Neuromyelitis Optica Spectrum Disorders

Subjects: Pharmacology & Pharmacy
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Keywords: neuromyelitis optica spectrum disorders ; B cells

1. Introduction

Neuromyelitis optica spectrum disorders (NMOSD) are a heterogeneous group of monophasic or recurrent autoinflammatory diseases of the central nervous system (CNS). Characteristically, symptoms like severe loss of vision, weakness or paralysis of extremities, loss of sensation, bowel and bladder dysfunction, area postrema clinical syndrome or respiratory failure are the result of rapidly sequential or bilateral optic neuritis, longitudinally extensive myelitis and inflammatory brain lesions affecting the circumventricular organs [1]. The first description of a patient suffering from amaurosis associated with autoptic-proven myelitis by Antoine Portal dates back to the year 1804, while the systematic description of ‘myelitis optica’ by Devic and Gault appeared by the end of the 19th century [2]. For many years, NMOSD were considered prognostically unfavorable variants of multiple sclerosis. When specific pathogenic aquaporin-4 (AQP4) autoantibodies were detected in a major subset of patients at the beginning of the 21st century, NMOSD were finally considered to belong to a disease entity distinct from multiple sclerosis [3].

According to the current diagnostic guidelines of 2015, the presence of at least one core manifestation is sufficient for NMOSD diagnosis in anti-AQP4 seropositive patients, which are now considered classical neuromyelitis optica patients, while two manifestations including optic neuritis, myelitis or area postrema syndrome are required for seronegative patients [4]. Within the population of AQP4 negative patients, a subset has been identified expressing antibodies against myelin oligodendrocyte glycoprotein (MOG) [5]. Based on clinical, radiological and immunologic features, this condition, now called ‘MOG-immunoglobulin G (IgG)-associated encephalomyelitis’, is considered a separate disease entity, distinct from AQP4-positive neuromyelitis optica as well as from multiple sclerosis [6][7].

2. The Role of B Cells and Antibodies in NMOSD

The integral transmembrane protein AQP4 was discovered in 1984 and is capable of conducting water through the cell membrane. It is the most abundant type of water channel in the CNS, located specifically at the astrocytic foot processes, which form the blood-brain barrier (BBB), but also at ependyma and glia limitans [8]. Outside the CNS, it can be found in lower concentrations on the epithelial cells of many organs like kidney and stomach, but AQP4 tetramers aggregate different than within the CNS [9]. According to the current disease concept of seropositive NMOSD, autoantibodies directly targeting AQP4 penetrate the BBB or derive from peripheral plasmablasts within the CNS: Pathogenic binding of AQP4-IgG to AQP4 causes complement-dependent cytotoxicity and subsequent chemotaxis of eosinophils, neutrophils, macrophages and lymphocytes. This leads to a direct destruction of astrocytes with a secondary, irreversible demise of oligodendrocytes, axons and neurons [10]. In contrast to multiple sclerosis, cortical demyelination is only seen after years of ongoing disease activity [11]. Serum AQP4 autoantibody titers were shown to correlate with the size of spinal cord lesions, clinical disease activity and therapeutic response, as they decrease after immunotherapy and remain low during remissions [12].

Since antibody-producing cells like plasmablasts and plasma cells are derived from B lymphocytes, the role of this very lymphocyte compartment is crucial for the pathophysiology of NMOSD [13]. This goes along with the finding that in affected patients, the number of antibody-producing plasmablasts is strongly elevated in the peripheral blood, peaking at relapses [14]. It is worth noting that, in contrast to multiple sclerosis, plasmablasts can barely be detected in the cerebrospinal fluid (CSF) of NMOSD patients [15][16]. Accordingly, NMOSD is now considered a humoral autoimmune disorder, where anti-AQP4 antibodies are mainly produced in the periphery [10][17]. In line, oligoclonal bands are rarely seen in NMOSD patients, often disappearing during disease development [8]. An inflammation-induced opening of the BBB is supposed to

be a prerequisite for the entry of peripherally secreted autoantibodies into the CNS. This is supported by the observation that a subset of NMOSD patients shows signs of viral infections just prior to clinical relapses [18]. Astonishingly, the permeability of the BBB has also been reported to be increased by IgG antibodies themselves [19]. Upon binding to their target on the astrocytic endfeet, AQP4 antibodies trigger the complement cascade, leading to the formation of a membrane attack complex with subsequent astrocytic edema, dysfunction, destruction and secondary neuronal injury [20]. It must be noted that T cells are also thought to be required for the disruption of the BBB and the orchestration of the immune attack in the CNS [21].

Besides antibody-mediated effects, B lymphocytes also inherit two potent, cellular functions contributing to disease activity in NMOSD: Firstly, activated B cells are capable of secreting pro-inflammatory cytokines like interleukin-(IL-)6 and tumor necrosis factor, further fostering inflammatory processes, especially by generating T helper 17 cells [22][23]. Interestingly, IL-6 in turn also supports B cell activation and growth [23]. NMOSD patients indeed display elevated IL-6 in the CSF along with an elevated number of circulating T helper 17 and IL-17-producing cytotoxic T cells [21][24]. Secondly, B lymphocytes act as antigen-presenting cells by specifically binding antigens on their B cell receptor, before internalizing, processing and presenting them to T helper cells via major histocompatibility factor II molecules on their surface [25]. It was shown that the antigen-presenting function of B cells is required for the induction of experimental CNS autoimmunity independent of their humoral involvement [26].

In conclusion, B cells uniquely contribute to disease progression in NMOSD by the provision of autoantibodies, the secretion of cytokines and the presentation of antigen.

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