PM standards should be reconsidered” (5). Although there would be costs to expanding the monitoring network and implementing additional air quality standards, these costs need to be weighed against the benefits to public health and quality of life and, as clearly shown here, costs that taxpayers are already shouldering through programs such as Medicaid.

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References


Sepsis-associated Encephalopathy Is Septic

Sepsis-associated brain dysfunction is considered to be unrelated to bacterial infection. That is why we commonly use the word “encephalopathy” rather than “encephalitis.” This assertion is challenged by Singer and colleagues (pp. 747–756) in the current issue of the Journal (1). The authors found that experimental septic encephalopathy results in gut-originating polymicrobial abscesses in approximately 10% of patients with septic shock (2). Second, the current results indicate that pathogens have crossed the blood–brain barrier (BBB). There are potentially three mechanisms: 1) the transcellular and paracellular pathways (for example, those used by leukocytes), 2) the neural route (5), and 3) the “Trojan horse” trick (6). The neural route has been implicated in Listeria monocytogenes can reach the brain via the cranial nerves (7). By analogy, the vagal nerve might be the gut–brain route for bacterial dissemination in the case of peritonitis. The Trojan horse pathway consists of

Identification of gut microbiota by direct gene sequencing of the brain during sepsis. These results raise several methodological, pathophysiological, and therapeutic issues.

First, the presence, in physiologic conditions, of bacteria in the central nervous system has been reported. A recent study reported the presence of α-proteobacteria in brain samples obtained during neurosurgery (3). These findings have raised several questions in the scientific community. Because the brain is considered an immune privileged organ, and isolated germs are considered as laboratory and operating-room contaminants, the concept of cerebral microbiota has not been widely accepted (4).

Second, the current results indicate that pathogens have crossed the blood–brain barrier (BBB). There are potentially three mechanisms: 1) the transcellular and paracellular pathways (for example, those used by leukocytes), 2) the neural route (5), and 3) the “Trojan horse” trick (6). The neural route has been implicated in Listeria monocytogenes can reach the brain via the cranial nerves (7). By analogy, the vagal nerve might be the gut–brain route for bacterial dissemination in the case of peritonitis. The Trojan horse pathway consists of
monocytes carrying microbes that are released into the brain parenchyma after cell migration (6). To illustrate the complexity of the mechanisms involved in crossing of the BBB by pathogens, the binding of the meningococcus to endothelial CD147 leads to the formation of bacterial colonies that can resist the blood flow, facilitating the paracellular crossing by impairing the BBB tight junctions (8). It is conceivable that in sepsis-associated encephalopathy the bacteria remain outside the brain, on the abluminal side of the endothelial cells. The absence of reactive gliosis, which is commonly observed in brain infection, might support this hypothesis. Electron microscopy might be useful for determining exactly the localization of the pathogens.

Third, irrespective of their localization, it would be interesting to assess the extent to which bacterial dissemination contributes to the ischemic and neuroinflammatory processes that serve as central mechanisms in the pathogenesis of sepsis-associated encephalopathy. The ischemic process results in both macrocirculatory and microcirculatory dysfunction, with the latter associated encephalopathy. The ischemic process results in both being related to endothelial activation and clotting disorder (2). Schematically, the neuroinflammatory process involves endothelial activation, BBB dysfunction, passage of inflammatory mediators, and microglial activation that amplifies this process by releasing more inflammatory mediators. Certainly, an assessment of BBB dysfunction as either a consequence or a cause of bacterial dissemination would be highly interesting, as it might identify potential therapeutic targets. The microglial cells, along with their role in immune surveillance of the brain, are involved in neuronal plasticity. The activation of microglial cells is a highly complex phenomenon (9). Microglial cells are highly reactive to various stimuli of diverse types (e.g., microbial or immune) and origins (humoral or neural). Therefore, the presence of bacteria can certainly activate microglial cells, along with many other stimuli. When activated, microglial cells can in time acquire different morphological (ranging from hyperamphied to amoeboid) and immune (proinflammatory to antiinflammatory) phenotypes that have increased neuroprotective or neurotoxic activity. At the end of this process, microglial cells may be primed, meaning that they will be particularly reactive to a second stimulus (10). However, there is no univocal relationship among morphology, immune status, functional properties, and pathogenic effects. This indicates how challenging it is to modulate microglial cells.

From a therapeutic point of view, before antiinflammatory interventions are attempted, antibiotic strategies should certainly be tested first. One might argue that the occurrence of encephalopathy in patients with sepsis should prompt the administration of prolonged antibiotic therapy, as in the treatment of meningitis or brain abscesses. Given our current state of knowledge, this certainly cannot be recommended. However, brain infection should be more systematically sought via brain imaging and cerebrospinal fluid analysis in the case of altered mental status in patients with sepsis.

In conclusion, the present study raises challenging issues about the mechanisms and consequences of bacterial dissemination into the brain during sepsis, emphasizes the necessity to rule out brain infection, and perhaps calls for reconsidering the duration of antibiotherapy in a patient with sepsis who is developing brain dysfunction. Finally, the article raises a semantic issue: should the term “sepsis-associated encephalopathy” be replaced by “sepsis-associated encephalitis”? ■

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