

## Experimental Models of Neuromyelitis Optica

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**Abstract:** Recently a specific auto-antibody response has been found in patients with neuromyelitis optica, which is directed against the astrocytic water channel aquaporin 4. In experimental models these antibodies do not induce disease or lesions in the central nervous system, when present in the circulation of normal rats. However, when T-cell mediated inflammation is induced in such animals, circulating antibodies against aquaporin 4 can reach the brain and induce lesions in the central nervous system, which are closely similar to those, seen in patients with neuromyelitis optica.

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Neuromyelitis optica (NMO) is defined as an inflammatory demyelinating disease, mainly affecting the spinal cord and the optic nerves (Devic 1894). It has for long been considered a variant of multiple sclerosis (MS), but recent data suggest that its pathogenesis may be different. A groundbreaking discovery in NMO was the identification of an auto-antibody response with high sensitivity and specificity for the disease (Lennon et al 2004), which later was found to be directed against the astrocytic water channel aquaporin 4 (AQP4; Lennon et al 2005). Indirect evidence from in vitro studies and from detailed immunopathology of the disease suggests that these auto-antibodies are pathogenic and play a major role in the formation of lesions in the central nervous system (Lucchinetti et al 2002, Takahashi et al 2007, Graber et al 2008). However, direct proof of their involvement in the disease process was absent until recently. Such a proof requires the establishment of an experimental animal model.

One possible approach to reach this goal is to induce disease by active sensitisation with AQP4. This has so far not been achieved. One possible reason for this failure is that the pathogenic epitope, which is recognized by human AQP4 antibodies from NMO patients is a complex conformational structure (Nichia et al 2008) and it is very difficult to induce such antibodies by active sensitisation.

Another approach to test for the pathogenicity of the auto-immune response in NMO patients is the direct systemic injection of purified AQP4 containing NMO immunoglobulins into animals (Bradl et al 2009). We have used this approach in normal rats, but the animals did not develop disease and detailed neuropathological analysis of the central nervous system did not reveal any focal lesions or other pathological alterations. This result is not surprising, since circulating im-

munoglobulins pass the normal blood brain barrier only to a very limited extent, and it is therefore unlikely that with this approach antibody titers can be reached in the central nervous system, which are sufficiently high to induce damage.

We then tested the possibility that AQP4 auto-antibodies may be pathogenic by amplifying disease and lesions in the context of pre-existing brain inflammation, as previously shown for demyelinating antibodies directed against myelin oligodendrocyte glycoprotein (Linnington et al 1988). We induced brain inflammation by passive transfer of T-lymphocytes directed against myelin basic protein. This leads to an acute and transient encephalitis with brain inflammation, blood brain barrier disturbance and recruitment of activated macrophages. At the onset of disease we systemically injected immunoglobulin of NMO patients with high titers of AQP4 antibodies. Under these conditions clinical disease was augmented. Furthermore, lesions were seen in the spinal cord and brain, which in addition to T-cell and macrophage infiltrates showed profound recruitment of granulocytes, perivascular destruction of astrocytes and massive loss of AQP4 within and around the perivascular inflammatory infiltrates. These lesions closely resembled those seen in NMO patients at early stages of their disease (Bradl et al 2009).

These results indicate that in NMO two different pathogenic factors have to act in concert. The first is the induction of brain inflammation, which apparently is not directly mediated by the auto-antibodies. The second is the presence of circulating auto-antibodies against AQP4, which can reach the brain at sites of inflammation and selectively target the AQP4 expressing astrocytes. In this context they are responsible for the formation of lesions, which are pathognomonic

for NMO. What induces inflammation in NMO patients is currently not known. The most attractive hypothesis is, that patients not only mount an auto-antibody response but also develop a pathogenic T-cell response against AQP4 itself.

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