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Cognitive and Functional Impairment After Severe Sepsis

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To the Editor: Dr Iwashyna and colleagues demonstrated high rates of new-onset cognitive and functional impairments among elderly survivors of severe sepsis.[1] Converging evidence from human and preclinical studies suggests such consequences of sepsis may be associated with the effects of the immune system on the brain.

Proinflammatory cytokines (ie, interleukins and tumor necrosis factor) released as result of inflammation can reach the brain in a number of ways: via peripheral afferents (ie, the vagus nerve), entry through leaky circumventricular areas in the blood-brain barrier, or active transport.[2] Once in the brain, the cytokine signal stimulates microglia to secrete inflammatory mediators (ie, cytokines, chemokines, and proteases) from its monocytes and macrophages.[3] These local inflammatory mediators can affect neuronal function and synaptic plasticity by increasing oxidative stress and weakening astrocytic tight junctions.[3] They also increase metabolism and reuptake of neurotransmitters (ie, serotonin, noradrenalin, and dopamine) and stimulate the hypothalamic-pituitary-adrenal axis.[2] We believe this may explain the occurrence of a range of cognitive and affective problems observed in sepsis survivors. In healthy volunteers, immune activation has been shown to increase circulating cytokines, induce anxiety and low mood, and decrease cognitive performance.[4]

Both normal aging and neurodegenerative disease have been shown to prime the microglia to produce an exaggerated inflammatory response during activation of the peripheral innate immune system.[5] Central acetylcholine, which seems to exert inhibitory control over microglia, can be reduced in elderly patients if they use drugs with anticholinergic properties or have (incipient) dementia.[3] Elderly patients are prone to develop delirium, even after apparently innocuous infection.[3] In an experimental mouse model of neurodegenerative disease, transient systemic inflammation was associated with acute exacerbation of cognitive and motor impairments and rapid disease progression.[5] Taken together, these findings may advance understanding of short- and long-term cognitive and functional impairments observed among patients of sepsis and why elderly patients can be particularly vulnerable.

Research has now focused on possible pathways to control microglial activation, by (1) direct inhibition by minocycline, a tetracyclic anti-inflammatory agent; (2) peripheral blockade of cytokines by, eg, anti-tumor necrosis factor; or (3) augmentation of inhibitory cholinergic control by cholinesterase inhibitors.[3] Minocycline has been shown to attenuate both microglial activation and behavioral changes following administration of an immune activating agent in mice.[3] More research in this area is required.

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