena with non-steroidal or steroidal anti-inflammatory agents as well as with monoclonal antibodies. Although considerable advances have been made, further research needs to be done in these areas to improve the prognosis of bacterial meningitis.

Bacterial meningitis remains a serious disease worldwide, often resulting in death or long-term morbidity. Although advances in antimicrobial therapy have been made in recent years, it is disappointing that these advances have failed to result in a significant overall reduction in mortality (1). One recent study from the USA found that for the years 1978–1981 most cases of meningitis were caused by *Haemophilus influenzae* (48.3 %), *Neisseria meningitidis* (19.6 %) and *Streptococcus pneumoniae* (13.3 %), with a mortality of 6 %, 10.3 % and 26.3 %, respectively (2). Twenty years earlier, Swartz and Dodge (3) found the mortality rate to be nearly the same (8 %, 15 % and 29 %, respectively). Also, the occurrence of long-term neurological sequelae, with an incidence of over 20 %, remains high, the most important sequelae being hearing impairment (4), epilepsy and mental retardation (5).

Recent laboratory investigations by ourselves and others have shown that live meningeal pathogens are not the only agents having a harmful effect on the central nervous system. Certain bacterial products, such as cell wall fragments and endotoxins, remaining in the subarachnoid space after bacterial killing by antibiotics are in themselves highly active components capable of inducing pathophysiologic alterations (6–8, Täuber, M. G., et al., 25th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 1985, Abstract. no. 683). It thus appears conceivable that further improvements in antibiotic therapy will not improve the outcome of meningitis as long as the effects of these bacterial products are not specifically addressed. It is consequently important to elucidate the mechanisms that lead to central nervous system damage. Schematically, the harmful stimulus, i. e. the microorganism, or parts of it, generates an inflammatory response in the subarachnoid space. This, combined with other pathophysiological alterations in the central nervous system, ultimately leads to structural damage of nervous tissue.

A common response of the brain to a variety of insults is the formation of edema. Klatzo (9–11) defined brain edema as an abnormal accumulation of fluid within the brain parenchyma associated with a volumetric enlargement of brain tissue. His classification of brain edema into vasogenic and cytotoxic edema (Table 1) has proven useful for studies of brain edema, even though it is exceptional that only one of the two mechanisms would be operating in an individual patient.

Vasogenic brain edema is caused by increased permeability of capillary endothelial cells of the blood-brain barrier and is localized mainly in the white matter. The edema fluid, which accumulates in the extracellular compartment, is composed of plasma filtrate and plasma proteins (9–11). Recently, Quagliarello et al. (12) utilized electron microscopic techniques to examine the cerebral capillary endothelium of rats with meningitis caused by encapsulated meningeal pathogens. A significant increase in pinocytotic vesicles was found, along with a separation of inter-

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cellular junctions, essentially demonstrating an anatomic substrate of the disturbed blood-brain barrier that may allow the development of vasogenic brain edema. Cytotoxic brain edema, on the other hand, develops mainly intracellularly in both gray and white matter as a response to a variety of cytotoxic agents and is associated with an increase in intracellular water and sodium (9–11) (Table 1). To these, Fishman (13) adds the third type of brain edema, interstitial edema, which occurs most often with obstructive hydrocephalus (Table 1). It is caused by a blockage of cerebrospinal fluid (CSF) absorption and affects mainly the periventricular white matter. This type of edema, like the vasogenic type, is extracellular. All three types of brain edema are thought to be potentially present in purulent meningitis.

Even though it is generally accepted that the development of brain edema, via an increase of the intracranial volume, leads to intracranial hypertension (13), there is little data to actually support this concept in the case of bacterial meningitis. In fact, recent studies in our laboratory have shown that there is not a uniform association between brain edema and increased intracranial pressure and that animals without brain edema may very well have intracranial hypertension (14). Data on the importance of brain edema and increased intracranial pressure in humans are scarce and difficult to obtain, and exactly where these parameters belong in the chain of cause and effect that determines the ultimate prognosis of bacterial meningitis has not been established. Consequently, animal models of experimental meningitis as well as additional clinical studies are essential in the pursuit of a more detailed knowledge of the pathophysiology of bacterial meningitis (15). The goal of this paper is to critically review what is known about the role of brain edema and increased intracranial pressure in the pathophysiology of bacterial meningitis and to derive directions for future research. It is hoped that a more detailed understanding of the pathophysiologic mechanisms leading to brain damage during meningitis will allow the design of therapies that can ultimately improve the outcome of affected patients.

Brain Edema and Increased Intracranial Pressure in Patients with Bacterial Meningitis

Few data on the occurrence of brain edema and raised intracranial pressure in patients afflicted with bacterial meningitis have been published. Most information about brain edema is derived from pathologic studies in fatal cases, mainly because of a lack of safe and easy measurement techniques. One exception, a study by Stovring and Snyder (16) using computerized tomography (CT), showed cerebral swelling in two of 21 pediatric patients with meningitis. Both of the children died, suggesting that the occurrence of brain edema early in the course of the illness is associated with a particularly poor prognosis. On the other hand, many children in this study failed to develop signs of brain edema on CT scans (16). Whether this is due to a lack of sensitivity of CT scans or to the fact that the occurrence of brain edema is not a uniform event in children with meningitis remains to be determined by the use of other methods, such as magnetic resonance imaging, which appears to have a high sensitivity in detecting brain edema (17).

In contrast to brain edema, a rough estimate of intracranial pressure can routinely be performed in patients with meningitis by means of lumbar puncture. A large retrospective study done by Swartz and Doge (18) on 207 patients with bacterial meingitis showed that CSF pressure was elevated (mean, 307 mm H_2O; normal value, 70–120 mm H_2O) in most patients who underwent lumbar puncture on the day of admission. Raised CSF pressure alone was not regarded as a reliable prognostic index by the authors, though patients with fatal pneumococcal meningitis had a

Table 1: Types of brain edema. (Adapted from Reference no. 13.)

	Vasogenic	Cytotoxic	Interstitial
Pathogenesis	increased capillary permeability	cellular swelling: glial, neuronal and endothelial	increased volume of CSF due to blocked absorption
Location	mainly white matter	both gray and white matter	mainly periventricular white matter in hydrocephalus
Composition of edema fluid	plasma filtrate, including plasma proteins	increased intracellular water and sodium	CSF
Extracellular fluid volume	increased	decreased	increased

higher pressure (mean, 480 mm H_2O) than other patients. Autopsy results of 29 patients who died of meningitis showed signs of brain edema in five cases and signs of cerebellar and/or cerebral herniation in ten cases (18). The latter can be diagnosed either on clinical grounds or on the basis of a pathologic exam in fatal cases. Herniation is thought to result from the combination of brain edema and increased intracranial pressure (13), and this complication has been documented in a substantial number of patients who died of meningitis.

Williams et al. (19) described seven meningitis patients with cerebral herniation, of which six survived. The authors attributed this favorable result to the use of intravenous urea therapy. Nugent et al. (20) also suggested that monitoring and aggressive treatment of elevated intracranial pressure might prevent death from cerebral herniation. Another more recent study examining 302 infants and children with bacterial meningitis stated that cerebral herniation occurred in three of ten fatal cases and in 15 surviving patients (21). The possible role of the administration of excessive fluids in promoting brain edema was pointed out by these authors as well as others. In a study of 27 patients with meningococcal meningitis, Connor and Mineally (22) showed that larger amounts of intravenous fluids given during treatment seemed to negatively affect the prognosis of the disease, probably because of a resultant increase in brain edema. None of the 21 surviving patients received more than normal i.v. maintenance fluids (75 ml/m^2/hr), whereas all of those who died did.

The effect of bacterial meningitis and raised intracranial pressure on cerebral blood flow is an important related aspect that has been the subject of very few studies. In an early paper Kety and associates (23) used the nitrous oxide technique to determine the cerebral blood flow of patients with elevated intracranial pressure and found the flow to be reduced. It was Paulson et al. (24) who first determined a reduced flow in patients with meningitis. The only study examining the association between increased intracranial pressure and cerebral blood flow in patients with meningitis was published by McMenamin and Volpe (25). Cerebral blood flow velocity in four neonates and four older infants (< 1 year of age) with meningitis was measured in the anterior cerebral arteries through the fontanels using Doppler velocimetry. A reduced flow velocity and raised intracranial pressure was found in the older infants but not in the newborns.

In summary, the few studies in humans cited above suggest that both brain edema and raised intracranial pressure may be present in varying degrees in patients with meningitis. If pronounced, these changes may be harmful by causing cerebral herniation and/or reduced cerebral blood flow. There is some indication from the data on humans that the occurrence of massive brain edema or intracranial hypertension is associated with an unfavorable outcome, but more studies are needed to confirm this association.

Experimental Data

Brain Edema and Increased Intracranial Pressure in Animal Models of Experimental Meningitis

A number of animal studies, particularly those utilizing the rabbit model of bacteria meningitis (15), have been performed to investigate the possible causes of raised intracranial pressure and brain edema. In general the amount of brain edema documented in these studies is comparatively small (6, 14, 26, 27, Syrogiannopoulos, G., et al., 25th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 1985, Abstract no. 685). A substantial portion of the edema appears to occur in the white matter of the rabbit brain, where we found an increase of 14 % in one study of experimental *Escherichia coli* meningitis (6). This suggests that vasogenic edema is an important component of brain edema during experimental meningitis in rabbits (13). It is important to point out that although the cited increases in brain water content are comparatively small, they do appear with a high degree of regularity in the models examined.

Several experimental studies (6, 14, 26, 27, Täuber, M. G., et al., 25th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 1985, Abstract no. 683) have documented the consistent occurrence of increased intracranial pressure during meningitis and delineated some of its harmful consequences. In the search for pathophysiological factors responsible for an increase in intracranial pressure during acute bacterial meningitis, Scheld and co-investigators devised a rabbit model that allowed a closer look at CSF hydrodynamics (28). To this end, they measured CSF outflow resistance under the premise that the failure of CSF to leave the cranium at a rate equal to its production results in an increase in intracranial pressure. The experiments showed that CSF outflow resistance, from the subarachnoid to the vascular space through the arachnoid villi system into the sagittal sinus, was markedly increased in patients with acute pneumococcal meningitis when compared to controls. This increased outflow resistance was partially countered through the administration of methylprednisolone early in the course of the infection. It is conceivable that this increased outflow resistance is at least in part responsible for the increased intracranial pressure observed during experimental meningitis (28).

The pathologic consequences of increased intracranial pressure are not well defined. There is some indication that it may damage brain tissue by reducing the cerebral perfusion pressure (defined as the difference between systemic arterial pressure and intracranial pressure), thus causing reduced cerebral blood flow, hypoxygenation and subsequent neuronal damage. An early study by Kety and associates (23) demonstrated that increased intracranial pressure is associated with an increase in cerebrovascular resistance, restricted cerebral blood flow and progressive cerebral hypoxia. In an experimental rabbit model of pneumococcal meningitis, Goitein et al. (29) showed a progressive increase in intracranial pressure and a consecutive decrease in perfusion pressure. They concluded that a postulated loss of cerebrovascular autoregulatory function in combination with reduced cerebral perfusion pressure could very well be a cause for cerebral ischemia.

Role of Neutrophils in the Development of Brain Edema and Increased Intracranial Pressure.

Studies done in our laboratory indicate that in contrast to the hypothesis of "granulocytic brain edema" proposed by Fishman (30), granulocytes appear to be only of minor relevance in the formation of brain edema during meningitis and do not contribute to intracranial hypertension (26). Pneumococcal meningitis caused a significant increase in the brain water content of the hemispheres of both normal and neutropenic rabbits compared to uninfected controls (403 ± 10 g water/100 g dry weight versus 392 ± 8 g), with no significant differences between the normal and neutropenic groups. In the same experiments increased intracranial pressure as measured in the cisterna magna occurred, but again there was no significant difference between normal and neutropenic rabbits (26).

In a second set of experiments the chemotactically active polypeptide formyl-Methionine-Leucine-Phenylalanine (fMLP) was administered intrathecally (26). Low doses of fMLP produced a sterile CSF pleocytosis without producing brain edema or increased intracranial pressure. Administration of very high doses of fMLP induced CSF pleocytosis in the range of that observed with low-dose fMLP, and brain edema occurred as well. However, despite the occurrence of brain edema, increased intracranial pressure was not evident, again pointing to the fact that brain edema and intracranial hypertension are not invariably associated with each other. In a third series of experiments high-dose fMLP was injected intracisternally into rabbits with pneumococcal meningitis, causing an increase in brain water content. This increase was associated with a decrease in intracisternal pressure (26).

The results of these studies suggest that granulocytes may play a role in the formation of brain edema, but only if adequately stimulated (in the presence of high dosage fMLP), while no effect of granulocytes on increased intracranial pressure could be documented. These results are somewhat in contrast to those reported from other clinical situations in which granulocytes have been clearly implicated in causing tissue damage (31). It is not immediately evident why we failed to observe an effect of the granulocytes, as long as they were not additionally stimulated, on the experimental parameters. However, Ernst et al. (32), using the same model of experimental pneumococcal meningitis, documented the ineffectiveness of granulocytes in reducing bacterial titers in the CSF. Also, changes in the CSF biochemistry during meningitis were similar in normal and neutropenic animals in these experiments (32). This could indicate that the granulocytes, unable to phagocytose the pneumococci, were not adequately stimulated during meningitis caused by encapsulated organisms and therefore failed to contribute to the alterations examined in these studies (26, 32). Whether stimulation of the CSF granulocytes occurs at other times in the course of the disease or after institution of therapy is presently unknown.

Role of Bacterial Products in the Development of Brain Edema and Increased Intracranial Pressure

Although high doses of antibiotics effectively kill the bacteria responsible for meningitis (33), bacterial products (such as cell wall fragments and endotoxins) may persist in the CSF beyond sterilization by antibiotics and may actually dramatically increase in concentration as a consequence of antibiotic-induced bacterial lysis (34). Several series of in vivo experiments performed by Tuomanen and colleagues (7, 8) and in our laboratory (Täuber, M. G., et al., 25th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 1985, Abstract no. 683, and Täuber, M.G., unpublished observations) have shown that whole cell wall preparations of pneumococci as well as fragments thereof (peptidoglycane, teichoic acid) are capable of causing inflammation, brain edema and increased intracranial pressure to the same extent as an equivalent concentration of live pneumococci.

Likewise, other animal studies show that *Escherichia coli* lipopolysaccharides (Täuber, M. G., et al., 27th Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, 1987, Abstract no. 615) induce brain edema and increased intracranial pressure in a manner very similar to infection with the living organism (6, Täuber, M. G., et al., 27th Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, 1987, Abstract no. 615). Direct

instillation of preparations of "smooth" lipopolysaccharides (containing polysaccharide side chains) at a wide range of concentrations failed to induce brain edema, while preparations of "rough" lipopolysaccharides (containing only the core moiety of lipopolysaccharide, mainly lipid A) were capable of increasing brain water content. However, both preparations were equally effective in inducing increased intracranial pressure and inflammatory changes in the CSF (Täuber, M. G., et al., 27th Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, 1987, Abstract no. 615). In similar experiments Syrogjannopoulos and colleagues (35) recently showed that *Haemophilus influenzae* type b oligosaccharide caused meningeal inflammation when injected directly into the cisterna magna of rabbits. Polymyxin B, which is capable of inactivating lipid A (36), or chemical alterations of the lipid A moiety abrogated the inflammatory potential of the lipo-oligosaccharide (35).

In animals with *Escherichia coli* meningitis, therapy with cefotaxime dramatically increased the concentration of CSF endotoxin and, at the same time, the degree of brain edema (6). The increase in endotoxin concentrations after institution of antibiotic therapy presumably reflects the liberation of endotoxin from live organisms by the lytic action of the antibiotics. This effect was completly neutralized by the administration of polymyxin B or by a monoclonal antibody that binds to conserved epitopes in the lipid A region of a variety of gram-negative pathogens (37). Thus, as in other situations, the lipid A moiety appears to be responsible for many of the biologic effects of endotoxin (38, 39, Täuber, M. G., et al., 27th Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, 1987, Abstract no. 615). In addition, these studies suggest that it is possible in bacterial meningitis to combine antibiotic therapy with substances specifically directed against potentially harmful bacterial products liberated by the action of antibiotics.

Molecular Considerations in the Pathogenesis of Brain Edema and Intracranial Hypertension in Meningitis

There are no experimental data presented to date that have directly identified the molecular basis for the development of brain edema or increased intracranial pressure during meningitis. Thus, in the context of this review, only very brief allusions are made to other areas of research that may have some bearing on the pathogensis of the discussed pathophysiologic changes during meningitis.

Role of Polyunsaturated Fatty Acids and Oxygen-Derived Free Radicals in the Development of Brain Edema

A large portion of the work elucidating the chain of events that culminate in the formation of brain edema was done by Fishman, Chan and colleagues, as summarized below (40–45). A variety of pathological insults, including cold injury, vascular injury, space-occupying lesions and infection are capable of disturbing the integrity of cell membranes, resulting in phospholipid hydrolysis and a subsequent release of free polyunsaturated fatty acids, notably arachidonic acid. These polyunsaturated fatty acids have been shown to be potent inducers of brain edema. Since polyunsaturated fatty acids are also major constituents of the granulocytic cell membrane, Fishman called this type of edema "granulocytic edema" (30). The release of arachidonic acid is accompanied by membrane alterations that result in decreased uptake of neurotransmitters, decreased (Na^+/K^+)-ATPase activity and increased transport of macromolecules across the blood-brain barrier (44). In other experiments it was demonstrated that oxygen-derived free radicals, which are produced enzymatically during the breakdown of arachidonic acid, also play a major role in membrane perturbation and in the production of cytotoxic edema (41). While these biochemical disturbances are considered to be key occurrences in the formation of brain edema due to various stimuli, it is not known whether this chain of events plays a determining role in the development of brain edema during meningitis. Also, it is not known which stimuli could induce such a chain of events in the case of meningitis. Among the possibilities are bacterial products, inflammatory mediators (e.g. interleukin-1 or arachidonic acid metabolites) or an altered microenvironment that disturbs the metabolism of brain cells. Further research will have to address these questions more closely.

Bacterial Products and the Generation of Inflammation

Much recent work on inflammation has documented the key role of inflammatory mediators such as interleukins, cachectin/tumor necrosis factor, the arachidonic acid metabolites and other inflammatory substances in mediating the changes induced by bacterial products, primarily endotoxin (46, 47). It is beyond the scope of this review to summarize even part of these findings. Suffice it to say that endotoxin and maybe cell wall fragments of gram-positive organisms are capable of inducing the release of interleukin-1 and cachectin from macrophages and other sources (46). The inflammatory mediators have a wide spectrum of target systems, including endothelial cells, and profoundly affect the function of the vasculature

and its interaction with neutrophils and other inflammatory cells (46). In addition, they activate secondary inflammatory systems such as the arachidonic acid metabolism (47). Although not examined in any detail in meningitis, it is likely that these pathways also play an important role in the pathogenesis of increased intracranial pressure and brain edema occurring in meningitis, perhaps, for instance, by altering cerebral blood flow, intracranial blood volume and the permeability of the cerebral vasculature (12).

Therapeutic Considerations

The literature on the therapeutic principles considered useful in the management of brain edema and intracranial pressure contains a vast array of concepts, including surgical decompression, shunts, controlled hypotension, urea and mannitol therapy, diuretics, hyperventilation, fluid restriction, non-steroidal anti-inflammatory agents and corticosteroid therapy. However, few of these options have been examined carefully with regard to their usefulness in meningitis, either in clinical studies or in appropriate animal models.

Mannitol

In the 1980 retrospective study by Horwitz et al. (21), 18 pediatric patients with bacterial meningitis and clinical signs of tentorial herniation showed definite improvement after administration of mannitol followed by dexamethasone. Signs of herniation resolved within 60 minutes in eight patients, and more gradually in eight others. The potential value of mannitol in the treatment of brain edema in bacterial meningitis was also demonstrated in a study by Syrogiannopoulos et al. using a rabbit model of *Haemophilus influenzae* meningitis (Table 2) (Syrogiannopoulos, G., et al., 25th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 1985, Abstract no. 685). Mannitol solution was infused intravenously and the intracranial pressure was recorded continuously over a period of four hours. After an initial transient increase in intracranial pressure, the mean intracranial pressure decreased by 25 % within 5 to 25 minutes after infusion. The CSF lactate concentration also decreased by 11 % four hours after infusion, with no change in brain water content measured. Again, the capacity of mannitol to reduce intracranial pressure without reducing brain edema indicates that brain edema was not the basis for the increase in intracranial pressure. Other mechanisms, such as cerebral blood flow or altered CSF hydrodynamics (28), must obviously play an important role in the pathogenesis of increased intracranial pressure during meningitis.

Table 2: Therapy of brain edema and intracranial hypertension with mannitol, corticosteroids and non-steroidal anti-inflammatory agents in experimental meningitis in rabbits.

Therapy	Dosage	Pathogen	Results	Reference no.
Mannitol (25 %)	1 gm/kg, 20 h p.i.	*H. influenzae*	25.5 % reduction of ICP lasting 1–4h, brain water content unchanged	Abs.[a]
Dexamethasone	0.5 mg/kg, 20 and 27 h p.i.	*H. influenzae*	significant decrease in ICP 9 h after treatment, significant decrease in brain water content	27
Ceftriaxone + dexamethasone	75 mg/kg + 0.5 mg/kg, 22 h p.i.	*H. influenzae*	no difference compared to the group treated with dexamethasone alone	27
Prednisone	30 mg/kg, 15 and 22 h p.i.	*S. pneumoniae*	significant decrease in brain water content, no decrease in ICP	14
Dexamethasone	1 mg/kg, 15 and 22 h p.i.	*S. pneumoniae*	significant decrease in brain water content and ICP (and CSF lactate)	14
Indomethacin	1.5 mg/kg, (at infection and 10 h p.i.)	*S. pneumoniae*	significant decrease in brain water content in gray and white matter, no change in ICP	52

[a] Syrogiannopoulos, G., et al., 25th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 1985, Abstract no. 685.

ICP = intracisternal pressure; p.i. = post innoculation (of the bacteria into the cisterna magna).

Corticosteroids

In 1985 we used a rabbit model of pneumococcal meningitis to show that corticosteroids might be beneficial in reducing brain edema and intracranial pressure (14). While both methyl prednisolone and dexamethasone were effective in reversing brain edema, only dexamethasone was capable of significantly reducing intracranial pressure as well as CSF lactate concentration (Table 2). The factors responsible for this difference between the two drugs have not been clearly delineated. The improved CSF lactate concentration in animals with reduced intracranial pressure (those treated with dexamethasone) suggests an improvement of the metabolic situation in the brain. This is possibly explained by improved microcirculation and improved glucose utilization. In 1987 other investigators employed the lapin model of *Haemophilus influenzae* meningitis to examine the effect of dexamethasone plus ceftriaxone on the development of brain edema, intracranial pressure and CSF lactate levels (27). Both intracranial pressure and CSF lactate levels, which had been significantly increased during the infection, were reduced after nine hours of treatment (Table 2). Although there was no statistically significant difference between those animals treated with ceftriaxone alone and those treated with ceftriaxone and dexamethasone, the values were consistently lower in the group treated with the drug combination.

The value of dexamethasone (0.6 mg/kg/day in 4 divided doses for 4 days) was recently demonstrated in a prospective, placebo-controlled study of 200 infants and children with bacterial meningitis (48). Not only was the period of fever significantly shorter for the group treated with dexamethasone, but six-week and one-year follow-up studies demonstrated a severe to profound hearing loss in only three patients from the dexamethasone group, while 13 patients from the placebo group exhibited such a hearing loss. Except for an earlier study using dexamethasone (49), which also showed a favorable result but may have been faulted by an uneven distribution of prognostic factors between the study groups, this is the first time that a clear benefit has been documented for the use of steroids in bacterial meningitis. However, while our experimental results would suggest that dexamethasone may be more potent than other corticosteroids (14), most clinical studies examining the effect of steroids in bacterial meningitis have used corticosteroids other than dexamethasone (50, 51).

Non-Steroidal Anti-Inflammatory Agents

Tuomanen and associates (34) investigated the therapeutic effect of nonsteroidal anti-inflammatory agents in rabbits that were previously challenged with intracisternally injected pneumococci. The bacterial lysis by ampicillin led to a significant increase in meningeal inflammation, which was prevented by cyclooxygenase inhibitors administered simultaneously with the antibiotic. In other experiments the ability of pneumococcal cell wall fragments to cause meningeal inflammation was also neutralized when rabbits were treated with cyclooxygenase but not lipoxygenase inhibitors (34). These findings are complemented by an earlier study by Tureen et al. (52), which showed that the development of brain edema during experimental pneumococcal meningitis was prevented by the administration of indomethacin, which also acts as a potent cyclooxygenase inhibitor (Table 2). Thus, both steroids and non-steroidal anti-inflammatory agents may be of benefit in preventing or reducing brain edema and increased intracranial pressure during meningitis, but their exact role in the management of patients with meningitis is presently unknown.

Conclusions

Bacterial meningitis remains a serious disease today, beset with therapeutic problems even for the experienced clinician armed with modern antimicrobial agents. Our understanding of the complex and multifactorial pathophysiologic phenomena, such as brain edema or intracranial hypertension, remains incomplete, even though recent work has to some extent refined our concept of their pathogenesis and management.

Several of the perspectives examined in this review may well provide data necessary for therapeutic improvements. While the work done by Fishman, Chan and colleagues has done much to illuminate our understanding of the biochemical factors that result in brain edema in general, research is still needed to find out whether and to what extent these mechanisms play a role in meningitis. It seems logical that if this is the case, therapeutic efforts might focus on the pathways of these mechanisms. For example, the blockage of phospholipase A2, which is essential in generating polyunsaturated fatty acids from cell membranes and can be inhibited by corticosteroids, would be one potential area of investigation (53). The same holds true for the research identifying specific bacterial products that play a key role in the pathophysiology of the disease. The more we know about which bacterial products, or more specifically, which cell wall components are responsible for the induction of pathophysiologic alterations during meningitis, the more we can concentrate on blocking or inactivating these products with for example, tools such as monoclonal antibodies (6).

Another area of interest includes the role of various inflammatory mediators. Only a detailed knowledge of these mediators will allow the design of a rational use of anti-inflammatory substances. Controlled clinical studies are then necessary to find out how effective corticosteroids and non-steroidal anti-inflammatory agents are in humans. Whether the control of brain edema and intracranial pressure is indeed reflected by an improved outcome, as measured by sophisticated analysis of cerebral functions in survivors of the disease, remains to be determined.

In the meantime, it seems prudent to advise the clinician to be watchful for signs of brain edema and raised intracranial pressure in patients suffering from purulent meningitis. This may be particularly important soon after the initiation of antibiotic therapy in critically ill patients, when additional brain edema or increased intracranial pressure, mediated by the sudden burst of bacterial products into the CSF, may be detrimental (6). Therapeutic suggestions include rigorous restriction of fluid intake and application of corticosteroids. Thus far, however, little data from humans exists to support any of these therapeutic interventions. Measures that may potentially reduce cerebral blood flow, such as hyperventilation and induced hypotension, should be used with extreme care, if at all, because little is known about the extent to which cerebral blood flow is critically reduced by the illness itself. An additional reduction in blood flow might make the difference between adequate oxygenation and cerebral ischemia.

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