Aquaporinopathy and Cerebral Inflammation

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Abstract

Many mammalian AQP s, including AQP1, AQP2, AQP4, AQP5 and AQP8, function primarily as bidirectional water-selective transporters. Cells expressing AQP s on their plasma membrane have an ~5- to 50-fold higher osmotic water permeability than membranes that do not. Water transport through single-file pores poses a biophysical limitation on the efficiency with which AQP s can transport water, so that AQP s must be present in the membrane at a high density to increase membrane water permeability substantially. Aquaporin-4 (AQP4), the target antigen of NMO-IgG, is a water channel protein highly concentrated in spinal cord gray matter, periaqueductal and periventricular regions, and astrocytic foot processes at the blood-brain barrier. It is now clear that NMO-IgG (anti-AQP4) plays a direct role in the pathogenesis of NMO. In MS lesions, the distribution of AQP4 protein expression depends upon the stage of demyelination, while in NMO lesions, there is a loss of AQP4 expression that is unrelated to the stage of demyelination. The inflammatory processes in NMO primarily targets astrocytes; the area postrema appears to be a preferential target of NMO-IgG antibodies that bind to astrocyte AQP4 water channels, leading to astrocyte dysfunction and the clinical manifestations of nausea and vomiting. Central nervous system involvement outside of the optic nerves and spinal cord is recognized in patients with NMO and NMOSD. Other suggestive symptoms include episodes of intractable nausea, vomiting, hiccups, excessive daytime somnolence or narcolepsy, reversible posterior leukoencephalopathy syndrome, neuroendocrine disorders, and (in children) seizures. While no clinical features are disease-specific, some are highly characteristic. Manifestations that can develop with NMO and NMOSD include encephalopathy, fulminant cerebral demyelination, hypothalamic dysfunction, and posterior reversible leukoencephalopathy. Symptoms related to bilateral hypothalamic lesions may include symptomatic narcolepsy or excessive daytime sleepiness, obesity, and various autonomic manifestations such as hypotension, bradycardia, and hypothermia. In rare cases, fulminant diffuse vasogenic edema can lead to brain herniation and death.

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