NEUROMYELITIS OPTICA SPECTRUM DISORDER: PATHOGENESIS AND CLINICAL DIAGNOSIS

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PATHOGENESIS

Disordered Immunoregulation and the Genesis of NMOSD

Neuromyelitis optica spectrum disorder (NMOSD) is associated in most patients with autoantibodies to aquaporin-4[1]. These antibodies have pathogenic potential and can cause NMOSD-typical pathology when passively transferred to rodents, either by direct cerebral injection[2] with human complement or by systemic administration in the presence of a disrupted blood brain barrier[3]. A minority of seronegative NMOSD patients has detectable MOG-IgG antibodies that also have pathogenic potential[4]. The discussion will concentrate on AQP4-IgG-associated NMOSD, which has been much more extensively studied. Most AQP4-IgG is produced systemically and crosses the blood brain barrier into the CNS, although B cells including plasmablasts are capable of directly accessing the CNS and producing AQP4-IgG intrathecally. AQP4-IgG has an IgG1 isotype; accordingly, AQP4-IgG secreting cells require T cell help. Clones of Th17 cells are sensitized in vivo to AQP4 as demonstrated by the different response to AQP4 exposure of T cells from NMOSD patients relative to controls[5]. The source of the inciting AQP4 antigen and the mechanism of breakdown of self-tolerance are poorly understood. In unusual NMOSD cases, activation can be associated with tumors, suggesting a paraneoplastic presentation by neoplasms that express AQP4[6]. AQP4 has sequence homology with a Clostridium perfringens protein; microbiome studies have suggested that C perfringens is overrepresented in gut flora of individuals with NMOSD[7].

NMOSD is associated with other autoimmune disease; rarely NMOSD occurred in individuals with disorders of immune activation such as Aicardi Goutieres disease[8]. NMOSD is not associated with MS-associated HLA antigens such as DRB1*1501, but is associated with DRB1*03, similar to systemic lupus erythematosus[9].

AQP4-IgG and Mechanism of Cellular Injury

AQP4 is expressed as tetramers on the surface of astrocytes abutting the abluminal surface of microvessels where it is held in place by the dystrophin complex. The level of expression of AQP4 is greatest in optic nerve and spinal cord compared to other sites in the CNS; in the optic nerve and spinal cord, there is a high level of "supramolecular aggregation" of AQP4 that facilitates dense binding of AQP4-IgG and C1q binding[10]. As this finding would predict, in the presence of AQP4-IgG, the dense expression as supramolecular aggregates facilitates complement-mediated toxicity. Pathologic studies show prominent terminal complement activation in association with immunoglobulin deposition in the perivascular regions where AQP4 is expressed. A variety of downstream effectors, including neutrophils and eosinophils appear to contribute to tissues damage. IL6 is also expressed in high levels and is correlated with tissue damage. Diffuse astrocyte activation occurs in NMOSD and activation of inflammatory cytokine cascades in response to AQP4-IgG in non-lesional tissue[11]. The significance of these changes to cognitive changes, depression or other possible manifestations of NMOSD remains to be established.

DIAGNOSIS

New diagnostic criteria

Neuromyelitis optica had been historically diagnosed in patients with a monophasic syndrome of bilateral optic neuritis and myelitis. Based on clinical observations, in the 1990's, the diagnosis was liberalized to include patients with unilateral optic neuritis and myelitis when other criteria were satisfied, such as having longitudinally extensive lesions in the spinal cord in the context of myelitis (LETM)[12]. After the discovery that aquaporin-4-IgG (AQP4-IgG) was a specific biomarker for NMOSD, the diagnosis could be made reliably at an early point after the initial symptoms. Furthermore, a much wider spectrum of clinical observations was reported in patients who had otherwise typical NMOSD and had aquaporin-4 antibodies, requiring liberalization of clinical requirements[13, 14]. An international panel recently updated diagnostic criteria for neuromyelitis optica and suggested that the disorder be formally recognized as a spectrum disorder (neuromyelitis optica spectrum disorder, NMOSD)[15]. Detection of AQP4-IgG reduces the clinical stringency to make the diagnosis. However, recognizing that about 30% of patients are seronegative, the panel established clinical and radiologic criteria for seronegative NMOSD, recognizing that there is greater potential for error in this subgroup.

NMOSD versus multiple sclerosis

No single criterion allows for reliable diagnosis of NMOSD. Although AQP4-IgG testing has greatly facilitated making an accurate diagnosis, false positives occur in 5% of patients who when the index of suspicion is high. Although this is not a major problem in the setting of high pretest probability (e.g. attacks of optic neuritis and longitudinally extensive myelitis), it is a major problem in low pretest probability settings (e.g. progressive myelopathy, myelitis with short lesions), particularly when ELISA testing is used. In low probability settings (e.g. screening large populations of patients diagnosed with MS), ELISA is more commonly false positive than true positive. One should be cautious about reaching a confident diagnosis primarily on the basis of serologic testing, and should confirm positive ELISA tests in low clinical probability settings with a more specific serologic assay, such as cell binding assay [16]. NMO typical features include longitudinally extensive myelitis, severe deficits from optic neuritis episodes, lack of oligoclonal bands in CSF and certain brain lesions (medulla, floor of 3rd and 4th ventricles, diffuse corpus callosum lesions). Conversely, features typical of MS should cause one to be cautious about a diagnosis of NMOSD, although, strictly, none exclude a diagnosis of NMOSD; such "red flags" include: partial transverse myelitis with peripheral short lesions in the cord, periventricular discrete brain lesions especially around the temporal horns, presence of oligoclonal bands in CSF, and secondary progressive course. However, these clinical and radiological "rules" are imperfect[17, 18]. LETM may occur in other conditions (e.g. viral myelitis, sarcoidosis, acute disseminated encephalomyelitis) and about 15% of patients with NMOSD do not have LETM at presentation, even though the majority ultimately experience LETM with relapses of myelitis[19]. It is necessary to consider the totality of the demographic, clinical and radiologic findings as well as serologic findings, but it usually possible to reach a confident distinction between NMOSD and MS. A variety of confounding and conflicting factors, including the following: 1. lack of informative imaging at the time of an acute myelitis; 2. occasional brain lesions, even symptomatic, in patients with NMOSD; 3. occasional detection of oligoclonal bands and other markers of intrathecal IgG synthesis in approximately 20% of patients with NMOSD. Recent studies suggest that even experts frequently disagree, although generally tend to give an NMO diagnosis and even more often recommend immunosuppression over MS disease modifying treatments when there are some features more typical of NMO than MS[18]. Several MS treatments have been suggested based on limited evidence to be ineffective (glatiramer acetate) or even potentially harmful (interferon beta, fingolimod, alemtuzumab) for NMOSD.

Atypical Presentations: An Extended Spectrum

Atypical presentations can be classified as follows:

1. Non-opticospinal presentation. The brain can be involved in a variety of ways, with some predilection for AQP4-expressing parts of the brain, such as area postrema and circumventricular organs as well as the ependymal surrounding the floor of the 4th ventricle[20]. Other extra-CNS tissues, including muscle can be involved, usually manifest as recurrent myalgia with elevated creatine kinase levels without significant muscle weakness[21].

2. Indirect effects. Hydrocephalus may occur as a result of ependymal inflammation in the brainstem and periaqueductal region with attendant aqueductal stenosis[22].

3. Comorbidity. NMOSD frequently coexists with other autoimmune diseases, including myasthenia gravis, systemic lupus erythematosus and Sjogren's syndrome. It is now know that NMOSD may also coexist or follow NMDA-receptor encephalitis or other autoimmune encephalitis. NMOSD may occur in some patients with coexisting cancer, and some cancers have been shown to express AQP4 and have inflammation suggesting that NMOSD in these patients may be a paraneoplastic disorder[6].

Non-MS NMOSD Mimics

A variety of diseases may cause optic neuritis/neuropathy and myelitis/myelopathy. There are long differential diagnoses of both syndromes. However a few conditions prove to be particularly problematic. Sarcoidosis can cause both optic neuritis and longitudinally extensive myelitis. Accurate distinction from NMOSD is usually possible[23]. Spinal cord sarcoidosis (SCS) typically develops more gradually than NMOSD myelitis, and usually does not conform to the time course of acute transverse myelitis (nadir within 3 weeks). SCS is often associated with constitutional symptoms, CSF hypoglycorrhachia and pleocytosis. Perhaps most helpful is the predilection for longitudinally extensive posterior/dorsal subpial gadolinium enhancement that is rarely detected in NMOSD. CRMP-5 associated paraneoplastic disease is associated with LETM and optic neuropathy[24]. A recently described inflammatory disorder associated with GFAPα autoantibodies may cause bilateral papilledema, mild encephalopathy and mild myelopathy associated with LETM[25]. Biotinidase deficiency has been reported to cause a syndrome that may closely mimic spinal cord, optic nerve and brain involvement seen in NMOSD[26].

CONCLUSIONS

The nature of the immune activation that culminates in production of pathogenic AQP4-IgG in patients with NMOSD remains poorly understood, but new clues as to immunopathogenesis include HLA associations, paraneoplastic NMOSD and evidence for potential molecular mimicry. AQP4 is highly expressed in optic nerve and spinal cord, which facilitates complement-mediated inflammatory cytotoxicity in these structures, which is the dominant pathogenic mechanism underlying acute attacks of optic neuritis and myelitis. However, other pathologic changes including diffuse astrocyte activation occur in NMOSD.

Clinicians must be aware of and vigilant for a variety of demographic, clinical, radiologic, and CSF findings that can help distinguish NMOSD from MS and other mimics. Diagnosis of NMOSD exclusively in those with inflammation confined to the optic nerve and spinal cord is a criterion that is neither specific for NMO nor is it satisfied by approximately half of patients with NMOSD. Appreciating the spectrum and awareness of mimics is especially important given the need for aggressive long term immunosuppression and lack of efficacy of many MS-directed immunomodulatory treatments.

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