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Review article

The role of AQP4 in neuromyelitis optica: More answers, more questions

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ABSTRACT

Neuromyelitis optica (NMO) is a recurrent inflammatory disease that preferentially targets the optic nerves and spinal cord. The presence of antibodies to the water channel protein aquaporin-4 (AQP4), expressed almost exclusively in astrocytes in the central nervous system (CNS), is a reliable biomarker for NMO. These antibodies, NMO-IgG, may be responsible for the sequential cascade of immune events, including IgG/IgM deposition, infiltration of granulocytes and complement-mediated cytotoxicity (i.e. astrocyte loss) and demyelination. This review summarizes current thinking about the role of NMO-IgG in the pathogenesis of this condition. New insights were also generated along with important additional questions.

Contents

1. Introduction

Neuromyelitis optica (NMO), also known as Devic's disease, is a severe, immune-mediated demyelinating disease of the central nervous system (CNS) that predominantly affects optic nerves and spinal cord (Awad and Stuve, 2011; Sellner et al., 2010). It is a rare disorder with a prevalence of ~1/100,000 in Western countries (Collongues et al., 2010) but more common in non-Caucasians (Wingerchuk et al., 2007), such as inhabitants of the West Indies (27% of CNS demyelinating diseases (Cabre et al., 2001)), Japanese (20–30%) (Kira, 2003; Yamasaki et al., 1999), East Asians (36–48%) (Das and Puvanendran, 1998; Lau et

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al., 2002), African Caribbean inhabitants (17%) (Cabre et al., 2001) and African Americans (~50%) (Oh and Levy, 2012). Patients with NMO frequently have multiple autoimmune disorders such as Sjögren syndrome, systemic lupus erythematosus (SLE), Hashimoto thyroiditis, anti-cardiolipin syndrome, or myasthenia gravis, and may express a variety of non-organ-specific autoantibodies (Jacob et al., 2007; Pittock et al., 2008; Wingerchuk and Weinshenker, 2012).

Traditionally, NMO has been classified as a variant of multiple sclerosis (MS). Some NMO clinical and pathological characteristics (Lucchinetti et al., 2002), however, are atypical for MS and recently it was discovered that a high percentage of NMO patients, but not MS patients, have a circulating IgG autoantibody to the water channel protein expressed by astrocytes called aquaporin-4 (AQP4) (Lennon et al., 2004). These antibodies, termed AQP4 Ab or NMO-IgG, are reported in the sera of NMO patients, but not in patients with MS (Lennon et al., 2004, 2005). The discovery that a high percentage of NMO patients have antibodies to AQP4 has attracted the attention of neuroscientists because it suggests a plausible molecular mechanism of disease causation. Namely, that autoimmune attack of astrocyte AQP4 water channels leads to an anatomically restricted inflammatory demyelinating disorder. In this way, NMO occupies a unique position in the spectrum of demyelinating diseases because it is the only such disorder that has an associated disease-specific antibody (Oh and Levy, 2012; Papadopoulos and Verkman, 2012a).

A convincing, but not conclusive, body of evidence supports the idea that AQP4 autoantibodies are involved in the pathogenesis of NMO and that modulating these autoantibodies has promise as a therapy for NMO (Awad and Stuve, 2011; Papadopoulos and Verkman, 2012b). Many important unsolved questions about this proposed relationship remain, however. For example, if NMO-IgG is pathogenic, why is the clinical pathology restricted to the optic nerves and spinal cord when AQP4 is expressed on astrocytes throughout the CNS and elsewhere in the body? What incites formation of AQP4 autoantibodies? Why is there no quantitative relationship between the sera titers of NMO-IgG and clinical manifestations, either at the time of diagnosis or after modulating antibody titer with interferon-β (INF-β) or immunosuppressive drugs? Some patients with clinically apparent NMO do not express AQP4 antibodies (e.g., Kitley et al., 2013). Are there other mechanisms that can cause this disease? Might this imply that AQP4 antibodies are only a useful biomarker, not the primary cause of NMO? There are conditions that resemble NMO but are more limited in their clinical manifestations such as sero-positive isolated longitudinally extended transverse myelitis (LETM) or optic neuritis (ON) (Miller et al., 2008; Papadopoulos and Verkman, 2012a; Sellner et al., 2010). Do these conditions have a similar pathophysiology? New drugs targeting NMO-IgG have entered into clinical trials (e.g., aquaporumab (a non-pathogenic antibody that blocks binding of AQP4-IgG), sivelestat (neutrophil elastase inhibitor), and eculizumab (complement inhibitor)), but remain unproven as effective therapies for NMO. This review on NMO focuses on what is known about this intriguing disease and draws attention to aspects of the disease that remain perplexing or poorly understood. Progress on the unanswered questions may lead to the next important breakthroughs in managing this challenging disease. These answers may also expand our general understanding about the molecular mechanisms underlying acute immune demyelination.

2. Aquaporins in the brain

Aquaporins (AQPs) are a family of membrane proteins that facilitate *trans*-membrane water movement, and are therefore referred to as 'water channel proteins' (Agre et al., 1993). These proteins were discovered in 1992 and a Nobel Prize was awarded for this achievement in 2003 (Miller, 2003). At present, 13 isoforms are known and AQP4 is the predominant form expressed in rodent brain, although small amounts of AQP1 and AQP9 are also detected (Zelenina, 2010). Electron microscopic (EM) studies have established that AQP4 is largely confined to astrocytes and ependymal cells (Amiry-Moghaddam et al., 2003; Papadopoulos and Verkman, 2012b; Zelenina, 2010). Astrocytes are complex cells that are often described as 'polarized' in the sense that they make anatomically specialized contacts, called 'endfeet', with blood vessels and with the pial layer of the meninges. Astrocyte endfeet enwrap cerebral blood vessels of all sizes and form the glial component of the plial-glial membrane (Mathiisen et al., 2010). Certain proteins are highly expressed on those endfeet including the inward rectifying K+ channel (Kir4.1), glucose transporters, Na^+/K^+ ATPase and AQPs (Jo et al., 2015; MacAulay and Zeuthen, 2010; Nagelhus et al., 2004). This arrangement of proteins endows the endfoot with special functional properties such as glucose uptake from blood and high water permeability.

Astrocytes in primates, including humans, have unique characteristics in comparison to rodent astrocytes (Oberheim et al., 2009). Human protoplasmic astrocytes are 2.6 times larger in diameter and have 10-fold more processes than protoplasmic astrocytes in rodents. Aquaporin expression in astrocytes is also different in primates, compared to rodents (Arcienega et al., 2010; Satoh et al., 2007). In primates, but not in rodents, AQP1 expression is roughly equal to AQP4 expression. Macroscopically, AQP4 is primarily expressed in grey matter while AQP1 is primarily expressed in white matter (Fig. 1). Microscopically, AQP4 is seen in the perivascular endfeet of astrocytes throughout the brain while AQP1 is seen predominately in the processes and endfeet of fibrous astrocytes, the subtype found exclusively in white matter (Arcienega et al., 2010; Satoh et al., 2007). Both AQP1 and AQP4 are seen in the pial-glial membrane covering the brain's surface. It has been suggested that less AQP4 is expressed in white matter because capillary density is lower in white matter compared to grey matter (Arcienega et al., 2010). Meanwhile, it is important to point out that white matter is greatly expanded in primates (~50% of forebrain volume) compared to rodents (<15% volume). AQP1 is highly expressed in choroid plexus endothelial cells, gallbladder, pancreas and cortex of kidney (Mobasheri and Marples, 2004; Nielsen et al., 1993). This distribution of AQP4 and AQP1 may account for the distinctive pathological features of NMO compared to typical MS, which mainly affects the white matter of brain.

Beneath astrocytic endfeet, vascular endothelial cells exhibit a curious lack of AQPs (AQP1 and AQP4) (Amiry-Moghaddam et al., 2003; Kobayashi et al., 2001; Nielsen et al., 1997). Blood vessel endothelial cells virtually everywhere else express AQP1 (Nielsen et al., 1993). This is obviously a design feature that likely contributes in some way to the special protection afforded by the blood-brain-barrier. In fact, it appears that astrocytes somehow suppress AQP1 expression in brain endothelial cells (Dolman et al., 2005). Finally, it is important to appreciate that AQP expression can be altered in certain disease states. Reactive astrocytes, for example, promote the expression of AQP1 (Arcienega et al., 2010). It would be important to know the pattern of AQP expression in patients with NMO.

3. Consequences of AQP4 antibody binding to AQP4 in NMO

No study to date has investigated the direct involvement of AQP4 in neuroinflammation, but several groups have explored the pathogenic role of AQP4 IgG. Sera from NMO patients showed immunoreactivity with AQP4 in mice followed by astrocyte loss and complement deposition in the lesions of inflammatory demyelination. Administration of NMO-IgG to the animal with EAE or along with complement to naïve animals produced pathology characteristic of NMO (Li et al., 2011). The NMO-IgG has been found capable of binding with AQP4, which could impair water flux directly (Hinson et al., 2012). A possible physiological consequence might be disruption of the recently described 'glymphatic system' that cleanses brain extracellular space (Lliff et al., 2012).

From an immunological perspective, Verkman summarized that antibodies can have several functional effects when bound to their target: modification of target function; target internalization, reducing surface expression; complement activation to cause cell death (complement-dependent cytotoxicity); and activation of effect cells, such as natural