Comprehensive review of tropical endemic infections and demyelinating diseases of the central nervous system

Abstract

Background: Although more prevalent in higher latitudes, Multiple Sclerosis (MS) also affects individuals who live in tropical areas. Neuromyelitis Optica Spectrum Disorders (NMOSD), on the other hand, is more prevalent in tropical regions. For both demyelinating conditions, endemic tropical infections may be a serious complicating factor.

Methods: This was a comprehensive review carried out by a panel of specialists. The most prevalent endemic infections found between latitudes 23˚27' (Tropic of Cancer) and -23˚27' (Tropic of Capricorn) were , tuberculosis, Hansen's disease, syphilis, leishmaniasis, leptospirosis, Human Immunodeficiency Virus (HIV), Human T-Lymphotropic Virus (HTLV), arboviruses and coronaviruses.

Results: Each of these infections was discussed in detail regarding the risk of affecting the clinical course of MS/NMOSD and the potential risks for individuals receiving immunomodulatory or immunosuppressive therapy.

Conclusion: Differential diagnoses between MS/NMOSD and the above-cited tropical infections are essential in endemic areas. Should the patient develop neurological symptoms during MS/NMOSD treatment, tropical infections need to form part of the differential diagnosis work-up when the patient lives in endemic areas. The risk of tropical infections in patients with MS/NMOSD needs to be taken into consideration regarding the choice of therapy. At present, most clinical trials, guidelines, and protocols have been developed and designed for high-latitude areas. Unfortunately, they do not consider potential infections that are prevalent in the tropical and equatorial zones.

Keywords: tropical medicine, neurology, multiple sclerosis, neuromyelitis optica

Introduction

Endemic infections have been an issue throughout history. An important cause of death for all age groups, viruses, bacteria, parasites, and fungus continue to be a problem in the 21st century. The recent coronavirus COVID-19 pandemic has just confirmed this [1]. For patients with autoimmune diseases, infections can mean an even higher threat of morbidity and mortality. For patients with Multiple Sclerosis (MS) and Neuromyelitis Optica Spectrum Disorders (NMOSD) the outcomes of infections may have additional negative influences [2,3].

For a long time, MS was considered a disease of high latitudes of the Northern hemisphere. It is now well-known that there are many patients with MS in tropical and equatorial regions of the globe [4]. While MS itself may be a complicating factor in infections, MS pharmacological therapy adds to the challenge [5]. Some tropical infections may simulate a bout of MS and immunosuppressive drugs are an added confounding factor [6].

NMOSD is a chronic neuroinflammatory demyelinating process primarily targeting the optic nerves, spinal cord, and brain [7]. Each bout of the disease tends to be aggressive and leave disabling sequelae [8]. In addition, NMOSD does not have a specific treatment and many patients are treated with continuous unspecific immunosuppressive drugs [8]. NMOSD is more prevalent in Afro-descendants, Latin-Americans, and Asians [9]. In general, NMOSD is often found in lower latitudes and developing countries [10]. Taking these parameters into consideration, patients with NMOSD seem to be under higher risk of complications from infectious diseases [11].

The present report is a comprehensive literature review related to the immunology of MS and NMOSD, their therapeutic options, and infections that patients may present. MS and NMOSD are not the same disease and do not share the same etiology. However, most neurologists who treat MS also treat NMOSD, as they both lead to demyelination of the central

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nervous system. The next section of the paper presents the different pathophysiology of MS and NMOSD.

The review did not require ethical approval. A group of eight neurologists reviewed the literature on the pathophysiology of NMOSD and its therapeutic options. An immunologist, a pathologist, an infectious disease specialist and a radiologist joined the discussion giving their input on the risk of infections in patients with NMOSD. A comprehensive review of the literature was individually carried out by all authors prior to remote meetings. Articles were selected for this review when at least 80% of the authors agreed the paper should be presented here. This paper was conceived after two meetings of the specialists and reflects the opinion and recommendations of this group.

Immunopathology of MS

MS etiology remains unknown, but it presumably involves an interaction between genetic and environmental factors leading to an aberrant autoimmune response [12]. Though a complex autoimmune and degenerative evolution is the hallmark of MS, the disease is basically characterized by the damage to myelin and axons of the Central Nervous System (CNS) [13]. The immunopathogenesis of MS involves recognition of CNS antigens by activated CD4+ myelin-reactive T cells, associated to a contribution of B cells responses [14] as well as astrocytes and microglia activation [13]. An intricate arrangement of pro and anti-inflammatory cytokines defines the molecular mechanisms of inflammation, degeneration, toxicity, and regeneration of lesions in the CNS tissue [15]. MS does not have specific biomarkers and, presently, prognoses rely on magnetic resonance image, with studies continuing for neurofilament light chain, chitinase 3-like 1 and 2, heat shock proteins, and tubulins [16].

Immunopathology of NMOSD

In the pathogenesis of NMOSD, the Anti-Aquaporin 4 (AQP4) antibody is expressed against the AQP4 channels that are present in the CNS. AQP4 is the most abundant water channel protein in astrocytes. It is one of the major peptide antigens presented via major histocompatibility complex type II (MHCII) [17]. Further interaction with CD4 T helper cells promotes B cell activation and isotype switch to IgG which triggering the autoimmune disease in NMOSD [18]. During the neuroinflammation, CD4 T cells are activated and undergo clonal expansion. Once they infiltrate the CNS, they are re-activated in situ by resident dendritic cells (antigen present cells) and microglia cells [19,20]. CD4 T cells secrete proinflammatory cytokines leading to astrocyte, microglial and endothelial cells activation. These new players increase the local neuroinflammation process [21]. NMOSD is also characterized by an inflammatory response associated with T helper 17 cells (Th17). The cytokines secreted by Th17 are responsible for the recruitment of neutrophils to the lesion site [22]. B cell action is mainly related to the production of self-responsive AQP4 immunoglobulin IgG1 antibodies [18,22] whose Fc portions trigger effector mechanisms, as complement binding and Antibody-Dependent Cytotoxicity (ADCC).

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Prevalent infectious diseases in low latitudes

Although some good studies and reviews discuss the risk of infections in patients with MS [23] these are typical of high latitudes. Endemic infectious found between latitudes 23˚27′ (Tropic of Cancer) and -23˚27′ (Tropic of Capricorn) are , tuberculosis, Hansen's disease, syphilis, leishmaniasis, leptospirosis, Human Immunodeficiency Virus (HIV), Human T-Lymphotropic Virus (HTLV), arboviruses and coronaviruses. These diseases have not been discussed in patients with MS/NMOSD who already have (or had) them, and those who live in high-risk areas. **TABLE 1** summarizes data on these infections.

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■ Malaria

Malaria may be caused by six different types of

TABLE 1. Summarized information on the most prevalent tropical infections.

Infection	Agent	Mode of transmission	Main symptoms	Main effects	Effect on T cells	Effect on B cells	Treatment options
Malaria	*Plasmodium (P) falciparum, P. vivax, P. ovale, P. malarie*	Mosquito (*Anopheles*)	Anemia, fever, respiratory distress, acidosis, hepatorenal failure, shock, and coma	Macrophage ingestion of merozoites, ruptured schizonts	Release of TNF-α, IFN-γ, IL-10	B cell polyclonal activation	Chloroquine, primaquine, artemisinin, artesunate
Tuberculosis	*Mycobacterium tuberculosis*	Airborne	Lung disease, systemic dissemination, cachexia	Alveolar macrophage phagocytosis	Release of NO, TNF-α, IFN-γ,	Antibody production by B-cell (tuberculosis granuloma)	Isoniazid, rifampin, ethambutol, pyrazinamide
Hansen's Disease	*Mycobacterium leprae*	Possibly airborne	Damage to peripheral nerves and skin. May affect eyes, mucous membranes, and bones	Direct invasion of nerve and skin	Decreased Th1 response	Antibody production and granuloma formation	Dapsone, rifampicin, with or without clofazimine
Syphilis	*Treponema pallidum*	Sexually transmitted or vertical	Systemic and central nervous system involvement at different stages	Tissue invasion and arteritis	Release of TNF-α, IFN-γ, IL-6, IL-17	Antibody production	Penicillin
Leishmaniasis	*Leishmania* sp.	Sandfly	Tissue invasion and destruction	Cutaneous, mucocutaneous or visceral invasion	Release of IL-β, IL-17, TNF-α, NO	Mainly unspecific antibody production	Pentavalent antimony, amphotericin B
Leptospirosis	*Leptospira* sp.	Mucosae and conjunctival penetration, abrasions	Rhabdomyolysis, liver and kidney failure, vascular damage	Bacteremia for one week followed by vascular damage and tissue invasion	"Cytokine storm" and increased IL-10	Antibodies are detectable in severe disease	Tetracyclines and beta-lactam/ cephalosporins
Human Immune-deficiency Virus (HIV)	HIV	Body fluids	Acquired immune-deficiency syndrome	Severe immune-deficient syndrome with systemic involvement	Marked decrease on CD4+ cells	Antibody production (several epitopes of HIV)	Antiretroviral therapy
Human T-Lymphotropic Virus (HTLV)	HTLV1 HTLV2	Blood products, breastfeeding	Tropical spastic paraparesis	Progressive paraparesis	Infection of Th1CD4+ cells mainly in spinal fluid	Antibody production	Symptomatic, corticosteroids if necessary
Arboviruses	Dengue, West Nile, Yellow fever, Chikungunya and Zika viruses	Arthropoda	Asymptomatic or mild symptoms to severe systemic disease	Fever, myalgia, respiratory and gastrointestinal symptoms	"Cytokine storm", cell death	Antibodies that are not effective against all viruses (ADE)	Symptomatic, hydration
Coronaviruses	Coronavirus	Airborne	Asymptomatic or mild symptoms to severe systemic disease	Acute respiratory syndrome, renal failure, neurological disease, and death	"Cytokine storm" IL-1, IL-6, IFNs Tipo complement activation and coagulopathy	Antibody production	Symptomatic drugs, hydration, corticosteroid, and anticoagulants if necessary

Plasmodia, the most common being *Plasmodium falciparum* and *Plasmodium vivax* [24]. Hundreds of millions of individuals are bitten by its vector, the mosquito *Anopheles*, every year [24] but not all of them will become ill. In the human circulation, the parasite can lead to macrophage activation and release of cytokines [25]. Although the release of interleukin-10 (IL-10) may have a beneficial effect, Tumor Necrose Factor Alpha (TNF-α) and Interferon Gamma (IFN-γ) will not help the underlying demyelinating MS/NMOSD. Antil treatment targets all stages of parasites and should not be a problem regarding MS/NMOSD [26]. Special care is recommended when using doxycycline, since it reduces the level of mycophenolate, a drug often used in NMOSD [27].

■ Tuberculosis

Tuberculosis remains the leading cause of death

by infectious diseases in adults worldwide [28]. *Mycobacterium tuberculosis* enters the host by air and is phagocytized by lung macrophages [29]. *M. tuberculosis* will survive and reproduce inside the macrophage thanks to a thick and protective waxy mycolic acid capsule [30]. There is a rapid elimination of the bacillus from the dead macrophage, either triggering the active tuberculosis infection or remaining silent, in the form of latent tuberculosis [30]. The release of bacilli will recruit leukocytes to the area inducing the formation of a granuloma which will further protect the *M. tuberculosis* [31]. Patients with MS/NMOSD with latent tuberculosis starting immunosuppressive treatment are at risk of reactivating the infection, since they will have alterations to their lymphocytes [32]. In addition, patients with long-term use of immunosuppressant's living in tuberculosis endemic areas may be infected or re-infected by *M. tuberculosis*. Patients who receive B-cell depleting therapies may fail to develop antibodies against *M. tuberculosis* [33]. Regardless of the immunosuppressive medication used for treating MS or NMOSD, testing for latent tuberculosis infection is of essence for patients at high risk of tuberculosis infection or reactivation [34].

■ Hansen's disease

Despite significant control of leprosy worldwide, the prevalence of the disease remains high in the 21st century [35]. Hansen's disease is caused by the *Mycobacterium leprae* bacillus leading to a chronic infection in humans. The disease affects mainly the peripheral nerves and skin but may also affect the eyes, mucous membranes, and bones [35]. Immunological response against the bacillus is impaired due to *M. leprae* specific T-cell unresponsiveness [36]. B-cells infiltrate the leprosy lesions inducing a granulomatous response [37]. There is a spectrum of disease severity and, while many patients can remain with a mild disease form, other can progress to great the proliferation of *M. leprae* bacilli in the body, causing extensive peripheral nerve damage [38]. Although there is a decrease in Th1 cell activation, patients who already have CNS disease (like MS/NMOSD), may suffer additional disability if there is damage to their peripheral nerves.

■ Syphilis

The disease is caused by *Treponema pallidum*, a spirochete renowned for its invasiveness and immune evasiveness [39]. The immunological response to *T. pallidum* is complex, starting with dendritic cells presenting treponemal antigens to T and B lymphocytes. The presence of opsonic antibodies and activated T cells cause inflammation with recruitment of macrophages, natural killer cells, histiocytes and plasma cells [40]. IFN-γ, TNF-α, IL-6 and IL-17 secreted on the site add to the intense inflammatory reaction, leading to endothelial cell swelling and proliferation that can evolve to frank endarteritis obliterans [39]. Despite the intense reactions, the spirochetes not only fail to be cleared but can replicate and circulate amid a prolific antibody response [41]. Regarding MS/NMOSD, immunosuppression in a patient with latent syphilis or a patient who later gets infected with *T. pallidum* will result in challenging treatment of both syphilis and MS/NMOSD [42]. Immunosuppressive agents can affect the cell-mediated and humoral immune response to *T. Pallidum* [43] and may also affect the response to serological tests for syphilis [44].

■ Leishmaniasis

Leishmania sp. is anthroponotic and zoonotic parasites that infect macrophages and dendritic cells [45]. The initial response to the bite of its vector, the sandfly, is innate, with neutrophils phagocytizing the parasite and later releasing it to the macrophages. Inside macrophages *Leishmania* replicate, eventually disrupting the cell, and invading more macrophages. Leishmaniasis can be cutaneous, mucocutaneous or visceral, depending on the species. The immunological response to macrophage invasion and destruction included IL-β, IL-17, TNF-α and No. The oxidative phosphorylation inside the macrophage leads to poorer cytokine production in response to the *Leishmania* invasion [46]. The B cell response to *Leishmania* is short lived and frequently unspecific for the parasite [47]. Patients with MS/NMOSD may have worse evolution due to the cytokine and oxidative responses induced by the parasite [48] as well as potential neurological complications of the disease [49].

■ Leptospirosis

Leptospirosis is an acute bacterial septicemic febrile disease caused by *Leptospira* sp. It is a zoonosis associated with chronically infected carrier animals [50]. In humans, leptospirosis has an initial septicemic phase of bacteremia followed by immune manifestations determined by a "cytokine storm" [51]. In the most severe form of the disease there is multisystem damage, including vascular, hepatic, renal, pulmonary, meningeal, and skeletal muscles injury [52]. The resulting severe disease is known as Weil's disease. In response to the "cytokine storm", there is an overwhelming production of IL-10, which will inhibit the protective Th1 response against the bacteria [52]. B cell response increases with the aggressiveness of the disease [53]. Although not confirmed, the severity of leptospirosis may increase in immunosuppressant conditions [54].

Patients with MS/NMOSD who live in areas without good sanitation and prone to heavy rainfall should be educated on the risks and avoid infections with *Lepstospira*.

■ Human Immunodeficiency Virus (HIV)

The association of the retrovirus HIV with NMOSD has been described in a few papers [55]. On the other hand, MS has been infrequently described in association with HIV infection [56] NMOSD is a B-cell mediated disease that appears to occur in the T-cell regulatory dysfunction secondary to HIV infection [55]. On the contrary, the very low count of T CD4 lymphocytes seems to be a protective factor for developing MS.

Although physicians might expect worsening of autoimmune diseases during retroviral therapy against HIV, this does not seem to occur [57]. While some authors reported that it is safe to prescribe azathioprine for patients with HIV [58]. The treatment of an immunosuppressive disease in conjunction with an autoimmune one remains challenging.

■ Human T-Lymphotropic Virus (HTLV)

Also known as "Human T-cell leukemia virus", HTLV is another retrovirus with four subtypes. For the present review, the authors concentrated on HTLV1, a virus associated to myelopathy leading to tropical spastic paraparesis [59,60]. The spastic paraparesis determined by HTLV1 is a differential diagnosis for patients with MS/NMOSD. Infection of Th1 CD4+ lymphocytes in the spinal fluid seems to be crucial for the development of paraparesis [61]. Modulation of pro- and anti-inflammatory T cell cytokines can alter the level of tissue damage in HTLV1 [62]. A lymphocytic infiltration and foamy macrophages are observed in the parenchyma of the mid- to lower spinal cord of patients with HTLV1. In addition, meninges are thickened and there is sparse white cells infiltration in the perivascular areas of the spinal cord and the brain [57]. As the B-cell response to HTLV1 is important [63,64], the use of anti B cell therapy for MS/NMOSD may be challenging. The paraparesis determined by this infection is often confounded with progressive MS.

■ Arboviruses

The family of vector-borne viruses known as arboviruses comprises Dengue Virus (DENV), West Nile Virus (WNV), Chikungunya Virus (CHIKV), Yellow Fever Virus (YFV) and Zika (ZIKV) [65] and many others. Some transmission cycles are relatively simple involving one vector and one host, like DENV, CHIKV and ZIKV [66]. Less often, as it happens with the WNV, there is a complex list of vectors and hosts. The infection is characterized by a "cytokine storm", a large increase of IL-10 and antibodies that are not specific to all viruses and to all viral strains [67]. It is important to highlight the "antibody-dependent enhancement" observed in further infections by arboviruses, mainly DENV during which viral internalization is facilitated by previously elicited low affinity non-neutralizing antibodies and FcγRs. Additional infections to the same individual tend to be more severe [68]. Optic neuritis and/or myelitis may follow dengue fever infection, suggesting a new relapse of a demyelinating disease [69,70].

■ Coronaviruses

Well-known for their extensive range of hosts, coronaviruses have the largest known viral RNA genome [71]. Human coronaviral infections are usually associated with upper respiratory tract infections, fever, headache, and cough [71]. In contrast, coronaviral infection associated to acute respiratory syndrome may remain asymptomatic; have mild or moderate influenza-like symptoms, or present severe pneumonia, dyspnea, renal insufficiency, and even death [72]. Declared a pandemic, the latest coronavirus outbreak in 2020 has changed the way people socialize, work, and relate to the world. This latest coronavirus disease is now known as COVID-19 (related to the first description in late 2019). The immunological response to this coronavirus in the lungs can be intense, with vast release of cytokines in the alveoli resulting in massive inflammatory reaction [73].

Therapeutic options for MS and NMOSD

Treatment of MS can be carried out with several immunomodulatory and immunosuppressive drugs, specially developed for this disease. On the other hand, NMOSD is treated with unspecific immunosuppressant's, corticosteroids or plasmapheresis. Potential therapies for NMOSD are being studied [74,75].

Summarized mechanisms of action of each drug currently used to treat MS and NMOSD are presented in **TABLE 2**.

Recommendations for treating patients with MS and NMOSD

Patients living in endemic zones should always be reminded and educated about potential infections. They need to know how to recognize the signs and symptoms of , tuberculosis, Hansen's disease, syphilis, leishmaniasis, leptospirosis, HIV, HTLV, arboviruses and coronaviruses. Patients must be aware that some

TABLE 2. Summarized mechanism of action of drugs used to treat multiple sclerosis and neuromyelitis optica spectrum disorders.

Drug	Main mechanism of action	Potential risks for tropical infections
1. Auto-injectables		
Interferon beta [67]	Increase the expression and concentration of anti-inflammatory agents while downregulating the expression of proinflammatory cytokines	None
Glatiramer acetate [68]	Expansion of T-helper 2 and regulatory T cells by targeting the antigen-presenting cells. Induction of neurotrophic factors release	None
2. Oral drugs		
Teriflunomide [69]	Selective and reversible inhibition of dihydro-orotate dehydrogenase, blocking the de novo pyrimidine synthesis pathway. Leads to a reduction in proliferation of T and B lymphocytes without causing cell death	Persistent, mild to moderate lymphopenia
Dimethyl fumarate [70]	Anti-inflammatory immune response due to nuclear factor erythroid-derived 2-related factor (Nrf2)-dependent and independent pathways activation. Anti-oxidative mechanisms. Increased Th2 cell differentiation. Neuroprotection	Persistent, mild to moderate lymphopenia
Fingolimod [71]	Modulation of sphingosine-1 phosphate receptors with subsequent prevention of lymphocyte efflux from lymphoid tissues	Persistent, moderate to severe lymphopenia
Cladribine [72]	It affects DNA synthesis and repair, leading to DNA strand breaks and ultimately cell death. Targets circulating T and B lymphocytes	Transient severe lymphopenia
Azathioprine [73]	Mercaptolysis mediated by a nucleophilic attack of the imidazole ring of the azathioprine molecule	Persistent, mild to moderate lymphopenia
Mofetil mycophenolate [74]	It is a potent and reversible uncompetitive inhibitor of inosine monophosphate dehydrogenase, affecting the de novo purine synthesis pathway. It suppresses dendritic cell maturation	Persistent, mild to moderate lymphopenia
Siponimod [75]	Newer generation of sphingosine-1 phosphate receptor modulator with subsequent prevention of lymphocyte efflux from lymphoid tissues	Persistent, moderate to severe lymphopenia
3. Monoclonal antibodies		
Natalizumab [76]	Anti-alpha-4 chain of the very late activating antigen 4 and α4β7 integrins, inhibits the translocation of activated VLA-4-expressing leukocytes across the blood-brain barrier into the central nervous system	No peripheral lymphopenia, but decreased immune vigilance of the central nervous system
Alemtuzumab [77]	Anti-CD52, leads to a rapid, but long-lasting depletion of CD52-bearing B and T cells with reprogramming effects on immune cell composition resulting in the restoration of tolerogenic networks	Transient severe lymphopenia
Ocrelizumab [78]	Anti-CD20, induces a complement-dependent lysis of and/or antibody-dependent cytotoxicity towards B cells	Transient severe B-cell lymphopenia
Rituximab [79]	Anti-CD20, complement-mediated and antibody-dependent cellular cytotoxicity leading to B lymphocytes depletion	Transient severe B-cell lymphopenia
4. Other drugs		
Corticosteroids [80]	Resolution of edema, reduction of T and B lymphocytes, and (at least partial) recovery of the blood-brain barrier permeability. Blockade of NF-KB dependent gene.	Transient mild lymphopenia
		If used in long-term, corticosteroids are immunosuppressive

of these diseases may worsen the underlying MS or NMOSD simply because they alter the cytokine profile or affect peripheral nerves. In fact, sometimes the tropical diseases may mimic a demyelinating attack of MS or NMOSD.

During the patients' clinical evaluation, epidemiological information on all these tropical diseases must be obtained. Clinical examination of the skin may suggest underlying diseases that have not been diagnosed before. Beyond usual recommendations for laboratory screening (for example, hepatitis, kidney disease etc.), we propose that patients living between the tropics of Cancer and Capricorn be regularly screened with the tuberculin Purified Protein Derivative (PPD), chest radiography, serological testing for HIV, HTLV1 and HTLV2, and syphilis. White cell counting for those patients using drugs leading to lymphopenia must be carried out every 30 days to 90 days. Routine Magnetic Resonance Image (MRI) does not help early identification of tropical infections in the CNS. Whenever spinal fluid is collected for evaluation, immunological testing for the abovementioned infections must be investigated.

In the presence of neurological symptoms during treatment, tropical infections must always be part of the differential diagnoses work-up if the patient lives in endemic areas. In addition, foreigners who visit endemic areas and later develop a probable "bout" of MS or NMOSD must be tested for tropical diseases. It is not rare that "flares" of MS or NMOSD are, in fact, manifestations of tropical infections in the CNS.

At a time when "no evidence of disease activity"

is the goal of MS therapy, protocols should not be the same for the whole world. The risk of infections in patients with MS is an important factor in the choice of therapy, and this risk is not the same everywhere. Therefore, protocols that are designed in high latitude areas may not consider potential infections that are prevalent in the tropical and equatorial zones.

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