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Review article

Infections in neuromyelitis optica spectrum disorder

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ABSTRACT

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory astrocytopathy that has both genetic and environmental causes. A growing body of evidence suggests that the presence of several infectious agents correlates with the development of NMOSD. In this review, we summarize studies that either support or present evidence against the hypothesized association between infection and NMOSD. We will also present an overview of potential mechanisms underlying the pathogenesis of NMOSD. Finally, we provide some beneficial properties that infectious elements may have based on "hygiene hypothesis". It is of great clinical significance to further investigate the complex mechanisms by which infections may affect autoimmune diseases to develop better strategies to prevent and treat them, although so far no causal link between infectious agents and NMOSD has been established.

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1. Introduction

Neuromyelitis optica (NMO) is an autoimmune astrocytopathy of the central nervous system (CNS), mainly characterized by recurrent episodes of optic neuritis and acute transverse myelitis [1].

Although NMO was once classified as a severe variant of multiple sclerosis (MS), the discovery in 2004 of a highly specific serum autoantibody (AQP4-IgG) against astrocytic water channel protein aquaporin-4 (AQP4) suggested that NMO is a distinct disease entity. This discovery paved the way for a better understanding of its pathogenesis and, in 2007, NMOSD was introduced to include individuals who fail to meet the diagnostic criteria of NMO (e.g., AQP4-IgG positive patients with recurrent optic neuritis or with other coexisting autoimmune diseases) [2–4]. The new 2015 diagnostic criteria state that NMOSD is composed of six core clinical characteristics (e.g., area postrema syndrome, acute brainstem syndrome) and produces atypical structural neuroimaging patterns, further broadening the concept of NMO [5].

East Asians are inherently at a higher risk for developing NMOSD compared with populations of non-Asian descent [6], which suggests the disease may have a genetic basis. Advanced gene-sequencing technology has identified several candidate genes that potentially increase the susceptibility to NMOSD. A prime candidate is the Human Leukocyte Antigen (*HLA*). Indeed, previous studies have found that the *HLA-DPB1*05:01* allele is more prevalent in Asian NMOSD populations, whereas *DRB1*03:01* is more common in Caucasian NMOSD populations [7–10]. These alleles may influence the HLA-based antigen presentation and subsequently induce excessive autoimmune processes. The potential implication of non-*HLA* genes, such as interleukin 17 receptor (*IL-17R*), *CD226*, and cholesterol 7α-hydroxylase (*CYP7A1*), has been inconsistent and shown to vary across different populations and studies [11–14]. Although the exact etiology and pathogenesis of NMOSD remain to be established, complex interactions between genetic and environmental factors are thought to be involved in its development. The overall prevalence of NMOSD has been on the rise, presumably reflecting the effect of some particular environmental shift, such as changes in sanitary habits and antibiotic use [12]. Infectious diseases have received particular attention since they have long been considered as triggers of many autoimmune disorders including MS, type I diabetes, and rheumatic diseases [15,16]. In addition, infectious agents such as *Tuberculosis* and *Helicobacter pylori* are more common in Asia than in Europe

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or North America, which parallels the high incidence of NMOSD [17,18].

Therefore, in this review, we will focus on studies that either support or provide evidence against the association between infection and NMOSD. We will furthermore discuss several potential mechanisms by which infection may trigger or exacerbate this autoimmune disorder. It is important to emphasize that since the vast majority of available studies were not performed with methodologically sound experimental designs, their conclusions remain speculative in nature. Finally, we will provide an overview of some of the beneficial properties that infectious agents may have based on evidence obtained from investigating other autoimmune diseases.

2. Pathogenesis of NMOSD

It is widely accepted that NMOSD is a humoral-mediated autoimmune astrocytopathy that begins with the entry of AQP4-IgG into the CNS via an impaired blood-brain barrier (BBB). The mechanisms underlying BBB disruption remain controversial and may initially be caused by AQP4-specific T cells or AQP4-IgG in the cerebrospinal fluid [19,20]. Subsequently, AQP4-IgG binds to the AQP4 channels on perivascular astrocyte endfeet, which subsequently activates the classical complement pathway. This process results in a membrane attack complex formation, an antibody-dependent cellular cytotoxicity and a complement-dependent cellular cytotoxicity, which can then produce astrocyte damage, demyelination, inflammatory infiltration, and neuronal loss [21]. A subtype of B cells, plasmablasts (PBs), is selectively elevated in NMOSD patients [22]. Several studies have indicated that interleukin (IL)-6 could facilitate both the survival of PBs and the production of AQP4-IgG, and may, therefore, serve as a biomarker of NMOSD [23].

The precise mechanisms that underlie AQP4-IgG production, BBB damage, and oligodendrocyte injury, remain unknown. Moreover, 10%–20% of patients with NMOSD are clinically AQP4-IgG seronegative, indicating there may exist other autoantibody-independent pathomechanisms. For instance, following the direct injection of lipopolysaccharide (LPS) into the spinal white matter of mice, Lassmann et al. observed a significant activation of microglial cells followed by astrocyte damage and subsequent axonal demyelination in the absence of AQP4-IgG [24]. Although the introduction of LPS, an important bacterial component, failed to produce a typical MS or NMOSD lesion, the resulting CNS damage suggests a pathogenic role of infection in NMOSD development. In a retrospective study, 31% of NMOSD patients suffered from a prodromal flu-like illness [25]. Furthermore, another report indicated that 25.4% NMOSD patients experienced an unspecific viral illness that preceded the disease onset [26]. Sellner et al. analyzed parainfectious NMOSD reports published between 1975 and 2009 and found on average a high prevalence of monophasic courses (88%) and a generally poor prognosis (with only a complete recovery in 25% of cases) in NMOSD patients [27]. Taken together, these findings strongly suggest that infectious agents may trigger or exacerbate the development of NMOSD in genetically susceptible patients (shown in Fig. 1). However, the pathogenic evidence linking infection to autoimmune disease varies greatly depending on the disease and is relatively weak and inconsistent in the case of NMOSD. Therefore, we only selected infection candidates that have been extensively studied.

3. Tuberculosis (TB)

A close relationship between pulmonary TB (PTB) and NMOSD has been proposed in a large body of case reports and few case-control studies that provided no evidence of TB invasion in the CNS [28–31]. Recently, Henning et al. presented a patient with recurrent NMOSD, where each relapse exhibited an unequivocal temporal relationship with episodes of active PTB (1- and 3-week interval from the onset of PTB, respectively) [32]. Rafai et al. reported two cases: one that was experiencing PTB symptoms before the onset of NMOSD and another who showed sputum smear-positive PTB symptoms only after the onset of NMOSD [28]. A report from South Africa, evaluating the clinical features of eight NMOSD patients with active PTB, depicted a relatively consistent pattern where the neurological complaints started soon after the occurrence of PTB symptoms (mean onset delay of 2.1 months)[31].

Similarly, an earlier study demonstrated that 5 out of 24 patients with NMOSD had suffered from PTB prior to NMOSD onset [33]. In line with these findings, a retrospective case-control report from South Africa indicated a close temporal association between the onsets of both conditions; indeed, 79% of NMOSD patients had previously received a diagnosis of active PTB with a median interval of four weeks between diagnoses. Furthermore, the frequency of TB infection is significantly greater in NMOSD patients than control groups (79% vs 14%) [34]. Although we failed to reproduce the previous result in our population recruited from southern China [17], another prospective research study in the same region demonstrated that anti-TB treatment (ATT) could improve the observed neurological deficits in patients suffering from steroid-refractory NMOSD [35]. Unfortunately, the abovementioned case-control reports did not examine AQP4-IgG or divide the NMOSD patients according to their autoantibody status when comparing them with controls. Since the pathomechanisms probably differ for NMOSD presenting with and without AQP4-IgG, future studies should take these differences into consideration.

Whether NMOSD is specifically associated with TB or if it is associated with multiples types of infection remains to be determined. Several mechanisms by which TB can exert an effect on NMOSD have previously been proposed. For instance, AQP4 could be detected on the epithelial cells of the human respiratory tract and kidney principal collecting duct cells [36,37]. Given that the aquaporin extracellular loops derived from Mycobacterium and Mycoplasma sp. share homologous epitopes to human AQP4, pulmonary or renal tuberculosis may, for example, induce lymphocytes that are sensitized against a bacterial epitope with self-proteins such as AQP4. Then, the entry of self-reactive lymphocytes, or their productions, into the CNS could potentially break down our CNS immunological tolerance and damage astrocytes [38,39]. Despite molecular mimicry, inflammatory demyelination was observed in the setting of an abnormal immune status caused by BK (*Bacillus Kochii*). This hypothesis is supported by experimental data that reproduced demyelination lesions by injecting either BK or tuberculin antigenic components [40]. However, the possibility of adverse effects associated with anti-TB drugs should also be taken into consideration because some drugs, such as ethambutol and isoniazid, can result in either necrotic myelopathy or optic neuropathy [30].

4. Helicobacter pylori (H. pylori)

H. pylori is a Gram-negative microaerophilic bacterium that colonizes the human stomach and remains throughout life. Although more than half of the world's population is affected by *H. pylori* early in life, only a minority of individuals (10%–20%) develop symptomatic diseases such as peptic ulcers, chronic gastritis, and gastric malignancies [41].

Recent studies have suggested a possible association between *H. pylori* infection and a broad spectrum of extragastric diseases.

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