Neuropsychiatric SLE Arises From Autoantibodies

Neuronal damage presents as cognitive and emotional impairment in two-thirds of patients with lupus.

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Boston — Recent evidence linking autoimmune disease, cognitive dysfunction and disorders of executive function are major components of disease morbidity," Dr. Diamond reported. "When one thinks about the pathogenesis of neuropsychiatric lupus, it’s logical to consider vascular occlusion or hemorrhage associated with antiphospholipid antibodies. And one might also consider cytokines, which in vitro can be toxic to neurons and alter neuronal function, but there has yet to be any correlation between any particular cytokine in cerebrospinal fluid (CSF) with any particular disease manifestation," said Dr. Diamond.

Medication, particularly steroids, could also be a contributing factor, although studies in lupus patients haven’t found any correlation between either steroid dose or duration with neuropsychiatric lupus, Dr. Diamond said.

"Of course, one can’t think about lupus without considering autoantibodies as part of the disease process, including the CNS sequelae,” said Dr. Diamond, whose recent research in this arena has borne promising fruit.

Specifically, Dr. Diamond and colleagues have determined that the loss of cognitive function is likely immunologically mediated but only in individuals in whom the blood-brain barrier has been compromised. "We’ve previously shown that anti-DNA antibodies [which bind to double-stranded DNA and are highly associated with SLE] will cross-react with peptides, including one that is present on subunits of the NMDA [N-methyl-D-aspartate] receptor," said Dr. Diamond. The NMDA receptor is expressed in neurons and has extremely high density in regions of the cerebral cortex that are associated with learning and memory functions. The anti-DNA antibodies bind to the NMDA receptors of nerve cells in these regions and produce apopotosis, she said.

However, the damage can only occur if the blood-brain barrier is compromised.

In studies with mice, "if the anti-DNA antibodies did not permeate the blood-brain barrier, there were no behavioral or cognitive changes," said Dr. Diamond. In contrast, when the barrier was broken, the antibodies bound to the areas of the brain involved in the regulation of emotion and memory, leading to cognitive and memory impairment. This finding helps explain why antibody titers in the serum of lupus patients may not correlate with clinical symptoms of neuropsychiatric SLE and why, in the presence of serum antibody, symptoms may not progress, she said.

In separate studies using mice with lupus antibodies, Dr. Diamond and colleagues forced open the blood-brain barrier by injecting the bacterial endotoxin lipopolysaccharide to simulate a mock bacterial infection and by injecting epinephrine to simulate the adrenaline spike associated with stress reactivity. In both cases, the autoantibodies were able to reach the cerebral cortex and cause neuropsychiatric symptoms.

Of interest, according to Dr. Diamond, was the fact that the simulated infection led to the death of nerve cells in the hippocampus, which mediates the stress reaction. "If it’s the breach in the blood-brain barrier that sets the stage for the changes, she said.

The findings of these studies suggest a new paradigm for an immunologically mediated, inflammatory loss of cognitive function, not only in SLE but possibly in other autoimmune conditions," said Dr. Diamond. In terms of clinical relevance, “blocking the brain cell receptor to which the anti-DNA antibodies bind could be a promising therapeutic option for neuropsychiatric SLE,” Dr. Diamond stated. In fact, in both of the aforementioned studies, the investigators demonstrated that immunization with the NMDA agonist memantine (Namenda), which is used to treat Alzheimer’s disease, protected the targeted neurons from damage and prevented behavioral alterations, as did immunization with the D-isomer of the consensus peptide.