Neuropsychiatric SLE Arises From Autoantibodies

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

BY DIANA MAHONEY
New England Bureau

BOSTON — Recent evidence linking autoantibodies to neuronal damage in systemic lupus erythematosus suggests a new paradigm for explaining the occurrence of cognitive and emotional impairment in patients with the autoimmune disorder, according to Dr. Betty Diamond of Columbia University in New York.

Nearly two-thirds of patients with systemic lupus erythematosus (SLE) experience neurologic and psychiatric symptoms—referred to collectively as neuropsychiatric SLE—ranging from headaches, mild impairment of thinking, or personality changes to stroke, epilepsy, and severe mental disorders. "And as our immunosuppressant therapies and armamentarium of antibiotics has improved and lupus patients are living longer than they used to, we're seeing more of the late sequelae of the disease and learning that cognitive dysfunction and disorders of executive function are major components of disease morbidity," Dr. Diamond reported at a rheumatology conference sponsored by Harvard Medical School.

The etiology of central nervous system (CNS) involvement in lupus has long eluded investigators, particularly because it occurs without evidence of cerebral vascular disease or telltale inflammation, said Dr. Diamond. In addition, in most studies, the progressive cognitive impairment has not been associated with disease activity or medication.

"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, she 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 throughout the brain and at a particularly 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 apoptosis, 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 neurocognitive symptoms.

Of interest, according to Dr. Diamond, was the fact that the simulated infection led to the death of nerve cells in the hippocampus while the simulated stress reaction attacked neurons in the amygdala. The "regional specificity" of neuronal damage might explain variations in the nature and extent of cognitive and emotional changes associated with neuropsychiatric lupus, but it is 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, noninflammatory 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-isoform of the consensus peptide. ■

Chorioretinopathy's Autoimmune Etiology Limited to Eye

BY NANCY WALSH
New York Bureau

SORRENTO, ITALY — The posterior uveitis known as birdshot chorioretinopathy appears to be an eye-restricted disease, reported Dr. Christian Pagnoux at the Fifth International Congress on Autoimmunity.

In a careful assessment of the largest series to date of patients with birdshot chorioretinopathy—so named because of the distinct shotgun-like scatter pattern of hypopigmented spots on the fundus—some were found to exhibit "intriguing" extraocular features, but there was no convincing evidence of systemic involvement, said Dr. Pagnoux of Cochin Hospital, Paris.

Previous studies of birdshot chorioretinopathy, in which patients complain of floaters, blurred vision, nyctalopia, and photophobia, have not addressed the possibility of patients having extraocular manifestations despite the likelihood that the disorder is autoimmune in nature.

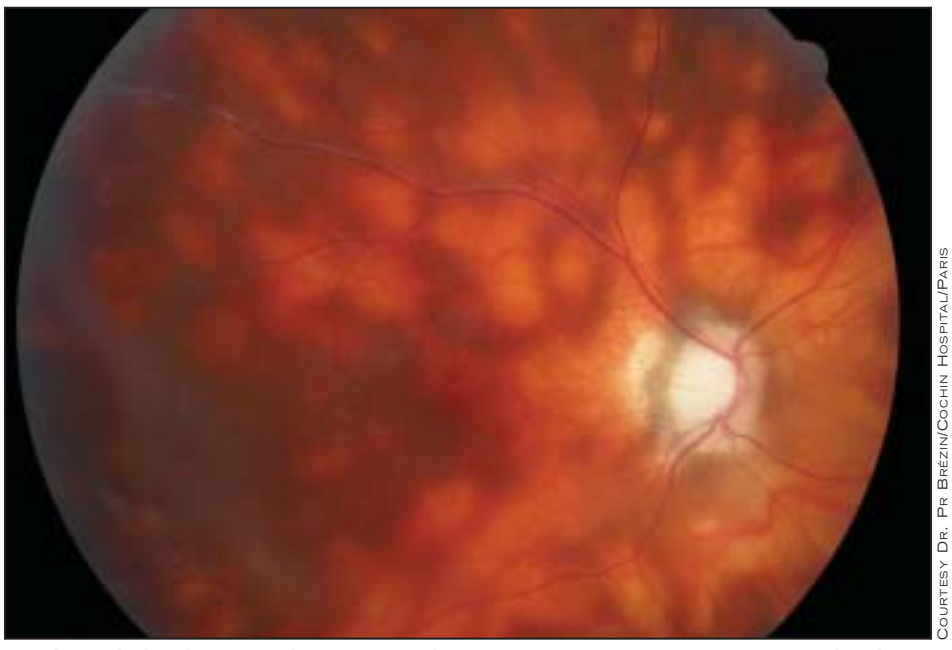
The evidence suggesting that birdshot chorioretinopathy is an autoimmune disorder includes a strong association with the human leukocyte antigen (HLA)-A*29 gene. Moreover, clinical features of the disease resemble autoimmune S-antigen–induced uveoretinitis, and some patients have granulomatous histology findings and features associated with vasculitis, according to Dr. Pagnoux. "However, if it indeed is an autoimmune disease, it would be one of the rare—and possibly the only—autoimmune disease that is restricted to one organ," he said in an interview.

A longitudinal cohort study initiated by ophthalmologists at Cochin Hospital, which is the French National Reference Center for Vasculitides, provided the opportunity for Dr. Pagnoux and his colleagues from the French Vasculitis Study Group to investigate disease manifestations in 118 patients.

Mean age was 51 years, and there was a slight male predominance. Each patient underwent a 30-minute medical interview using a standardized report form, and data on medical history before and after the onset of birdshot chorioretinopathy were collected.

Among the study findings were that 16% had drug allergies, 9% had asthma, 8% had diabetes, and 10% had thyroid disease. One patient had antiphospholipid syndrome, three had Raynaud's phenomenon, and five reported a history of psoriasis. In addition, 27% were hypertensive, and 14% had sinusitis. Hearing loss was reported by 7%. At the time of disease onset, 19% of patients also reported arthralgias, but none had arthritis or synovitis, Dr. Pagnoux said.

The incidence of these maladies is quite similar to those reported by the French general population, he said. "We also did not find any manifestations suggesting inflammation outside the eyes, such as elevated C-reactive protein levels. "I think one could say today, with a certain degree of confidence, that birdshot chorioretinopathy is indeed an eye-restricted disease," he said.



COURTESY DR. PR BRÉZIN/COCHIN HOSPITAL/PARIS

Multiple distinctive hypopigmented lesions shown clustered around the optic disk: Retinal depigmentation reveals veins on transparency, and slight edema is visible.

Nonetheless, certain findings such as hearing loss, hypertension, and psoriasis are of interest and merit further attention as potential extraocular disease manifestations. Study limitations include the non–population control design and the potential for recall bias. However, the use of standardized report forms by physicians specializing in vasculitis may counterbalance these potential drawbacks, he said.

The study is ongoing, and patients will be re-evaluated every 5 years with the goal of providing a clearer picture of the natural history of the disease, particularly when macular edema occurs and visual acuity is lost. ■