REVIEW

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Neuromyelitis optica spectrum disorder: an overview

Pooja Ramakrishnan and Devipriya Nagarajan*

Radiation Biology Laboratory, School of Chemical and Biotechnology, SASTRA University, Thanjavur, Tamil Nadu, India,
** E-mail: devipriya@scbt.sastra.edu*

Neuromyelitis optica also known as Devic's syndrome is a rare autoimmune disorder that predominantly targets the optic nerves and the spinal cord. It is a debilitating disorder that damages a person's health. Initially it was considered as a variant of multiple sclerosis (MS). But, in 2004, a water channel protein associated antibody was found to be responsible for the disease. This helped in distinguishing the disease from multiple sclerosis. Multiple molecular mechanisms like complement dependent cytotoxicity, antibody-dependent cellular cytotoxicity etc. contribute to the disease. Certain environmental and genetic factors have been identified as risk factors of the disease. Initially, the disease was thought to affect only the optic nerves and the spinal cord. But certain regions of the brain have also been found to be attacked during the course of the disease. A small proportion of the patients have been found to be seronegative for the AQP4-IgG. Recently, the term neuromyelitis optica spectrum disorder has been framed to include all the features of the disease. The disease remains incurable despite the availability of various treatment modalities. This review presents critical information obtained from prior studies regarding the disease and also raise several questions to understand the research gaps in this field.

Key words: neuromyelitis optica, AQP4, ADCC, CDC, multiple sclerosis, NMOSD, pain, Th17 cytokines

INTRODUCTION

The human immune system is a highly complex and regulated system and its primary function is to defend the body against harmful pathogens (Chaplin, 2010; Nicholson, 2016). Dysregulation of the immune system can result in the development of autoimmune disorders wherein the immune system starts reacting to self-molecules (Wang et al., 2015; Rosenblum et al., 2015). Autoimmunity has several unfortunate targets with the nervous system being one amongst them. Autoimmune disorders initially cause inflammation and are progressive in nature. When autoimmunity is directed towards the components of the nervous system, it causes neuro-inflammation and ultimately neurodegeneration (Rubin et al., 2018, López- Chiriboga and Flanagan 2018). Neuromyelitis optica (NMO) is a rare, autoimmune, inflammatory, demyelinating and neurodegenerative disorder of the central nervous system (CNS). The characteristic symptoms of the disease are optic neuritis and myelitis (Jarius et al., 2014). For several years, NMO was considered to be a variant of the disease multiple sclerosis (MS), a CNS autoimmune disorder that results in severe demyelination. In 2004, antibody specific for the water channel protein called aquaporin 4 (AQP4) was found to cause NMO which led to NMO being identified as a separate disease (Lennon et al., 2004). Initially when identified, the disease was thought to present necrotic and demyelinating lesions only in the optic nerve and the spinal cord (Devic, 1894). So NMO was thought to preferentially attack only the optic nerves and the spinal cord and not the brain. Over the years, however, evidence from various studies have proven that several regions of the brain are also affected during the course of the disease (Pittock et al., 2006; Chan et al., 2011; Kim et al., 2012). Additionally, some patients presenting the features of the disease were found to be seronegative for anti-AQP4 antibodies (Jiao et al., 2013; Sato et al., 2014; Badri et al., 2016). These findings necessitated the need for coining a new term "neuromyelitis optica spectrum disorders (NMOSD)" to describe all the fea-

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tures of the disease (Wingerchuk et al., 2015). This review provides a basic overview of the disease based on the major findings pertaining to the disease.

HISTORY

In 1894, Eugéne Devic, a French neurologist reported the case of a 45-year old French woman admitted at the Hôtel-Dieu Hospital, Lyon in 1892 (Devic, 1894). The woman suffered from unmanageable headache and depression. She later developed urinary retention, complete paraplegia and blindness and died within a few months. Her autopsy revealed lesions with severe demyelination, necrosis and cellular infiltration in the spinal cord and optic nerves. Devic (1894) pointed out the similarities of the disease with multiple sclerosis but also identified the distinctive localization of the disease to the optic nerves and spinal cord. Following him, his doctoral student Gault studied 17 cases of the same disease in detail. In 1907, the eponym Devic's disease was suggested by Acchiote (1907), (Miyazawa et al., 2002). However, the term neuromyelitis optica was coined by Devic (Uzawa et al., 2013). In the following years, case studies showed that NMO doesn't attack the optic nerves and spinal cord alone but also some regions of the brain (Pittock et al., 2006; Wingerchuk et al., 2007). Some of the patients who presented the disease symptoms were found to be seronegative for the AQP4-antibody that causes the disease. Therefore, to include all these observations and improve disease diagnosis, Wingerchuk et al. (2015) coined the term NMOSD.

EPIDEMIOLOGY

Age of onset

There is no accurate median age of onset in NMOSD. However, it ranges between 30-40 years. Geographical and racial differences have been observed with respect to the age of onset. Data obtained from prevalence studies indicate that the median age of onset is 30 years in Denmark (Asgari et al., 2011), 30.5 years in Cuba (Cabrera-Gómez et al., 2009), 39.5 years in South east Wales (Cossburn et al., 2012) and 55.2 years in Austria (Aboul-Enein et al., 2013). In a study conducted by Kim et al. (2018) Afro-American/Afro-European and Asian patients displayed an earlier age of onset compared to Caucasian patients. The mean ages of onset were 35.8 and 33.4 for Asian and Afro-American/Afro-European patients respectively. Whereas in Caucasian patients it was 43.8 (Kim et al., 2018).

Although rare, 3-5% of patients can have a paediatric onset (Quek et al., 2012). The paediatric age of onset is below 18 years typically ranging between 10-12 years (Chitnis et al., 2016). But, NMOSD has been reported in a patient as young as 16 months as well (Quek et al., 2012). In one study that analysed paediatric NMOSD, differences in ethnicities was observed. Of the affected individuals, 37% were Afro-American, 11 % were Asian and 13% were Hispanic/Latino (Chitnis et al., 2016).

In contrast to paediatric onset, late onset NMOSD accounted for about 25% of cases in a cohort study (Quek et al., 2012). The median age of onset for late NMOSD is >50 years. A retrospective study that studied late onset NMOSD utilized a total of 37 patients. Of the 37 patients analysed, 22 were whites and 15 were Africans (Fragoso et al., 2019). From the above discussed results, ethnic differences seem to be important in determining the age of onset. In general, Afro-American patients tend to have a younger age of onset. Studies involving patients from other parts of the world are needed to clearly understand the role of ethnicity.

Incidence and prevalence

Several studies have investigated the incidence rates of NMOSD in different regions of the world. In a Cuban population incidence rate was identified to be 0.053 per 100,000 individuals (Cabrera-Gómez et al., 2019). One prospective study identified the incidence rate of NMOSD to be 0.07 per 100,000 persons in Denmark (Papp et al., 2018). In Sweden, the average yearly incidence rate was found to be 0.79 per 1 million persons (Jonsson et al., 2019). The incidence rate of NMOSD in Merseyside county, UK was found to be 0.8 per million persons (Jacob et al., 2013). One group of investigators identified the incidence rate of NMOSD per year in Australia and New Zealand to be 0.33 per million individuals (Bukhari et al., 2017). In a Catalonian study, 47 patients were studied and the incidence rate was calculated to be 0.63 per million individuals (Sepúlveda et al., 2017). In Martinique and Guadeloupe (The French West Indies), an incidence rate of 0.19 per 100,000 individuals was calculated (Cabre, 2009). A retrospective study identified the NMOSD incidence rate in Austria to be 0.054 per 100,000 persons (Aboul-Enein et al., 2013). Different groups of investigators have studied the prevalence rates in various regions. The prevalence rates were found to be 0.52 per 100,000 in Cuba, 1.09 per 100,000 persons in Denmark (Papp et al., 2018), 10.4 per 1 million individuals in Sweden (Jonsson et al., 2019), 7.2 per million persons in the Merseyside county, UK (Jacob et al., 2013), 0.7 per 100,000 individuals in Australia and New Zealand (Bukhari et al., 2017),

0.89 per 100,000 in Catalonia (Sepúlveda et al., 2017), 0.71 per 100,000 in Austria (Aboul-Enein et al., 2013), 2.6 per 100, 000 persons in India (Pandit 2015) and 4.1 per 100,000 in Japan (Houzen et al., 2017).

From these studies, a wide range in incidence and prevalence can be observed suggesting that geographical and ethnic differences are key determinants of NMOSD incidence and prevalence.

IMMUNOPATHOGENIC MECHANISMS

Aquaporin 4 – the target autoantigen

Aquaporins are membrane proteins that serve as water channels. Around 13 distinctive families of aquaporins have been identified which are expressed in various organs like the brain, blood vessels, kidney tubules, eye, ear etc. (Takata et al., 2004). Among them, AQP4 has been identified as the target antigen in NMOSD (Lennon et al., 2004). Although AQP4 is present in other organs like the kidneys etc., its expression is highest in the CNS, particularly in the astrocytic foot processes of optic nerve, spinal cord and brain regions such as area postrema, hypothalamus etc. (Neely et al., 1999; Matiello et al., 2013; Gleiser et al., 2016). AQP4 is required for the clearance of interstitial water, waste and various soluble proteins in the brain (Nagelhus and Ottersen, 2013; Mitsdoerffer et al., 2013). In most NMOSD patients, AQP4 is targeted by self-reactive immunoglobulin G (IgG) antibodies called the NMO-IgG or AQP4-IgG (Lennon et al., 2004). AQP4 forms groups of tetramers called orthogonal arrays of particles (OAPs) mainly in the membranes of astrocytes (Bukhari et al., 2012). AQP4-IgGs or the NMO-IgGs have a predilection for binding to OAPs. After binding, AQP4-IgG initiates the complement dependent cytotoxicity (CDC) pathway that leads to the development of necrotic lesions through the formation of membrane attack complex (MAC). Apart from MAC formation, CDC also produces chemotaxins which in turn amplify CDC through cellular infiltration and cytokine production (Lachmann et al., 1984; Ricklin et al., 2010; Zhang et al., 2011; Bukhari et al., 2012; Rateldale et al., 2012; Soltys et al., 2019). Once cellular infiltration occurs, the anti- AQP4 IgG interacts with the natural killer (NK) cells and causes antibody-dependent cellular cytotoxicity (ADCC) resulting in astrocyte death (Rateldale et al., 2012) which is identified by the loss of glial fibrillary acidic protein (GFAP), the astrocytic marker (Misu et al., 2005). Glutamate is an excitatory neurotransmitter which when present in excessive amounts is highly toxic. One of the important functions of astrocytes is to uptake the excessive glutamate. Since glutamate uptake is an important function of astrocytes, a major consequence of astrocyte damage is glutamate excitotoxicity (Schousboe et al., 2004). Glutamate excitotoxicity is hypothesised to damage the oligodendrocytes and cause demyelination (Hinson et al., 2008; Marignier et al., 2010). Since astrocytes are mainly lost, NMOSD is usually considered as an astrocytopathic disease (Fujihara et al., 2012; Lucchinetti et al., 2014; Bennett and Owens, 2017).

Role of microglia in disease development

Microglia are the myeloid cells that reside in the CNS (Wake and Fields, 2011; Ransohoff and Khoury, 2015). The role of microglia in NMOSD progression is still elusive. Astrocyte death is believed to cause autoimmune microglial activation (Serhan and Savill, 2005; Serhan, 2007; Levy et al., 2014). Various studies have shown that activated microglia respond to astrocyte death by mediating blood brain barrier (BBB) disruption through cytokines' and inflammatory modulators' release (da Fonseca et al., 2014; Shigemoto-Mogami et al., 2018; Chen et al., 2019; Thurgur and Pinteaux, 2019). Disrupted BBB then paves the way for the peripheral immune cells to the CNS which then cause neuro-inflammation (Levy et al., 2014). In addition to neuro-inflammation, microglial activation is also believed to play a role in demyelination. However, its role in demyelination is not fully delineated. A study that analysed the immunoreactivity of myelin specific recombinant IgGs utilizing mice identified that microglial activation accompanied demyelination (Liu et al., 2017). In another study, transcriptome analyses and functional assays indicated that microglial activation helps in removal of myelin debris, secretion of growth factors and extracellular matrix (ECM) remodelling needed for remyelination (Lloyd et al., 2017; Liu et al., 2018). From the above discussed findings, it can be assumed that microglial activation plays a dual role depending on disease severity. Time-dependent studies are required to identify whether or not activated microglia play a role in demyelination.

Immune dysregulation and molecular mimicry by infectious microbes

Recent studies suggest *Helicobacter pylori (H. pylori)* infection as an NMOSD risk factor (Long et al., 2013; Zaidi et al., 2016). A large number of patients have been found to be seropositive for *H. pylori* infection and anti-HP-NAP antibodies (Li et al., 2009; Long et al., 2013). This is because *H. pylori* possesses the *H. pylori* neutrophil-activating protein (HP-NAP), a virulence

factor that recruits and activates neutrophils (D'Elios et al., 2007) through the T-helper 17 (Th17) pathway (Algood et al., 2007; Caruso et al., 2007). *H. pylori* is also believed to trigger an abnormal immune response through antigen cross presentation since it possesses some water channel proteins that might resemble AQP4. This phenomenon is called molecular mimicry (Kira and Isobe, 2019).

T-cell dependent humoral response towards AQP4 is one of the driving forces of NMOSD progression (Lennon et al., 2005). A recent discovery pointed out that the amino acids 66-75 of AQP4 peptide (p) 63–76 recognised by the T-cells in NMOSD share a 90% homology with the amino acids 207-216 of *Clostridium perfringens*' adenosine triphosphate-binding cassette transporter permease (ABC-TP). The AQP4 T-cells exhibited cross reactivity with ABC-TP in addition to manifesting a Th17 polarization. Based on the findings, researchers have proposed three hypotheses. First, gut microbes could be a potential link to NMOSD. Second, excessive presence of *C. perfringens* could be causing immune dysregulation and NMOSD susceptibility. Third, *C. perfringens* might be playing a role in other CNS autoimmune disorders as well (Cree et al., 2016). *C. perfringens* has been shown to secrete more than 20 different toxins (Revitt-Mills et al., 2015; Kiu and Hall, 2018) and it is one of the common causes of food poisoning (Briggs et al., 2011). The toxins secreted could trigger an abnormal immune response or they could act as immunological adjuvants that could culminate in NMOSD and therefore their roles need to be studied as well. Studies should be conducted to see if NMOSD patients have an history of food poisoning caused due to *C. perfringens. C. perfringens* has been considered as a risk factor mainly because of its ability to cross-react. ABC-TP could be highly conserved in different members of the genus *Clostridium*. Role of other *Clostridium spp.* present in the gut microbiota should be evaluated as well. *C. perfringens* is part of the normal gut flora and therefore it is commonly present. On the contrary, the disease NMOSD is extremely rare. This insinuates that for C. perfringens to be an NMOSD risk factor, it needs to act in concert with other risk factors.

Mumps, an infection caused by the mumps virus is primarily characterised by the inflammation of the salivary glands. CNS is commonly affected in mumps patients (Bruyn et al., 1957). A study aimed at analysing the relationship between viruses and NMO identified that 25% of the 8 NMO patients harboured mumps viral RNA in their cerebrospinal fluid (CSF). An interesting observation is that both the patients were women and their expanded disability status scale (EDSS) was 9 (Mori et al., 2011). Another group of researchers found that 7 of the 15 patients had viral specific IgM in their sera. Of the 7, 3 patients were found to have mumps infection (Koga et al., 2011). An observational study conducted using 25 NMO patients identified 76% of patients with anti-mumps IgG in their sera. The researchers concluded that the high levels of IgG titre may indicate an older infection (Jazini et al., 2019). The results of these studies are not highly significant to prove mumps virus as a significant risk factor. A major limitation of these studies is the lower sample size. Of the few patient samples analysed, diminutive samples show a positive correlation between NMOSD and mumps virus. From these studies mumps virus cannot be considered as a causative agent but it may accelerate the disease progression by aiding in neurodegeneration. This is because encephalomyelitis is a serious complication of the CNS caused by mumps virus (Bruyn et al., 1957; Unal et al., 2005). The EDSS of 9 in the 2 patients of the first study supports this hypothesis. Studies involving larger samples are required. Even if a positive correlation is obtained between mumps virus and NMOSD, how mumps virus accelerates NMOSD needs to be investigated.

Cellular infiltration and adaptive immunity

As discussed above, binding of AQP4-IgG along with microglial activation causes cellular infiltration. Among the cells, neutrophils and eosinophils play crucial roles in disease continuance. Following BBB disruption, the levels of peripheral immune cells in the CSF increase significantly (Jarius et al., 2011). ENA 78, a chemokine causes neutrophil and eosinophil migration, aggregation and hyper activation (Persson et al., 2003; Yang et al., 2016). Upon activation, they cause cellular damage mainly through degranulation and phagocytosis (Segal, 2005; Levy et al., 2014). Cellular infiltration amplifies adaptive immune responses. NMOSD is primarily an antibody-mediated disease but T-cells are equally important for disease sustenance. T-cells respond with a greater magnitude and frequency to AQP4 in NMO patients. Among all the T-cell subtypes, Th17 subtype is known to increase antibody production in naïve B-cells and the cytokines produced by them play a very crucial role in NMOSD (Varrin-Doyer et al., 2012). Although peptides 21-40 (p21-40) of AQP4 have been shown to form the immunodominant determinant required for CD4+ T- cells (Nelson et al., 2010), AQP4 p61-80 have been found to constitute the T-cell determinant which is targeted by pathogenic AQP4-IgGs' and p61-80 specific Th17 cells are present in greater numbers in NMOSD (Varrin-Doyer et al., 2012). Plasma cells produce IgG in the bone marrow (Radbruch et al., 2006). Plasmablasts, the plasma cell precursors are present in large numbers in the CSF of NMOSD patients. Clonally

expanded populations of AQP4 targeting plasmablasts have been identified in NMOSD (Bennett et al., 2009). B-cells have been suggested to expedite disease development by secreting pro-inflammatory cytokines such as IL-6 that initiate pathogenic T-cell responses. These T-cell responses increase autoantibody production (Varrin-Doyer et al., 2012; Bennet et al., 2015). The trigger(s) for auto-antibody production remains unknown. Pre-germinal centre failure of self-tolerance in B-cells has been suggested as an initiating factor for auto-antibody production since naïve B-cells were seen to produce AQP4-IgG. Once the disease has started, the presence of antigen isn't required for continuing auto antibody production (Wilson et al., 2018).

Th17 cytokines – the disease accelerators

Cytokines, which are proteins secreted by certain immune cells like macrophages etc. play a key role in inflammation and the development of pathological pain states (Zhang and An, 2007). Since NMOSD is an autoimmune disorder, cytokines play essential roles in disease progression. Several researchers who have analysed the cytokine levels in NMOSD found IL-6, IL-17, IL-21 and IL-1β, the Th17 cytokines to be elevated in majority of the cases (Ishizu et al., 2005; Wang et al., 2011; Herges et al., 2012; Wu et al., 2012; Linhares et al., 2013; Barros et al., 2015). One study reported elevated IL-6 levels in patients with the relapsing form of NMOSD and proposed IL-6 to be a key player in NMOSD progression (Uzawa et al., 2013). This hypothesis can be proved by previous studies which demonstrated that IL-6 causes progressive weakness with myelin loss, inflammation and dendrite degeneration (Kaplin et al., 2005) and also exacerbates spinal cord lesions in mice (Zhang et al., 2011). IL-6 could be a pro-nociceptive cytokine since administration of anti-IL6 antibodies reduced pain sensitivity in rats (Wei et al., 2013; Bradl et al., 2014). In that case, tocilizumab, an IL-6 targeting monoclonal antibody might be a potential therapeutic agent for treating pain in NMOSD. IL-17 might be contributing to NMOSD progression through auto-antibody production (Hsu et al., 2008; Vaknin-Dembinsky et al., 2016), neutrophil infiltration (Ishizu et al., 2005; Wojkowska et al., 2014) and NMDA-receptor mediated nociception (Meng et al., 2013). IL-21 is capable of promoting Th17 cell proliferation while simultaneously inhibiting T-reg cell differentiation (Barros et al., 2013) and therefore might be increasing disease severity (Wu et al., 2012). A recent study suggests that IL-1β contributes to necrosis and disease severity by accumulating complement proteins, facilitating neutrophil entry, exacerbating lesions, mediating BBB breakdown and increasing cellular infiltration (Kitic et al., 2013). IL-1β also enhances nociception by enhancing glutamatergic signalling (Gruber-Schoffnegger et al., 2013). An inference that can be made from these findings is that these cytokines do not play independent roles in NMOSD progression. Instead, they appear to be playing an interlinked and synergistic role. Rather than targeting the individual cytokines, inhibitors that target the Th17 cells might be beneficial in curbing disease progression, severity and pain.

AQP4 IgG SERONEGATIVE NMOSD

Over the years, a small proportion of patients have been found to be seronegative for AQP4-IgG. Seronegative NMOSD cases do not exhibit female preponderance. Caucasian patients are frequently affected compared to other ethnicities. Simultaneous manifestation of optic neuritis and myelitis is observed during disease onset. Visual impairment has been found to be less severe in seronegative patients (Marignier et al., 2013). Approximately 40% of seronegative patients have been found to present NMOSD symptoms with anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibodies (Hamid et al., 2017). MOG is a protein located on the myelin sheath. Anti-MOG mediated disease was found to be non-astrocytopathic. Differences in disease patterns such as lack of optic chiasm involvement have been observed in anti-MOG disease. Some anti-MOG positive patients do not fulfil the diagnostic criteria. These findings indicate that anti-MOG disease might a distinctive clinical entity (Kaneko et al., 2016). A subset of patients presenting NMOSD symptoms but seronegative for both AQP4 and MOG have also been identified (Sato et al., 2014). The target antigen in such patients remains unknown.

PATHOLOGY OF NMOSD

General pathology of NMOSD lesions

NMOSD as discussed previously is an astrocytopathic disease characterised by a range of lesions. Lucchinetti et al. (2002) analysed the role of humoral mechanisms in NMO lesion pathology. The group examined around 82 lesions which were categorised into 4 categories namely early active demyelinating lesions, late active demyelinating lesions, remyelinating lesions and inactive demyelinated lesions. Early active demyelinating lesions showed diffuse infiltration of macrophages that were immunoreactive for all myelin proteins. Late active demyelinating lesions showed greater

myelin degradation and were immunoreactive for the major myelin proteins myelin basic protein (MBP) and myelin proteolipid protein (PLP). Irregular arrangement of uniformly thin myelin sheaths was observed in remyelinating lesions and the inactive demyelinated lesions exhibited complete demyelination without any active demyelinating processes. The active lesions exhibited profound inflammation and abundant granulocyte infiltration. Excessive complement activation along with vascular fibrosis were observed in the active lesions. Preferential activation of the MAC in the perivascular regions was indicated by the presence of C9neo, an epitope of the complement C9. Extensive microglial activation was also observed in the active lesions (Lucchinetti et al., 2002). Misu et al. (2013) further classified the active lesions into 6 types based on the extent of immune infiltration and tissue injury. Type-1 lesions exhibited profound immunoglobulin deposition, complement activation and granulocyte infiltration. In these lesions, some astrocytes and their processes were either partly covered with activated complement or were partially lost. Cell necrosis was evident in these astrocytes and was characterised by the presence of fragmented and diffusely distributed DNA. These lesions also underwent active demyelination characterised by the presence of myelin degradation products and loss of oligodendrocytes. Type-2 lesions were characterised by the loss of cell components which were replaced by fluid filled cysts. Lesions exhibited macrophage infiltration and AQP4 loss (Misu et al., 2013). GFAP-positive debris along with disintegrated astrocytes were also observed in cystic lesions in a different study (Parratt and Prineas, 2010). Type-3 lesions were those present in the spinal cord white matter and displayed profound loss of myelin, axons and oligodendrocytes along with gliosis. Type-4 lesions were the lesions present near the active lesions. These were characterized by mild to moderate immune filtration without complement activation. Complete loss of AQP4 was evident in these lesions. Type-5 lesions showed immune filtration consisting mainly T-cells and macrophages. Clasmatodendrosis of astrocytes was profound in these lesions. Type-6 lesions were separate areas with complete demyelination. They displayed extensive loss of axons and oligodendrocytes. T-cell and macrophage infiltration was excessive. Variable degree of astrocyte damage and GFAP reactivity were observed (Misu et al., 2013). The diversity of lesions observed reinforce the fact that multiple immune mechanisms drive NMOSD. Therefore, development of combinatorial therapies that can simultaneously curb different pathways might help in the treatment of NMOSD. A limitation in the above discussed studies is that the patients were selected based on the diagnostic criteria formed in 2006. AQP4 seronegativity and involvement of brain regions were introduced in the revised criteria formed in 2015. Therefore, pathological studies utilizing patients selected according to the 2015 Wingerchuk clinical criteria will provide an insight into the mechanisms involved in seronegative NMOSD.

The anterior visual pathway lesions

Optic neuritis (ON) is one of the first symptoms of NMOSD in most patients. ON is caused due to severe damage to the structures of the anterior visual pathway which includes the optic nerves, retina, chiasm and the optic tracts. ON is a symptom of MS as well. But, ON in NMOSD tends to be more severe and recurrent with a greater reduction in the visual activity. This is due to the unique and more damaging lesion pattern observed in NMOSD that have been characterized *via* MRI studies. The median length of optic nerve lesions in NMOSD is 28.2 mm whereas in MS, it is 10.5 mm. The optic nerve lesions in NMOSD are usually bilateral and longitudinally extensive involving 2 or more optic nerve segments i.e., more than half the length of the optic nerve. Contrastingly in MS, the lesions are usually focal and localized to one segment. Moreover, lesions observed in MS are in the anterior regions of the optic nerve. But, in NMOSD, lesions are localized in more posterior regions of the optic nerve and often involve the optic chiasm (Khanna et al., 2012; Mealy et al., 2015). In one study reported by Li et al. (2008) 33 patients were studied. Among them, 16 patients reported recurrent optic neuritis. The optic nerve MRIs of the 16 patients were analysed and optic nerve sheath thickening was found in all the cases indicating optic nerve inflammation and edema (Li et al., 2008). In another study that utilized 10 patients MRIs of 6 patients exhibited optic nerve hypersensitivity (Wang et al., 2011). Optic nerve atrophy is also observed in some chronic patients (Dutra et al., 2018). Optical coherence tomography tests of ON eyes exhibit significant thinning of the retinal nerve fibre layer and ganglion cell complex. (de Seze et al., 2009; Hokari et al., 2016; Shen et al., 2019). Microcystic macular edema (MME) caused due to alterations in the inner nuclear layer of the retina has been observed in about 20% of NMOSD patients. MME is not unique to NMOSD and therefore the exact mechanisms that cause MME in NMOSD patients remain unknown (Sotirchos et al., 2013; Kaufhold et al., 2013; Gelfand et al., 2013). Severe axonal damage including axonal loss, swollen axons and axonal spheroids are observed in NMOSD patients. The mitochondria in the axons were found to be shortened, fragmented or swollen indicating that

mitochondrial damage plays a key role in axonal damage. In addition to mitochondrial damage, aberrant expression of the cation channel protein TRPM4 was also observed in swollen and damaged axons. The anterior visual pathway lesions are mostly astrocyte-destructive lesions and are caused due to a breach in the pial septa, a structure that serves as an immunological barrier against the CNS immune infiltrates. Microglial activation characterized by the increased expression of Iba-1, a microglia specific protein has been observed. This microglial activation results in the production of matrix metalloproteinase which disrupts the pial septa. Subsequently, T-cells direct the immune attacks against the various structures. Apart from this, optic nerve faces direct damage through AQP4-IgG mediated mechanisms such as CDC, ADCC etc. since astrocytic endfeet in the optic nerve express great amounts of OAPs (Hokari et al., 2012). Mueller cells, the astrocytic cells of the retina are highly targeted in NMOSD since they greatly express AQP4. Mueller cells have been found to be targeted in a complement-independent manner. Studies involving experimental models showed that the blood retinal barrier (BRB) was infiltrated by T-cells which then activated the microglia thereby causing retinal damage (Felix et al., 2016; Zeka et al., 2016; 2017).

Spinal cord lesions

Longitudinally extensive transverse myelitis (LETM) is one of the important clinical features of NMOSD (Wingerchuk et al., 2015). LETM is caused due to lesion formation in the spinal cord. Typical NMOSD spinal cord lesions are longitudinally extensive and involve 3 or more vertebral segments (Wingerchuk et al., 2007). Nakamura et al. (2008) identified that the lesions predominantly involve the central grey matter of the spinal cord which expresses AQP4 abundantly. These lesions were found to exhibit AQP4 loss together with increased vascular proliferation, cavity formation and necrosis. Gliosis was identified in the region surrounding the lesions (Misu et al., 2006). The segments that are mostly affected by the lesions include the cervical, thoracic or cervicothoracic segments. Lesions affecting the cervical region can extend into the brainstem. Spinal cord magnetic resonance images (MRI) show that the lesions are usually located centrally or both centrally and peripherally and involve ≥50% of cord area (Pekcevik et al., 2016). Two MRI features have been described to distinguish NMOSD lesions from other spinal cord lesions. Bright spotty lesions (BSLs) with strong hypersensitivity in T2-weighted images and dark lesions on T1-weighted images. These lesions are believed to be caused due to severe necrosis, focal edema and microcystic alterations driven by profound spinal cord demyelination (Yonezu et al., 2014; Pekcevik et al., 2016). Although not common, ring-enhancement lesions in the spinal cord also occurs in around 32% of patients and helps distinguish NMOSD from other cases of longitudinally extensive myelitis. The ring enhancement lesions are often lens shaped and are often found to enclose a bright spotty lesion. In 44% of patients with myelitis, ring enhancement lesions were found to involve 3 or more vertebral segments. Pathological features of ring enhancement lesions have not been widely studied. Yet biopsy of one patient revealed that the edges of ring enhancement lesions exhibited profound demyelination along with AQP4 loss and gliosis without macrophage infiltration (Zalewski et al., 2017). Spinal cord atrophy has been observed in some NMOSD patients without any prior history of myelitis indicating that spinal cord atrophy might occur prior to neurodegenerative attacks and lesion formation (Ventura et al., 2016). Spinal cord atrophy along with fragmented lesions have also been observed during remission (Asgari et al., 2013; Wingerchuk et al., 2015). Apart from the central grey matter, posterior and lateral column white matter was also found to be affected during the early stages of the disease. Perivascular lesions exhibiting loss of astrocyte proteins such as AQP4 and Cx43 have been observed in the white matter. Immune infiltration along with complement deposition and gliosis has been identified in these lesions (Hayashida et al., 2017). Recently, short transverse myelitis (STM) involving < 3 vertebral segments have been observed in a proportion of patients (Flanagan et al., 2015). STM has been proposed to be the initial manifestation of NMOSD (Huh et al., 2017; Fang et al., 2020). The pathology of short transverse lesions is yet to be studied.

Brain lesions

Initially NMO was considered to be a disease that specifically targets only the optic nerves and spinal cord without any brain MRI abnormalities during disease onset (Wingerchuk et al., 1999). However, Pittock et al. (2006) identified that NMO is not restricted to optic nerves and spinal cord but also targets some brain regions that exhibit high AQP4 expression. Brain lesions characteristic of NMO were found to be predominantly surround the third and fourth ventricles and cerebral aqueduct. These lesions were called the diencephalic lesions and thalamus, hypothalamus and the anterior border of the mid-brain were found to be the regions affected. These lesions are now called

the periependymal lesions. Of these periependymal lesions, a lesion involving the dorsal brainstem that affects area postrema and nucleus tracts solitarius has been found to be characteristic of NMOSD. This lesion is responsible for causing area postrema syndrome, one of the core clinical characteristics of NMOSD (Kim et al., 2015). In a study conducted by Popescu et al. (2011) 40% of the analysed patients were found to harbour dorsal brainstem lesions. Pathological analysis revealed loss of AQP4 reactivity in these lesions. Thickened blood vessels were also observed. Microglia were found to be activated in the lesion. GFAP positive, complement deposited astrocytes were harboured in the lesions. Immune infiltrates present in the lesions included CD3+ T-cells, CD8+ T-cells, B-cells, Plasma cells and eosinophils (Popescu et al., 2011). Another type of periependymal lesion is the medullary lesion that often assumes a linear shape and extends to the central canal of the spinal cord. Rosette-like complement deposition was evident in these lesions (Roemer et al., 2007). Corpus callosum lesions are large, oedematous and disseminated with a marble-like appearance and form immediately next to the lateral ventricles along the ependymal lining. Sometimes, these lesions involve the splenium and form a unique arch-bridge pattern lesion (Nakamura et al., 2009; Kim et al., 2010). The callosal lesions are often radial and heterogeneous. Occasionally, these lesions might extend along the white matter into the cerebrum (Cai et al., 2019). Cortical lesions are considered to be "red flag" imaging feature (Wingerchuk et al., 2015). Cerebral cortex lesions are formed in very rare cases. Cortical lesions frequently involve the frontal lobes and exhibit leptomeningeal enhancement (Sun et al., 2019). Kim et al. (2016) suggested that cortical lesions are formed in patients who are not treated with appropriate immunosuppressive drugs. Intense gliosis along with neuronal pyknosis without demyelination have been observed in the cortical lesions (Popescu et al., 2010). Reactive astrocytes carrying swollen cell bodies without complement activation were seen in all cortical layers. AQP4 reactivity was found to be lost in cortical layer I but preserved in layers II-VI. However, microgliosis was observed in cortical layer II and loss of cortical neurons was identified in cortical layers II-IV (Saji et al., 2013).

CLINICAL FEATURES

ON and transverse myelitis are the hallmark features of NMOSD (Oh and Levy, 2012). Prior studies have shown that ON is caused due to the abundant expression of AQP4 and large OAPs in the optic nerve and astrocyte feet respectively (Amiry-Moghaddam et al., 2004; Nicchia et al., 2008; Saini et al., 2010). There are two common forms of the disease: a monophasic form occurring in only 10% of the patients with simultaneous ON and myelitis and a relapsing form with intermittent ON and myelitis attacks (Wingerchuk et al., 1999). ON is the first symptom in approximately 60% of the patients (de Seze, 2013). Onset of ON is severe and acute. NMOSD patients experience profound and persistent reduction in visual function due to ON (Merle et al., 2007). One study that analysed visual field activity during and after optic neuritis attacks identified that 40% of the patients exhibited total visual loss following the first attack (Merle et al., 2013). Another study identified that the initial attack led to blindness (Merle et al., 2007). ON attacks are mostly unilateral. However, they tend to become bilateral during the course of the disease (Papais-Alvarenga et al., 2008). Patients with relapsing form experience a more severe visual impairment. In these patients, severe visual loss occurred in the first eye within the first two years of disease onset and within 13 years in the second eye (Merle et al., 2007). Scotoma, a visual defect has been found to be associated with MS and NMOSD. However, central scotoma was observed more often in MS patients and non-central scotoma was observed in NMOSD patients. NMOSD patients with non-central scotoma frequently developed altitudinal hemianopia. Since altitudinal hemianopia is characteristic of ischemic optic neuropathy, Nakajima et al. (2010) suggested that anti-AQP-IgG might mediate optic neuritis through an ischemic mechanism. Retro-orbital pain is the pain syndrome commonly caused due to optic neuritis in NMOSD patients (Qian et al., 2012).

Spinal cord involvement in NMOSD usually occurs in the form of longitudinally extensive transverse myelitis characterized by paraparesis or quadriparesis, bilateral sensory loss, sphincter dysfunction. Respiratory failure due to myelitis has been observed in a portion of patients. Respiratory failure is more common in patients with the relapsing form of the disease than the patients with the monophasic form. Radicular pain, Lhermitte sign and paroxysmal tonic spasms have been found to accompany myelitis (Wingerchuk et al., 1999; Wingerchuk and Weinshenker, 2003; Qian et al., 2012; Elsone et al., 2013).

Area postrema syndrome (APS) is one of the core clinical characters of NMOSD. Area postrema is the emetic reflex centre present in the brain that houses chemo-sensitive neurons and regulates fluid balance, osmoregulation, hiccups and other physiological functions (Misu et al., 2005; Duvernoy et al., 2007). Dorsal brain stem lesion extending into the Area postrema has been shown to cause APS (Kim et al., 2015). In 12% of

NMOSD patients, APS is the initial presenting symptom (Pittock and Lucchinetti, 2016). Symptoms of APS include intractable hiccups, vomiting and nausea. Several authors have presented case reports of NMOSD patients presenting APS. Shosha et al., in 2019 studied APS in a population of NMOSD patients and identified that 73% of the patients experienced only one APS attack whereas 27% of the patients experienced multiple APS attacks during disease progression. Acute nausea ranging for 6 hours or more per day was experienced by 57% of the patients. Vomiting attacks were episodic in all the patients. No of episodes ranged between 4-8 times per day. 54% of the patients experienced acute hiccups and the duration of the attack ranged between 3-12 hours per day (Shosha et al., 2018).

Acute brainstem syndrome (ABS) is another core clinical manifestation of NMOSD. Symptoms of ABS such as intractable nausea, vomiting and hiccups overlap with APS symptoms. But, ABS includes other symptoms such as oculomotor dysfunction, pruritus, hearing loss, facial palsy, trigeminal neuralgia and other cranial nerve symptoms. Among these symptoms, pruritus was very commonly observed (Kremer et al., 2014). Pruritus has been found to frequently accompany Painful tonic spasms (PTS), a common pain syndrome observed in NMOSD patients (Qian et al., 2012). Pruritus is also suspected to be an indicator of pain onset depending on the location of the lesions (Bradl et al., 2014; Netravathi et al., 2017).

Narcolepsy, a sleep disorder has been found to be an important clinical manifestation of NMOSD. Narcolepsy is caused due to the deficiency of a neuropeptide called hypocretin caused mainly due to the loss of hypocretin containing neurons. Narcolepsy is symptomatic of diencephalic lesions observed in some NMOSD patients and has been reported in several cases (Kanbayashi et al., 2009; Kallollimath et al., 2018). Some patients experience cerebral syndrome symptoms during the disease course. These symptoms include posterior reversible encephalopathy syndrome (PRES), confusion, seizures, aphasia, apraxia, cognitive impairment and other psychiatric symptoms (Lana-Peixoto and Callegaro, 2012; (Lana-Peixoto and Talim, 2019).

Most of the clinical features described above are painful and 80-85% of the NMOSD patients experience severe pain (Qian et al., 2012; Bradl et al., 2014). Pain is a significantly important risk factor for mental disorders (de Heer et al., 2018). Since more than 80% of patients experience intractable pain, mental health disorders are one of the common comorbidities of NMO. Cognitive impairment, depression, psychomotor agitation, anxiety and psychogenic polydipsia are some of the mental health disorders observed in NMO patients (Oertel et al., 2019).

RISK FACTORS AND BIOMARKERS

Low intake of dairy products, fish, multivitamins, iron, life style habits like smoking, alcohol consumption, physical inactivity have been found to significantly increase the risk of developing NMO (Eskandarieh et al., 2018). Among all vitamins, reduced levels of vitamin D is said to increase disease risk (Min et al., 2014). This is understandable since vitamin D is required for proper functioning of T-reg cells needed for preventing autoimmunity (Chambers and Hawrylowicz, 2011). Efforts have been made recently to understand the genetic factors like mutations, polymorphisms etc. that might increase NMO risk. The HLA- DRB*03 allele is very common among European NMO patients (Zephir et al., 2009; Deschamps et al., 2011). Single nucleotide polymorphisms (SNPs) in the 3' untranslated region (UTR) region of AQP4 gene also increase risk of NMO in Chinese patients (Wei et al., 2014). Polymorphisms in IL-17 and programmed death 1 (PD-1) receptor gene are also associated with NMO (Wang et al., 2012; Asgari et al., 2012).

Presence of other autoimmune disorders could also be a risk factor for NMOSD. Autoimmune disorders in general share several common features and sometimes they tend to co-exist within a single individual. This condition is called polyautoimmunity (Anaya et al., 2012). NMOSD is sometimes associated with other autoimmune disorders especially myasthenia gravis (MG). Presence of significant levels of MG specific antibodies in NMO patients has been described previously (McKeon et al., 2009). NMOSD and MG are autoimmune channelopathies caused by IgG antibodies with a high female preponderance (Waters et al., 2008; Meriggioli and Sanders 2009). In some rare cases, where co-presentation of NMOSD and MG is observed, NMOSD initiation is preceded by MG onset and thymectomy (Uzawa et al., 2009; Waters et al., 2012; Oh and Levy 2012; Leite et al., 2012). Thymomas which are known to cause MG were found to express AQP4 in some patients (Kay et al., 2008). Some of the other autoimmune syndromes associated with NMOSD include Sjogren's syndrome (Jayarangaiah et al., 2014; Carvalho et al., 2014), systemic lupus erythematosus (SLE) (Wingerchuk and Weinshenker, 2012), rheumatoid arthritis (Pittock et al., 2008), sarcoidosis (Sawaya and Radwan, 2013), anti-phospholipid antibody syndrome (Mehta et al., 2008), ankylosing spondylitis (Jeong et al., 2018), systemic sclerosis (Deeb et al., 2019).

Lately, various types of antibodies, cytokines, other proteins and metabolites have been identified as biomarkers of NMO. These biomarkers help in making an accurate diagnosis. AQP4 though predominant is not the only antibody marker of NMO. A number of non-organ-specific autoantibodies such as anti-nuclear an-

tibody (ANA) have also been found in large proportions in NMO and other systemic autoimmune disorders. Other than antibodies, Th17 and Th1 cytokines, micro RNAs (miRNAs) and GFAP have also been suggested as NMO markers. Table I shows the various potential markers and their roles in NMO.

Table I. Potential biomarkers of NMO and their role in disease.

Biomarker category	The marker	Role in disease	References
Antibodies	Anti-AQP4	Binds AQP4, the target autoantigen and initiates disease through mechanisms like CDC, ADCC, etc.	Chang et al., 2015, Cheng et al., 2016, Rateldale et al., 2012
	Anti-MOG	Antibody marker in AQP4 seronegative cases. Associated with relapsing bilateral optic neuritis	Melamed et al., 2015
	ANA (anti-nuclear antigen)	Suspected protective role	Masuda et al., 2016, Lee et al., 2019, Chang et al., 2015
	Anti-SSA	Accelerates chronic inflammation by activating gene expression of pro-inflammatory cytokines mainly through the NF-κB pathway	Masuda et al., 2016, Lisi et al., 2012, Chang et al., 2015
B-cells	AQP4 specific plasmablasts	Produce high numbers of AQP4-reactive B-cells	Melamed et al., 2015, Bennet et al., 2009
Th17 cytokines	IL-6	Causes progressive weakness, exacerbates lesions, increases nociception	Chang et al., 2015, Uzawa et al., 2013, Kaplin AI et al., 2005, Bradl et al., 2014, Wei et al., 2013, Guptarak et al., 2013, DeLeo et al., 1996, Arruda et al., 2000
	IL-17	Enhances auto-antibody production, neutrophil infiltration, NMDA receptor mediated nociception	Cheng et al., 2015, Hsu et al., 2008, Vaknin-Dembinsky et al., 2015, Ishizu et al., 2015, Wojkowska et al., 2014, Meng et al., 2013
	IL-21	Promotes Th17 proliferation	Chang et al., 2015, Barros et al., 2013, Wu et al., 2012
	IL-8	Increases inflammation	Melamed et al., 2015
	IL-1β	Accumulates complement proteins, increases neutrophil infiltration, lesion development and glutamatergic signalling	Kitic et al., 2013, Gruber-Schoffnegger et al., 2013
Th2 cytokines	IL-4	Regulates inflammation	Tahani et al., 2019
	IL-13	Promotes inflammation	Mao et al., 2019
	IL-5	Attracts eosinophils and induces eosinophil mediated inflammation	Kouro et al., 2009
Astrocyte injury marker	GFAP	Activates astrocytes	Takano et al., 2008, Chang et al., 2015
Complement proteins	C5, C5b-9	Mediate CDC, form MAC	Chang et al., 2015, Laursen et al., 2012
Others	High-mobility group box protein 1 (HMGB1)	Accelerates inflammation	Chang et al., 2015
	Haptoglobin	Reduces inflammation and oxidative stress	Chang et al., 2015
	miR-135a, miR-135b, miR-125b, miR-134, miR-138, miR-760	Unknown	Vaknin-Dembinsky, 2016

TREATMENT

Treatment options currently available for NMOSD aim at reducing acute attacks and preventing future attacks. Acute NMO attacks are usually treated with high doses (1000 mg for 3-5 days) of intravenous methylprednisolone (Trebst et al., 2014). If methylprednisolone administration does not alleviate the symptoms, some patients are treated by plasma exchange therapy (3-5 cycles) (Kowarik et al., 2014). Immunosuppressive drugs such as azathioprine, mycophenolic acid, methotrexate, mitoxantrone, rituximab, eculizumab etc. are administered for preventing future attacks (Jacob et al., 2009, Kim et al., 2010; 2013; Costanzi et al., 2011; Pittock et al., 2013; Kitley et al., 2013). Despite all these available options, NMOSD remains incurable. Immune insults in addition to causing neurodegeneration, might also activate certain RNA or protein products which could exacerbate these symptoms. Targeting these products (if any) might help in alleviating NMOSD symptoms. Recently, repulsive guidance molecule-a (RGMa) inhibition has been shown to reduce neurodegeneration and repair astrocytes in an NMO model (Harada et al., 2018). Similarly, in MS, a synaptic protein called Bassoon was found to drive neurodegeneration (Schattling et al., 2019). Since MS and NMO share certain common features, analysing the role of Bassoon protein in NMO might help in developing potential treatments. Analysing CNS cellular profiles during the disease state would also be beneficial. Developing combinatorial therapies that target autoimmunity, pain syndromes and neurodegeneration will help patients survive this debilitating disorder.

CONCLUSION

Neuromyelitis optica spectrum disorder is an autoimmune disorder of the CNS characterised primarily by optic neuritis and longitudinally extensive transverse myelitis. Even after a hundred years since it was first characterised, certain features of the disease are baffling. Some questions need to be addressed to bridge research gaps in the field and to obtain a holistic picture. The main target auto-antigen of NMOSD is AQP4, a water channel protein. CNS houses a plethora of proteins. Studies must identify why among all other proteins, AQP4 is specifically targeted in NMO.

Extensive research has led to the identification of different mechanisms and components that cause NMOSD but then there are no reports that explain how the autoantibodies that initiate the disease cross the BBB prior to its disruption since BBB breakdown is a downstream event in the disease.

Like many other autoimmune disorders, a higher female preponderance is observed in NMO. No clear reports are present to explain the gender bias. Oestrogen, a female hormone has been hypothesised to be a significant contributor to neurological disorders (Scharfman and Lusky, 2008). Studies must be carried out to identify whether oestrogen contributes to the female preponderance in NMO.

Myelination in the CNS is mediated by the oligodendrocytes which are targeted by the auto- antibodies in multiple sclerosis but not in NMOSD. But severe demyelination is observed in NMO. Demyelination could be a bystander effect caused due to glutamate excitotoxicity (Marignier et al., 2010). There are sparse reports to explain demyelination and are mostly inconclusive and hypothetical.

Recently, anti-MOG NMOSD has been identified. Although anti-MOG antibodies are present in AQP4 seronegative NMO patients, their clinical features are different from NMO. Therefore, research must clarify whether anti-MOG syndrome is a part of the spectrum or a distinctive disease.

T-cells as discussed in the prior sections are crucial for disease progression. How are these autoreactive T-cells produced? Is it a result of an impaired thymus negative selection mechanism? If so, what causes the impairment? Only if the cause is known, an efficient targeting mechanism can be developed.

The trigger for autoimmunity in NMOSD remains unknown. In some rare cases, NMO develops following MG onset and thymectomy. It is understandable that thymectomy results in decreased production of immunosuppressive T-cells. Thymus dysfunction might then be the cause of NMO autoimmunity but experimental evidence is needed to arrive at a conclusion.

Experimental animal models are pivotal for understanding diseases. Unfortunately, there is no standardized model for NMO. Many experimental models are available for NMO and are highly valuable for research. But none of them have replicated all the features of the disease. As suggested by Bradl and Lassmann (2014) the next generation of models must take into account the different genetic and environmental factors that contribute to the disease. It will take a few more years to answer all these questions. One of the major limitations in carrying out studies related to this disease is its rarity. But, if all the above raised questions are answered, accurate treatment options that increase patients' quality of life can be developed.

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