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# Experimental strategies to prevent brain damage in pediatric bacterial meningitis

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Bacterial meningitis is a devastating infectious disease of the brain that causes persistent neurofunctional deficits including cerebral palsy, hearing loss, and impairment of learning and memory in up to half of the surviving children. Brain injury to the cortical hemispheres and the hippocampus has been identified as histomorphologic correlate of neurological sequelae. Using disease models that exhibit important forms of brain injury found in the human disease, gene expression profiling in acute, i.e. 6 h and late disease, i.e. 30 h after initiation of antibiotic therapy, pointed towards mechanisms of brain injury and regeneration that were evaluated for their functional relevance and therapeutic potential.

Brain damage in the cerebral cortex was found to be associated with the occurrence of vasculitis, brain edema, endothelin induced vasospasms, and subsequent focal ischemia. In the hippocampus, a brain region involved in learning and memory function, cells undergo caspase-3 dependent apoptosis primarily affecting immature neurons in the subgranular zone of the dentate gyrus. Genes found to be significantly regulated in the cortex and the hippocampus during the acute disease, were predominantly associated with host immune response and inflammation. In acute diseases, bacteriolysis by antibiotic therapy triggered an upsurge of inflammatory mediators including matrix metalloproteinases (MMPs) resulting in excessive protease activity and degradation of collagen. Consequently, therapy with inhibitors of MMPs and non-bacteriolytic antibiotics significantly attenuated cortical injury. During the later disease phase the transcriptome remained associated with immune response in the cortex, while in the hippocampus, the majority of regulated genes were related to tissue remodelling and neurogenesis. This was reflected by the documentation of increased cellular proliferation in the subgranular zone of the hippocampal dentate gyrus after meningitis. The induction of tissue repair mechanisms as early as 30 h after the initiation of antibiotic therapy, suggests that antiproliferative therapies may be detrimental, while treatment strategies that support tissue repair and regeneration may be beneficial when given in addition to antibiotics. Indeed, adjuvant dexamethasone increased, while trophic support by brain derived neuroptrophic factor (BDNF) decreased hippocampal damage. Other strategies to attenuate hippocampal apoptosis included Vitamin B6 which prevented the decrease in cellular energy stores in the hippocampus and the combined inhibition of MMPs and TNF-alpha converting enzyme (TACE) led to improved learning and memory function. Thus prevention of bacteriolysis, inhibition of MMPs and TACE, trophic support and Vitamin B6 are among the promising experimental therapies aimed at attenuation of neurological sequelae from bacterial meningitis.