Myelin Oligodendrocyte Glycoprotein Immunopathology, Treatment and Visual Outcome

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Contributor: Keiko Tanaka, Takeshi Kezuka, Hitoshi Ishikawa, Masami Tanaka, Kenji Sakimura, Manabu Abe, Meiko Kawamura

The International Consensus Group on MOG autoantibody-associated disease (MOGAD) has proposed that the diagnostic criteria for MOGAD should include the presence of anti-MOG autoantibodies detected using cell-based assays. MOGAD is typically associated with acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), and transverse myelitis (TM) and is less commonly associated with cerebral cortical encephalitis, brainstem or cerebellar symptoms, and clinical presentations including the combination of several phenotypes and sometimes accompanies other autoantibodies such as anti-*N*-methy-D aspartate receptor (NMDAR) autoantibodies with symptoms of autoimmune encephalitis.

Keywords: myelin oligodendrocyte glycoprotein ; autoantibody ; optic neuritis ; antibody-binding epitope

1. Introduction

Myelin oligodendrocyte glycoprotein (MOG), which is exclusively expressed in oligodendrocytes, is a component of the outer surface of myelin in the central nervous system (CNS) [1]. Although a quantitatively minor component, MOG has strong antigenicity. In fact, MOG was initially identified as an immunodominant target for demyelinating autoantibodies in a guinea pig model of experimental autoimmune encephalomyelitis (EAE) [2][3]. Subsequent studies have demonstrated that immunization with MOG peptides can induce an EAE variant that exhibits many of the clinical and pathologic characteristics of multiple sclerosis (MS) in both rats and primates. Litzenburger T. et al. demonstrated the persistent presence of MOG-reactive B cells in the peripheral immune system and suggesting their potential roles as modifiers in inflammatory CNS diseases using transgenic mice producing MOG-specific immunoglobulins [2]. Anti-MOG autoantibodies have been detected in many EAE variants, inciting many promising studies in patients with CNS demyelinating diseases. Over the years, extensive studies conducted in patients with MS have investigated the presence of anti-MOG autoantibodies using Western blotting and enzyme-linked immunosorbent assays targeting recombinant mouse MOG, without clear relation and specificity with MS [4]. Pöllinger B. et al. developed transgenic mice bearing MOG peptide-specific T cell receptors, resulting in spontaneous relapsing–remitting EAE along with the expansion of autoreactive B cells that produce autoantibodies binding to a conformational epitope on the native MOG protein [3]. This important finding that the pathogenic autoantibodies recognize a conformational epitope on the native antigen protein led to the designation of the human anti-MOG autoantibody-associated disease [5][6].

In recent years, the presence of anti-MOG autoantibodies has been extensively tested in patients with CNS inflammatory diseases using a cell-based assay that preserves the conformational structure of the full-length human MOG [7]. The International Consensus Group on MOG autoantibody-associated disease (MOGAD) has proposed that the diagnostic criteria for MOGAD should include the presence of anti-MOG autoantibodies detected using cell-based assays [8]. MOGAD is typically associated with acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), and transverse myelitis (TM) and is less commonly associated with cerebral cortical encephalitis, brainstem or cerebellar symptoms, and clinical presentations including the combination of several phenotypes and sometimes accompanies other autoantibodies such as anti-*N*-methy-D aspartate receptor (NMDAR) autoantibodies with symptoms of autoimmune encephalitis [9]. MOGAD can have a monophasic or relapsing disease course; therefore, detecting anti-MOG autoantibodies using cell-based assays is essential for diagnostic accuracy.

The majority of adult patients who are positive for anti-MOG autoantibodies exhibit ON or TM, while ADEM with or without ON is the most frequent presentation in pediatric patients with MOGAD. Factors that determine age-specific clinical phenotypes and CNS lesions in patients with MOGAD remain unclear. Furthermore, the MOG protein function and the pathogenicity of anti-MOG autoantibodies in MOGAD have not been fully clarified.

The development of appropriate models is critical to elucidate the specific functions of anti-MOG autoantibodies. However, the low affinity of human anti-MOG autoantibodies for mouse MOG has hindered the establishment of reliable models.

Several studies have shown that the recognition of MOG by anti-MOG autoantibodies involves highly complex mechanisms [10][11][12]. The antigen-recognition patterns of MOGAD might differ from those of anti-aquaporin 4 (AQP4) autoantibody-related neuromyelitis optica spectrum disorders (NMOSDs) and anti-NMDAR autoantibody-related autoimmune encephalitis, two clinical presentations with well-characterized antibody-binding sites on the disease-related antigen [13][14].

2. Immunopathology of MOGAD

Although systematic neuropathological evaluation of MOGAD patients is rare, several studies including autopsy and biopsy samples from patients with anti-MOG autoantibodies have revealed a distinct pattern of perivenous and confluent demyelination in white matter, cortex, and deep gray matter structures [15][16][17].

In a study of biopsy samples, meningeal inflammation was observed in 86% of the cases, subpial lesions were present, and active demyelinating areas showed an abundance of myelin-laden macrophages/microglial cells [15]. However, the majority of the infiltrating lymphocytes were CD4-positive, with few B cells and CD8+ T cells [15][16].

In some studies, complement activation was demonstrated in active lesions, resembling pattern II demyelinating lesions of MS [15], but it was largely absent in another study of 11 biopsies [16]. Additionally, the destruction of oligodendrocytes displayed a varying pattern and selective MOG loss was not observed [15]. However, the loss of MOG expression was described in another study by Takai et al. [16] who showed that most of the demyelinating lesions exhibited a perivenous demyelinating or fusion pattern mainly in the corticomedullary junction and white matter, suggesting that ADEM-like perivenous inflammatory demyelination was a characteristic finding of MOGAD. The early-phase demyelinating lesions of MOGAD exhibited MOG-dominant myelin loss with relatively preserved oligodendrocytes. This feature distinguishes MOGAD from anti-AQP4 autoantibody-related NMOSD, including pronounced perivascular deposition of immunoglobulins and complement together with demyelinating lesions containing myelin degradation products in numerous macrophages [18]. The pathologic features of MOGAD are clearly different from those of MS and NMOSD, suggesting an independent autoimmune demyelinating disease entity [16]. The optic nerve is a vulnerable organ in MOGAD which might be based on that both the protein and mRNA expression levels of MOG are higher in the optic nerve than in the spinal cord and brain in mice [19][20].

3. Treatment and Visual Outcome

There are currently no randomized control trials or evidence-based guidelines for the treatment of acute disease and relapse in patients with MOGAD [21]. In the acute stage, most patients with MOGAD are treated with high-dose methylprednisolone pulse therapy with or without intravenous immunoglobulin therapy (IVIg) and plasmapheresis, with favorable response observed. Recovery was significantly better in patients with anti-MOG autoantibodies than in those with anti-AQP4 autoantibodies who require additional plasmapheresis [22]. In patients displaying resistance to these mentioned treatments, alternative therapeutic approaches, such as immunosuppressants (azathioprine, cyclophosphamide, tacrolimus, mycophenolate mofetil), satralizumab, or B cell depletion therapy, may be considered [23][24][25][26]. In the nationwide survey of epidemiological and clinical characteristics of Japanese patients with MOGAD, the favorable therapeutic effect of tacrolimus was shown as 72.7% (40 out of 55 treated with tacrolimus) [27].

While monthly intravenous immunoglobulin treatment was associated with a reduction in annual relapse rate in pediatric and adult cohorts, 20–71% of treated patients experienced relapses [28]. Moreover, some disease-modifying treatments used for MS, including fingolimod or natalizumab, might induce severe relapse in patients with MOGAD [29].

3.1. Recent Novel Therapeutics

3.1.1. IL-6 Receptor Inhibitor

IL-6 is a proinflammatory cytokine whose signaling pathway is triggered by complement deposition; IL-6 promotes B cell stimulation, blood–brain barrier dysfunction, leukocyte migration, and cytokine and chemokine production [30][31][32]. In one study, 73% (n = 11) of the patients with MOGAD treated with tocilizumab, a humanized IL-6 receptor inhibitor, for 12 months remained relapse-free, which was higher than the relapse-free rate of 57% (n = 28) observed in patients with anti-AQP4 autoantibody-related NMOSD [32].

3.1.2. Rituximab

One of the most frequently used drugs in MOGAD is rituximab, which targets CD20+ B cells [33]. However, despite efficient B cell depletion, only 55% and 33% of the patients treated with rituximab were relapse-free in 1 and 2 years after

treatment, respectively [34]. Thus, B cell depletion was less effective in patients with MOGAD than in those with anti-AQP4 autoantibody-related NMOSD, indicating that B cells are not the only effector in MOGAD.

3.1.3. Inebilizumab

Regarding inebilizumab, a humanized anti-CD19 monoclonal antibody, six of seven patients with anti-MOG autoantibody positivity did not experience relapse during the follow-up period of 210 days [35]. Inebilizumab was generally well tolerated and the adverse event profile observed was similar to that of anti-AQP4-positive patients.

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