Microorganisms in Pathogenesis and Management of Neuromyelitis Optica Spectrum Disorder

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Abstract

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory disease of the central nervous system with astrocytopathy characteristics. Antibodies against aquaporin-4 water channels which are mainly located in astrocyte podocytes play an important role in NMOSD pathogenesis. Like other autoimmune disorders, it seems that both genetic and environmental factors are involved in NMOSD risk, but the role of environmental risk factors is more significant. Infections are known to be an effective factor not only in the incidence but also in the exacerbation of autoimmune diseases. In this chapter, the roles of microorganisms in two categories of viruses and bacteria in the pathogenesis and management of NMOSD patients are discussed. In this regard the relation between infection with tuberculosis, *Helicobacter pylori*, Epstein–Barr virus, SARS-CoV-2, varicella-zoster virus, dengue virus, cytomegalovirus, herpes simplex virus 2 and Zika virus, as well as gut microbiome and NMOSD occurrence are mentioned. On the other hand, susceptibility of NMOSD patients for developing infectious diseases due to receiving immunosuppressive drugs and the role of infection in NMOSD attack and disease exacerbation are outlined.

Keywords

Neuromyelitis optica spectrum disorder · Environmental risk factors · Microorganisms · Viruses · Bacteria · Infection · Gut microbiome

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10.1 Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory disease of the central nervous system (CNS), which mainly involves the optic nerve and spinal cord, so it can consequently cause many disabilities (Wingerchuk et al. 2015). The prevalence of this disease varies from 0.51 to 4.4 per 100 thousand people (Eskandarieh et al. 2017b). As well, in this disease, the ratio of women to men is 3:1 to 9:1, and the average age of prevalence is 20–40 years (Sahraian et al. 2017), which is higher than that of multiple sclerosis (MS), as a similar disease (Eskandarieh et al. 2017a). Our knowledge of this disease is increasing progressively. The disease was once considered as a part of MS disease. The similarity of the symptoms, especially blurred vision and paresis, which are common in both of these diseases, added to this suspicion. However, it became gradually clear that these two diseases are two separate diseases with separate pathogenesis and different factors involved in them. Recognition of NMOSD entered into a new phase, especially in 2005 (Lennon et al. 2005) with the discovery of the aquaporin 4 antibody. Since then, it has been established that NMOSD is an autoimmune disease in which specific antibodies, which are responsible for many manifestations of the disease, can cause the disease (Wu et al. 2019). Moreover, it was found that the disease, unlike MS that is a demyelinating disease, is an astrocytopathy, and the antibody is more prone to attack the water channels located in the astrocyte podocytes (Wu et al. 2019). Therefore, the more the water channel, the more likely to be involved with this disease. Accordingly, this explains many of the symptoms of this disease. With the discovery of aquaporin 4 antibody, it was revealed that the disease is more of a spectrum than a specific disease, and we can also observe different forms of involvement in this disease (Wingerchuk et al. 2015). Apart from the spinal cord and optic nerve, which are known as the most involved areas in this disease, other areas of the central nervous system such as the diencephalon, area postrema, and the hemispheres can also be involved in this disease (Wang et al. 2018). Additionally, it has been shown that this disease can involve some areas outside the central nervous system such as the middle ear, myocardium, and placenta (Lennon et al. 2005). Of note, the next issue that can complicate the form of the disease is its association with other autoimmune diseases. This disease was found to be associated with a wide range of autoimmune diseases such as myasthenia gravis, lupus, and Sjögren's, so this leads its manifestations to become more diverse (Shahmohammadi et al. 2019). Although a significant proportion of patients with this disease are seropositive, and antibodies can also be detected in them, about 23% of these patients are seronegative who are clinically and radiologically different from seropositive cases (Wingerchuk et al. 2015). It has been found that the disease in these patients is less severe and only associated with a lower degree of disability (Dauby et al. 2021). However, in recent years, it has been found that some seronegative patients are resulted as positive for antibodies against myelin oligodendrocyte glycoprotein (MOG) that form a separate and different group (Ojha et al. 2020). Therefore, there is a possibility that other unknown antibodies may also be resulted as positive in seronegative patients who are negative for anti-MOG; accordingly, this requires further studies.

10.2 Pathogenesis

As mentioned earlier, NMOSD is an astrocytopathy, and antibodies against water channels were observed to play a very important role in the pathogenesis of this disease (Papadopoulos and Verkman 2012). This antibody is an IgG1 that binds to water channels, which are mainly located in astrocyte podocytes, and consequently causes the process of astrocytopathy and some subsequent clinical manifestations (Ikeshima-Kataoka 2016). Although antibodies play key roles in the development of the disease and its pathogenesis, this is a very complex process and involves several stages, each one of which is considered the basis for creating new drugs. Complement-mediated astrocyte damage occurs after the antibody binding to these water channels. Subsequently, it leads to granulocyte infiltration, oligodendrocyte death, and finally neuronal death (Duhan et al. 2009). This antibody is also involved in IgG/IgM deposition (Roemer et al. 2007). Apart from all the above-mentioned consequences, other elements and cells are also involved in the pathogenesis of the disease. It is currently known that mast cells are also involved in the pathogenesis of this disease. Correspondingly, these can be involved in the pathogenesis of this disease as innate and adaptive immune response regulators (Kim et al. 2019). The roles of Th17, Th2, and their cytokines have been widely discussed in the pathogenesis of this disease. These cytokines, which include IL-6, IL-1β, IL-17, IL-21, IL-22, IL-23, and TGF-β, along with the cells, can play a direct role in the pathogenesis of the disease. Moreover, they can cause brain damage by stimulating B cells as well as inducing antibody production by these cells (Zhang et al. 2018; Uzawa et al. 2014; Lin et al. 2016). It was found that the levels of these cytokines in both serum and cerebrospinal fluid samples of these patients are significantly higher than those of healthy individuals, showing their direct role in causing disease (Lin et al. 2016). This also indicates the complexity of the pathogenesis of this disease. Since the attacks of this disease can be debilitating and even fatal, the recognition of the risk factors and the factors involved in causing the disease or in causing the attacks can play an important role in preventing the disability resulted from that. In this chapter, we firstly took a brief look at the risk factors related to this disease and then focused on the roles of microorganisms in causing the disease and in attacks, and how to treat the disease.

10.3 Risk Factors

Similar to many other diseases of the immune system, the risk factors for this disease are divided into two general categories as follows: environmental and genetic (Naser Moghadasi 2020). It seems that the role of genetic factors in a person developing NMOSD is less than their role in patients with MS (Naser Moghadasi 2020). One study found that having a family history of MS, unlike NMOSD, can be considered as a risk factor (Eskandarieh et al. 2017a). While the rate of familial MS is reported to be 13% (Salehi et al. 2020), which appears to be increasing (Eskandarieh et al. 2018a), in a small number of studies conducted on familial NMOSD, this rate has

been reported to be 3% (Matiello et al. 2010). However, several cases of familial NMOSD have been reported in this regard. Additionally, those studies on the genetic risk factors indicated the role of various genes such as HLA-DRB1 alleles and luster of differentiation 58 (CD58) polymorphism in the development of the disease (Matsushita et al. 2020; Kim et al. 2014). As mentioned earlier, the role of environmental factors in the development of NMOSD was found to be more significant. Nevertheless, limited studies have been done in this field. In the study by Eskandarieh et al., some factors such as low sea food intake and low dairy consumption have been reported as the risk factors for NMOSD (Eskandarieh et al. 2018b). In some other studies, high fat intake and little consumption of grains and vegetables have been reported as nutritional factors that can increase the risk of NMOSD (Rezaeimanesh et al. 2021, 2020). Infections have always been considered as a predisposing factor in all autoimmune diseases. Moreover, they are not only involved in causing these diseases, but can also exacerbate them. As well, numerous microorganisms such as *Mycobacterium tuberculosis*, *Helicobacter pylori*, and varicella zoster virus have been implicated in causing these diseases. At the beginning of the COVID-19 pandemic, the possibility of the virus involvement in the development of NMOSD as well as the intensification of its attacks has been raised. In the following, the roles of microorganisms in the pathogenesis and management of patients with NMOSD are discussed.

10.4 The Role of Microorganisms in the Pathogenesis of Neuromyelitis Optica

10.4.1 Bacteria

10.4.1.1 *Mycobacterium tuberculosis*

Numerous studies have been conducted on the relationship between tuberculosis (caused by *M. tuberculosis)* and NMOSD, either as a case report or as a cross-sectional study. However, the relationship between these two diseases is controversial yet. In this regard, some case reports stated different conditions for the relationship between the two diseases. In some cases, it was found that NMOSD occurs after or during tuberculosis. Grieve et al. in their study reported a 48-year-old patient who developed blurred vision and sensory disturbances during treatment for tuberculosis; therefore, the patient was diagnosed with NMOSD after performing a thorough examination (Grieve et al. 2020).

In another case reported by de Saráchaga et al., a 34-year-old woman presenting weakness and progressive numbness of the limbs followed by dysarthria was diagnosed with NMOSD. However, during her treatment, she suffered from respiratory distress and pleural effusion, and with further examinations, tuberculosis was diagnosed (de Saráchaga et al. 2020). In this case, unlike the previous case, tuberculosis was diagnosed after NMOSD. In a similar report, Bhatty et al. described a young girl who was referred because of paraplegia and treated with the diagnosis of

NMOSD. However, during her treatment, she developed ascites and was eventually diagnosed with abdominal tuberculosis (Bhatty et al. 2015).

Besides the above-mentioned case reports, two other studies have also been published on the association between NMOSD and tuberculosis, which gave contradictory answers to the possibility of an association between these two diseases. The study by Zatjirua V et al. in 2011 examined 14 patients with NMOSD, of whom 11 cases had tuberculosis either before or at the time of the diagnosis of NMOSD. The average time of developing TB to NMOSD was estimated as 4 weeks. The authors concluded that these data suggest an association between tuberculosis and NMOSD, which may possibly be due to the role of the mediated immune mechanism (Zatjirua et al. 2011). However, in the Li et al.'s study published in 2014, this association was not confirmed. Correspondingly, they found no significant difference in terms of tuberculosis between patients with NMOSD and the control subjects (Li et al. 2014). It is possible that these accompaniments may be random (Zayet et al. 2021); therefore, further investigations are required in this regard. Based on the available data, it is not possible yet to provide a definitive theory on the role of *Mycobacterium tuberculosis* in the pathogenesis of this disease.

10.4.1.2 Gut Microbiome

The role of the intestinal microbiome in the development of autoimmune diseases is increasingly considered, and NMOSD is no exception in this regard. Several studies have previously shown that the intestinal microbiome of these patients is different from those of MS patients and healthy individuals, in terms of both the content and percentage of available strains.

Shi et al. published a paper in 2020 to compare the intestinal microbiome of people with NMOSD with that of healthy people. Accordingly, they found that the rate of pathogenic strains (*Flavonifractor* and *Streptococcus*) was higher in people with NMOSD than that of healthy people. Additionally, the strains of *Faecalibacterium*, *Lachnospiracea_incertae_sedis*, *Prevotella, Blautia, Roseburia, Romboutsia, Coprococcus*, and *Fusicatenibacter* were observed to be less than the microbiome of healthy individuals (Shi et al. 2020). As well, it has been found that the characteristics of the intestinal microbiome are different among seropositive and seronegative patients (Zhang et al. 2020).

In a study conducted by Cree et al. on 16 NMOSD patients and 16 healthy individuals, it was found that the type of intestinal microbiome in the patients was completely different from that of the healthy individuals, especially the amount of *Clostridium perfringens* in the intestines of these patients, which was significantly overrepresented (Cree et al. 2016). *Clostridium perfringens*, which are located in the intestines of these patients, can play a role in regulating the balance between the regulatory T cells and Th17 cells; thus, these can be involved in the pathogenesis of these patients (Zamvil et al. 2018). In another study by Pandit L et al., it was found that the amount of *Clostridium bolteae* was significantly higher in seropositive patients compared to seronegative patients; however, the microorganism was not observed in their studied healthy individuals. This microorganism has been found to contain aquaporin-related proteins bearing a striking sequence similarity to

aquaporin-4 peptides. So, this highlighted its role in stimulating T cells as well as its participation in the pathogenesis of the disease (Pandit et al. 2021).

Due to the above-mentioned reasons and the roles of intestinal microbiome in the development and pathogenesis of other autoimmune diseases, a microbiota intervention can be considered as the treatment for these patients. It was indicated that the regulation of the intestinal microbiome can repair the intestinal mucosal barrier and also modulate intestinal immunity and peripheral immunity (Cui et al. 2020). Consequently, this fact opens up new therapeutic horizons for scientists in this field.

10.4.1.3 *Helicobacter pylori*

Due to the high prevalence of *Helicobacter pylori* in the community, this microbe has always been considered as a stimulant of the immune system, and consequently, it was shown that it is involved in the development of autoimmune diseases. Accordingly, some studies have also been published on its possible role in the development of NMOSD. Li et al. in their study examined the immune response to *Helicobacter pylori* neutrophil-activating protein in patients with MS and NMOSD, as well as normal individuals. As a result, it was found that *Helicobacter pylori* seropositivity was higher in patients with NMOSD. Moreover, this was true for anti-*Helicobacter pylori* neutrophil-activating protein antibody, and in this regard, the interesting point is that the titer of this antibody is directly related to the degree of disability (Li et al. 2009).

Furthermore, Yoshimura et al. found that a history of *Helicobacter pylori* infection is a risk factor for NMOSD seropositive cases (Yoshimura et al. 2013). The same result was also confirmed in another study performed by Long et al. (2013).

Although these studies are limited, however, these studies indicated the role of *Helicobacter pylori* in the development of neuromyelitis optica. It may also be involved in the development of disability in people with this disease. Nevertheless, whether the early treatment of *Helicobacter pylori* can reduce the risk of developing NMOSD still is a question that should be considered to be answered in future studies.

10.4.2 Viruses

10.4.2.1 Epstein–Barr Virus (EBV)

Given the prominent role of EBV in the pathogenesis of MS (Bar-Or et al. 2020), so it is reasonable to consider its possible role in NMOSD as well. However, the role of this virus seems to be different in these two diseases. Correspondingly, the obtained results are completely contradictory, which can be related to the small sample size in all studies. In another study, Simon et al. found no association between anti-Epstein–Barr nuclear antigen (anti-EBNA) titers and NMOSD (Simon et al. 2015). In addition, Graves et al. came to the same conclusion in examining the environmental risk factors for NMOSD (Graves et al. 2014).

On the other hand, Masuda et al. in their research reported a different conclusion. They found that the serum level of anti-early antigen IgG antibodies in NMOSD

patients was significantly higher than those of MS patients and healthy individuals, indicating the active EBV replication in these patients (Masuda et al. 2015). Moreover, Mori found that although a history of EBV is associated with a higher risk of developing MS, with regard to NMOSD, it is the re-activation of EBV that exacerbates the risk of NMOSD in patients in the future (Mori 2015). However, more studies are required to confirm this finding.

10.4.2.2 SARS-CoV-2

Soon after the start of the COVID-19 pandemic in December 2019, scientists realized that the extent of the infection with this virus goes far beyond a contagious deadly infection manifesting itself with lung involvement. As well, from the very beginning, it was realized that the virus could not only directly infect the brain (Montalvan et al. 2020); however, it is an immunogenic virus that could cause various autoimmune diseases (Montalvan et al. 2020; Naser Moghadasi 2021). Immediately after the start of the pandemic, numerous reports of various autoimmune diseases, including autoimmune diseases related to the brain, were published (Montalvan et al. 2020). Of note, NMOSD was no exception in this regard. Additionally, there have been some reports of NMOSD during or after COVID-19, showing new angles of the relationship between the coronavirus and NMOSD.

Ghosh et al. reported a 20-year-old man who experienced nausea, vomiting, and hiccups, as well as manifesting progressive limb weakness by passing 10 days from developing COVID-19, who was finally diagnosed with NMOSD and treated with methylprednisolone and rituximab (Ghosh et al. 2020). Ruijter et al. also reported a 15-year-old man presenting with blurred vision in both eyes by passing a few weeks from developing COVID-19. Finally, he was diagnosed with NMOSD and then treated with methylprednisolone (de Ruijter et al. 2020). On the other hand, Batum et al. reported a 50-year-old woman presented with fever, malaise, cough, and lower extremity weakness and after performing necessary examinations, she was diagnosed with co-infection of COVID-19 and NMOSD (Batum et al. 2020). Shaw et al. also reported a man who developed blurred vision, lower limb weakness, and sphincter disorder by passing 9 days from developing COVID-19. Unfortunately, the patient died due to the exacerbation of COVID-19, but his anti-aquaporin 4 antibody test resulted as positive (Shaw et al. 2020).

As indicated, the association between COVID-19 and NMOSD can occur at any age and in both sexes with any clinical pattern. So, this shows the possible role of Coronavirus in the pathogenesis of this disease. In fact, this is an issue that is not limited to the age and gender of the affected individuals. Due to the current COVID-19 pandemic, we should probably expect more cases of NMOSD.

10.4.2.3 Varicella Zoster Virus (VZV)

There is an increasing trend toward the reports of the role of this virus in the pathogenesis of NMOSD, and it seems that we need more extensive and comprehensive studies in order to better understand the role of this virus in the pathogenesis of the disease. In 2009, Heerlein K et al. in their study reported a 63-year-old woman diagnosed with shingles in her lumbar area. By passing 2 weeks from developing

shingles, the patient was presented with weakness and numbness in his left leg, and on magnetic resonance imaging (MRI), longitudinal extensive transverse myelitis (LETM) was seen in both the cervical and thoracic spinal cords. The anti-aquaporin 4 antibody test was positive; therefore, the patient was diagnosed with NMOSD and then treated with corticosteroid (Heerlein et al. 2009).

In another study, Park et al. reported a young woman who developed LETM following herpes zoster and was under the treatment for herpes-related LETM. However, with the recurrence of myelitis and positive anti-aquaporin 4 antibody, she was treated with a diagnosis of parainfectious NMOSD (Park et al. 2013). Machado et al. also reported a 77-year-old woman who was hospitalized with shingles; however, she quickly developed paraparesis, urinary incontinence, and sensory problems. Moreover, LETM was seen on thoracic MRI. Six months later, the patient developed chorea symptoms. As well, brain MRI showed periependymal involvement of the fourth ventricle. Due to the fact that this feature is mostly observed in NMOSD, so the patient was checked for anti-aquaporin 4 antibody at this stage, which resulted as positive, and subsequently the patient was treated with azathioprine and prednisolone with a diagnosis of NMOSD (Machado et al. 2015).

Furthermore, Suda et al. reported a 53-year-old man who developed myelitis 7 days after varicella zoster. While the patient was diagnosed with zoster-induced myelitis, his test was positive for anti-aquaporin 4 antibody (Suda et al. 2017). In reviewing the previously performed case reports, it is important to note that the clinical manifestations of both varicella zoster and NMOSD are quite diverse in both sexes and at different ages of involvement. Matsumoto et al. in their study reported a 26-year-old woman who developed both NMOSD and extensive zoster during pregnancy, and her situation was improved with intravenous immunoglobulin (IVIG) injection (Matsumoto et al. 2018). Eguchi et al. reported a 55-year-old woman who was concurrently suffering from NMOSD and VZV radiculomyelitis (Eguchi et al. 2020). Finally, in 2020, Turco et al. reported the first child case who had VZV infection along with NMOSD (Turco et al. 2020).

As stated earlier, reports on the co-occurrence of VZV infection and NMOSD are increasing. However, all the reported cases were in the case reports, and a comprehensive study has not been done on antibody levels against zoster virus in these patients and its comparison with healthy individuals yet. Correspondingly, such a study could determine the possible role of varicella zoster virus in NMOSD.

10.4.2.4 Dengue Virus

It was indicated that dengue virus can lead to fever, headache, myalgia, and skin lesions, and in less common cases, to bleeding and death (Muller et al. 2017). As well, there have been reports of dengue fever associated with NMOSD. In 2007, an 11-year-old Japanese girl living in northern Brazil was reported with the developed NMOSD along with blurred vision and myelitis after a week of suffering from dengue fever. Eventually, she was treated with corticosteroids and then recovered. Notably, dengue fever is confirmed by IgM testing against the virus in cerebrospinal fluid (de Sousa et al. 2006). Puccioni-Sohler et al. also reported a 17-year-old girl who developed both NMOSD and dengue fever concurrently. Although the antibody

was negative in this patient, the combination of clinical symptoms and MRI findings finally confirmed the diagnosis of NMOSD (Puccioni-Sohler et al. 2017).

All the above-mentioned cases were seronegative in terms of antibodies against aquaporin 4. However, in 2018, Lana-Peixoto et al. in their study reported two patients who had NMOSD concurrent with dengue fever. Accordingly, one of the patients was presented with optic blurred vision and an initial diagnosis of optic neuritis and the other one presented brainstem symptoms, but unlike the previous cases, both patients resulted as positive for anti-aquaporin 4 antibody (Lana-Peixoto et al. 2018).

10.4.2.5 Cytomegalovirus (CMV)

Similar to other viruses, the occurrence of NMOSD has been reported after infection with CMV. In 2007, Tran et al. reported a 34-year-old patient who developed myelopathy and blurred vision after being infected by CMV, and was then diagnosed with NMOSD (Tran et al. 2007).

Luo et al. also reported a 40-year-old woman who was diagnosed with NMOSD and then treated with methylprednisolone and IVIG, followed by plasmapheresis. However, no improvement was observed. Therefore, she was referred to another center to receive a better treatment. On the third day of hospitalization, the patient developed hematochezia, which was eventually diagnosed as CMV infection using a biopsy; therefore, she was treated with ganciclovir. Following the CMV treatment, the patient's condition in terms of limb weakness and blurred vision was improved. Moreover, the authors concluded that the patient's symptoms did not improve due to an infection that might itself play a role in the development of NMOSD, since the treatment of the infection consequently led to the improvement of NMOSD condition (Luo et al. 2020). In cases with the occurrence of NMOSD after the development of an infection, whether the treatment of that infection would improve the NMOSD condition or not, they should be considered in further studies.

10.4.2.6 Herpes Simplex Virus 2 (HSV2)

The role of herpes in many autoimmune diseases like MS has been previously discussed in many studies done in this regard (Ishaq et al. 2015). However, there have been few reports of the association between this virus and NMOSD. Marin Collazo et al. reported a 66-year-old man referred to the hospital with lower extremity weakness, paresthesia, and urinary problems. This patient had a history of recurrent genital infections with the herpes virus from 40 years ago. Although he did not have a herpes infection at the time of admission, an examination of the cerebrospinal fluid using polymerase chain reaction (PCR) method revealed HSV-2 DNA, which confirmed the HSV infection of the central nervous system. Anti-aquaporin 4 antibody also was positive in further studies, which indicated the simultaneous presence of two diseases of central nervous system infection, as herpes and NMOSD, in this patient. Therefore, the patient was treated simultaneously with both methylprednisolone and acyclovir (Collazo et al. 2018).

As mentioned earlier, despite the prominent role of this virus in various autoimmune diseases, there have been few reports on its association with NMOSD. In this

regard, Etemadifar et al. in 2019 studied the level of antibodies against HSV in the serum of patients with MS and NMOSD, as well healthy individuals; however, they found no significant differences among them (Etemadifar et al. 2019).

10.4.2.7 Zika

In 2019, MC et al. reported a 35-year-old Brazilian man presented with fever, myalgia, and arthralgia. Four days later, he reported suffering from urinary retention with paraparesis. In addition, brain MRI was normal, but hyperactive lesions were observed in cervical and thoracic MRI. Due to the infectious symptoms and endemicity of Zika in the area, this patient was examined for other infectious diseases, and Zika PCR was positive in cerebrospinal fluid. As well, methylprednisolone was started for the patient, but the patient's symptoms did not improve, and he then reported constipation, vomiting, and hearing loss. On re-MRI, the lesions of the central nervous system increased, and this time, a lesion was also observed in the pons.

Therefore, despite the negative result of anti-aquaporin 4 antibody, the patient was diagnosed with NMOSD. Afterward, although he was treated with IVIG, he developed blurred vision with pain in the right eye, and according to the MRI in which optic nerve involvement was evident, he was then treated with methylprednisolone and finally recovered. So, the authors concluded that in cases where the diagnosis of NMOSD is made in an area where Zika infection is endemic, it is better to consider it as a factor involved in the pathogenesis of the disease (Aspahan et al. 2019).

10.5 Diagnostic of NMOSD

Infections can be considered in several ways when diagnosing NMOSD. Firstly, many infections can mimic the symptoms of NMOSD in various ways, including some diseases such as human immunodeficiency viruses (HIV) (Brew and Garber 2018), syphilis (Kabanovski et al. 2021), or Lyme (Summer and Rupprecht 2019). Consequently, it was shown that these diseases can cause some symptoms such as myelopathy or blurred vision; therefore, they can be considered as differential diagnoses of NMOSD. Due to newly appeared viral diseases such as COVID-19, it is very important to pay more attention to these differential diagnoses. Currently, we know that COVID-19 could be associated with the central nervous system involvement (Montalvan et al. 2020), as well; some reports were published on myelitis following COVID-19 (Chakraborty et al. 2020) and subsequent optic neuritis (Tisdale and Chwalisz 2020). These cases are also among the main symptoms of NMOSD.

On the other hand, a number of the microorganisms discussed earlier can lead to the presentation of some symptoms such as myelitis in their involvement. Since these microorganisms are also involved in the development of NMOSD disease, so in these cases, it is better to check for NMOSD and not attribute everything to the complications resulted from the microorganism itself as an infectious agent.

The next issue, as was discussed, was the association between numbers of infections with NMOSD itself, which are important to be considered in several ways. The first point is that later or no diagnosis of infections can be dangerous for the patient, as the treatments used in NMOSD are immunosuppressive therapies. Accordingly, these therapies, if co-infected with an infectious disease, can exacerbate the associated infectious disease and even be fatal to the patient.

As the second point, as seen in the association of NMOSD and CMV (Luo et al. 2020), failure to treat infections can consequently lead to NMOSD treatment failure. Therefore, it is very important to pay more attention to possible concomitant infectious diseases, especially in areas that are considered as endemic in terms of a particular infectious disease.

10.6 The Role of Infections in Causing an Attack in Patients with NMOSD

Attacks play an extremely important role in NMOSD, because they can cause severe kinds of disability in patients. Therefore, it is important to pay attention to the factors predisposing NMOSD patients to attacks and then to prevent them. Infections in autoimmune diseases have always been considered as causative agents of the relapses. As well, the same is true for NMOSD. Therefore, the prevention of infectious diseases can be effective on preventing disability in these patients (He et al. 2019; Saab et al. 2016). On the other hand, any infection in these patients should be considered and treated. This can reduce the risk of attacks in these patients.

10.7 Infection of NMOSD Patients with Infectious Diseases and Its Complications

It was indicated that NMOSD patients are prone to side effects due to taking immunosuppressive drugs, especially the increased risk of developing various infectious diseases. Several reports have been published on the complications of these infectious. Pneumonia and urinary tract infections are known as the side effects of rituximab (Moghadasi et al. 2019; Damato et al. 2016). Cases of death following infection have also been reported in patients consuming this drug (Kim et al. 2015).

Studies on the risk and morbidity of patients with NMOSD who developed COVID-19 have shown higher rates of hospitalization (Sahraian et al. 2020) and mortality in them who were mainly rituximab users (Esmaeili et al. 2021). So, these have made the treatment of these patients a challenge for neurologists as the situation can happen with any other infectious disease.

10.8 Management of NMOSD Through Microorganisms

It has not yet been established whether probiotic, prebiotic, and synbiotic supplementation can alleviate NMOSD symptoms or not. But, there are growing evidences on the beneficial role of using them in the management of MS. An altered gut microbiota is reported in MS patients compared with healthy population. RCT designed studies showed the effect of intervention by probiotics in improvement of mood, disability, quality of life (depression, anxiety, stress, general health and fatigue), metabolic and clinical markers vs. placebo group in MS patients (Kouchaki et al. 2017; Blais et al. 2021). A human study outlined induction in anti-inflammatory peripheral immune response by probiotics administration (Tankou et al. 2018). In another study experimental autoimmune encephalomyelitis (EAE) was suppressed using a mixture of five probiotics, due to inducing regulatory T cells and reducing T helper 1 and 17 polarization (Evans et al. 2018; Kwon et al. 2013).

It seems that dietary intake could be effective in the alternation of microflora. So that western diet could lead to dysbiosis while physical activity, higher intake of fruits, vegetables, legumes, fish, prebiotics, and probiotics cause restoration or maintenance of a healthy symbiotic gut microbiota (Riccio and Rossano 2015). Riccio et al. in 2015 suggested consumption of probiotics such as *Bifidobacterium lactis, Clostridium butyricum*, and *Lactococcus lactis* and prebiotics including oligofructose, inulin, bran, and lactosucrose in MS patients. They also highly recommended the combination of prebiotics and probiotics in these patients (Riccio and Rossano 2015).

Based on our knowledge, there are no human study on commensal therapy in NMOSD or MS. But some studies investigated the role of commensal therapy in animal models of MS (Blais et al. 2021). Commensal therapies resulted in delay in EAE onset and reduction in incidence, clinical scores, demyelination, and inflammatory CNS infiltration (Blais et al. 2021).

Due to evidences on beneficial effects of probiotics or commensal therapies in MS patients, it could be concluded that these complementary therapies may be helpful for NMOSD patients, too. But investigation in this area is needed to prove this hypothesis.

10.9 Conclusion

Although the risk factors for NMOSD have not been studied extensively, some evidences suggested that infections play an important role in the pathogenesis of the disease. Infections can also be regarded as an effective factor on facilitating attacks of this disease. On the other hand, due to the use of immunosuppressive drugs, the risk of infection in these patients is high, which can even increase the risk of death. Therefore, it is very important to pay attention to the roles of microorganisms in the development and course of the disease.

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