

## **A Role for Humoral Mechanisms in the Pathogenesis of Devic's Neuromyelitis Optica**

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Devic's disease (neuromyelitis optica [NMO]) is an inflammatory demyelinating disease of the CNS characterized by attacks of optic neuritis and myelitis. The mechanisms that result in selective localization of inflammatory demyelinating lesions to the optic nerves and spinal cord are unknown. Serologic and clinical evidence of B cell autoimmunity has been observed in many NMO patients. The purpose of this study was to investigate the importance of humoral mechanisms including complement activation, in producing the necrotizing demyelination seen in the spinal cord and optic nerves.

82 lesions were examined from 9 autopsy cases of clinically confirmed Devic's disease. Demyelinating activity in the lesions was immunocytochemically classified as early active (21 lesions), late active (18 lesions), inactive (35 lesions), and remyelinating (8 lesions) by examining the antigenic profile of myelin degradation products within macrophages (PLP and MOG). The pathology of the lesions was analyzed using a broad spectrum of immunological and neurobiological markers, and lesions were defined on the basis of myelin protein loss, the geography and extension of plaques, the patterns of oligodendrocyte destruction and the immunopathological evidence of complement activation.

Histories were available on all nine cases (8 female; 1 male; average age 50 yrs (range 16-80). The clinical course was relapsing in 8 patients, and monophasic in a single case. Mean disease duration was 2.4 yrs (SEM +/- .8 yrs), with all patients dying from respiratory compromise. Three patients had a history of associated autoimmune disorders (hypothyroidism (2), pernicious anemia (1), thrombocytopenic purpura (1).

The pathology was identical in all 9 patients. Extensive demyelination was present across multiple spinal cord levels, associated with cavitation, necrosis, and acute axonal pathology. Lesions were typically located within central portions of the spinal cord, with peripheral rims of myelin preservation. There was a pronounced loss of oligodendrocytes within the lesions, with occasional Schwann cell remyelination (4 lesions). No OG apoptosis was found, and comparative immunocytochemistry revealed no selective loss of MAG (a marker of oligodendrocyte dystrophy). Optic nerves and/or chiasm demonstrated inactive demyelination or partial remyelination in all subjects, with no evidence of ongoing demyelinating activity. The inflammatory infiltrates in actively demyelinating spinal cord lesions were characterized by extensive macrophage infiltration associated with large numbers of perivascular granulocytes and eosinophils and rare CD3+ T cells. There was a pronounced perivascular deposition of immunoglobulins (IgM>IgG) and complement C9 neo antigen (a marker of complement

activation). There was evidence of vascular fibrosis and vessel proliferation in active spinal cord lesions, with no clear evidence of fibrinoid necrosis.

The extent of complement activation, eosinophil infiltration, and vascular fibrosis observed in the Devic cases is more prominent compared to typical MS, and supports a role for humoral immunity in the pathogenesis of NMO. Future therapeutic strategies designed to limit the deleterious effects of complement activation, eosinophil degranulation, and neutrophil/macrophage/microglial activation are worthy of investigation based on this study.