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Identifying the culprits in neurological autoimmune diseases

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ABSTRACT

The target organ of neurological autoimmune diseases (NADs) is the central or peripheral nervous system. Multiple sclerosis (MS) is the most common NAD, whereas Guillain-Barré syndrome (GBS), myasthenia gravis (MG), and neuromyelitis optica (NMO) are less common NADs, but the incidence of these diseases has increased exponentially in the last few years. The identification of a specific culprit in NADs is challenging since a myriad of triggering factors interplay with each other to cause an autoimmune response. Among the factors that have been associated with NADs are genetic susceptibility, epigenetic mechanisms, and environmental factors such as infection, microbiota, vitamins, etc. This review focuses on the most studied culprits as well as the mechanisms used by these to trigger NADs.

1. Introduction

Autoimmune diseases (ADs) are chronic conditions initiated by the loss of immunological tolerance to self-antigens and represent a heterogeneous group of disorders that affect specific target organs or multiple organ systems [1]. Neurological autoimmune diseases (NADs) are organ specific ADs that affect the central or peripheral nervous system. Although these diseases are well-categorized, some of their manifestations are found in non-neurological conditions, thus hindering the effort to differentiate them from either systemic or organ specific ADs. Multiple sclerosis (MS) is the most common NAD with a prevalence of 30.1 cases per 100.000 people worldwide, and an increase in cases per year of around 22.5 per 100.000/habitants between 1999 and 2016. This represents a global increase in the burden associated with this condition in the last two decades [2]. Other NADs such as Guillain-Barré syndrome (GBS), myasthenia gravis (MG), and neuromyelitis optica (NMO) are less common than MS with an incidence of 3.3/100.000/year, 1–9/100.000/year 0.5–10/100.000 respectively. These NADs have shown an exponential increase in occurrence in recent years [3].

The highest incidence of NADs is observed in industrialized areas, especially in North America and Europe. This could be explained by a continuous interplay between genetic and environmental factors such as low levels of vitamin D [4] and the lack of exposure to parasites (i.e. hygiene hypothesis) [5]. Among the environmental culprits incriminated for triggering and exacerbating NADs, the ones that have been studied the most are infections, gut microbiota which are closely related to diet, smoking, air pollution, vitamins, stress, vaccination, and medication.

2. Neurological autoimmune diseases

NADs affect the central nervous system (CNS) and the peripheral nervous system (PNS). These ADs can be recognized based on their immunological mechanism:

1. Autoantibody: Pathogenic autoantibodies bind antigens such as aquaporin-4 (AQP4), N-methyl-D- aspartic receptor, and acetylcholine receptor (AChR). Antagonist effects, receptor interlacing, complement activation, and cytotoxicity mediate the mechanisms of cellular dysfunction or injury.
2. T-cell: Effector T cells induce cell death.
3. Neuroinflammation: Histiocytes participate in chronic inflammation since activated macrophages interact with $CD4^+$ T cells.
4. Iatrogenic autoimmunity: Immune checkpoint inhibitors can lead to adverse events related to neurological disorders [6].

In the following sections, the most relevant clinical and pathophysiological features of MS, GBS, MG and NMO are described.

2.1. Multiple sclerosis

MS is a chronic AD which mainly targets the CNS. The immune system attacks myelin and neuron proteins, thus inducing demyelination of neuronal axons, cell death, and astrocytic gliosis. MS patients can develop different degrees of neurological disorders that lead to chronic disability due to sensory, motor, autonomic, visual, and cognitive damage [7]. $CD4^+$ T cells are key to MS progression through the release of

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Abbreviations

AChR	acetylcholine receptor
AD	autoimmune diseases
AhR	aryl hydrocarbon receptor
AIDP	acute inflammatory demyelinating polyneuropathy
AMAN	acute motor axonal neuropathy
AMSAN	acute motor sensory axonal neuropathy
APC	antigen-presenting cell
AQP4	aquaporin-4
BBB	blood-brain barrier
C. jejuni	*Campylobacter jejuni*
CHIKV	Chikungunya virus
C. pneumoniae	*Chlamydia pneumoniae*
CMV	Cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CTLA-4	cytotoxic T-lymphocyte antigen 4
DENV	Dengue virus
DMP	differentially methylated position
DNMT	DNA methyltransferases
EAE	experimental autoimmune encephalomyelitis
EAMG	experimental autoimmune myasthenia gravis
EBNA1	Epstein-Barr nuclear antigen 1
EBV	Epstein-Barr virus
EOMG	early-onset myasthenia gravis
EWAS	epigenome-wide-association studies
GBS	Guillain-barré syndrome
GC	germinal center
GM-CSF	granulocyte macrophage colony-stimulating factor
GPR15	G protein-coupled receptor 15
HDAC	histone deacetylases
HEV	Hepatitis E virus
HHV	human Herpes virus
IFN	interferon
IL	interleukin
LOMG	late-onset myasthenia gravis
LTA	lipoteichoic acid
MAPK	mitogen-activated protein kinase
MBP	myelin basic protein
MFS	Miller-Fisher syndrome
MG	myasthenia gravis
MHC	major histocompatibility complex
miRNA	microRNA
MOG	myelin oligodendrocyte glycoprotein
MRI	magnetic resonance imaging
MS	multiple sclerosis
M. pneumoniae	*Mycoplasma pneumoniae*
MZ	monozygotic
NAD	neurological autoimmune diseases
NFkB	nuclear factor kappa B
NMO	neuromyelitis optica
NMOSD	NMO spectrum disorders
NO2	nitrogen dioxide
O3	ozone
PADI	peptidyl arginine deaminases
PBMCs	peripheral blood mononuclear cells
PM	particulate matter
PNS	peripheral nervous system
PTPN22	protein tyrosine phosphatase non-receptor type 22
RRMS	relapsing-remitting multiple sclerosis
SNP	single-nucleotide polymorphism
STAT4	signal transducer and activator of transcription 4
S. pneumoniae	*Streptococcus pneumoniae*
TA	teichoic acid
TET	ten-eleven-translocation
TLR	toll-like receptor
TNF	tumor necrosis factor
VDR	vitamin D receptor
VDRE	vitamin D response element
ZIKV	Zika virus

pro-inflammatory cytokines by Th1 and Th17 cells that induce infiltration of immune cells into the CNS, thus beginning an autoimmune reaction to neuronal components [8]. Cytotoxic T cells contribute to MS by recognizing peptides presented by MHC-I on the surface of neuronal axons which leads to glial cell death [9]. In addition, there is evidence that B cells also participate in the MS pathogenesis. Phagocytic cells and macrophages boost the pro-inflammatory response of T and B cells thus causing tissue damage. During the progressive phase of MS, immune responses are restricted to microglia activation, monocytic and lymphocytic infiltrates, degeneration of demyelinated axons, and alteration of astrocytes [10].

2.2. Guillain-Barré syndrome

GBS, an inflammatory autoimmune demyelinating disease and the most severe acute paralytic neuropathy, is characterized by symmetrical and rapidly evolving weakness of arms and legs, hypo- or areflexia alterations, and autonomic alterations [11]. Several subtypes with different clinical and pathological features represent GBS. Acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN) are the most common GBS subtypes, whereas Miller-Fisher syndrome (MFS) is the least frequent one. GBS development is mainly preceded by infections which trigger molecular mimicry against gangliosides along the membrane of the peripheral nerves. This induces an aberrant autoimmune response that results in damage or a blockade of nerve conduction [12]. Infection with *Campylobacter jejuni* *(C. jejuni)* is the most common factor in GBS development. However, genetic, epigenetic, and environmental factors might play an important role in the etiology of this disease.

2.3. Myasthenia gravis

This is a rare autoimmune neuromuscular disease characterized by muscle weakness and fatigability. It is mediated by B and T cell responses, complement, and pathogenic autoantibodies reacting to proteins such as AChR, lipoprotein receptor-related protein 4, which is present in the postsynaptic membrane, or to the muscle-specific kinase in the neuromuscular junctions [13]. Patients with MG show elevated anti-AChR Th1 cells, which stimulate B cells to produce anti-AChR antibodies. Moreover, these Th1 cells in the experimental autoimmune myasthenia gravis (EAMG) model produce IFN-γ, and TNF-α, thus maintaining the pro-inflammatory environment. On the other hand, anti-AChR Th2 have contrary dual functions since these cells can be protective, but their secreting cytokines IL-5, IL-6, and IL-10 seem to exacerbate EAMG [14]. In addition, APCs induce the secretion of IL-18, which stimulates NKs to produce IFN-γ, thus polarizing T cells to Th1 which maintains EAMG pathogenesis.

2.4. Neuromyelitis optica

NMO is an AD of the CNS that predominantly affects the optic nerves and spinal cord. It is sometimes referred to as NMO spectrum disorder

(NMOSD). A study of active lesions in NMO patients showed extensive demyelination, necrosis, cavitation, and acute axonal damage. These findings were correlated with infiltration of macrophages, neutrophils, eosinophils, but seldom T cells or deposition of antibodies and complement [15]. The immunological hallmark of NMO is the presence of antibodies against AQP4, a protein involved in water and ion homeostasis maintenance in the CNS. Cytotoxicity is mediated by anti-AQP4 and complement, which are responsible for the astrocyte lesions. Other non-inflammatory mechanisms that contribute to injury are internalization of AQP4 and the glutamate transporter [16].

3. Genetic factors

Today, with the use of high-throughput technologies such as genome-wide association in large studies, it is possible to identify genetic variants or polymorphisms associated with ADs in different populations. These alterations are related to not only disease risk, but also specific clinical manifestations [17]. In MS, a large number of susceptibility variants have been identified in or close to more than 100 immunologically and neurologically important genes. Of these, 110 are non-HLA related, and 13 are HLA-related genetic loci [18]. One of the most important risk gene variants is *HLA-DRB1*15:01*, which increases the risk 3-fold [19]. Presentation of peptides by *HLA-DRB1*15:01* is important in regulating T cells, which are essential in MS pathogenesis. These peptides are considered to be hydrophobic and are among several proteins in the myelin sheath [20]. Molecular mimicry and epitope spreading are mechanisms whereby *HLA-DRB1*15* participates in the activation of T cells, by presenting myelin and Epstein-Barr virus (EBV) peptides [21]. Moreover, interactions between *HLA-DQA1*01:01/HLA-DRB1*15:01* and *HLA-DQB1*03:01/HLA-DQB1*03:02* alleles contribute substantially to the risk of MS development [22]. As mentioned above, non-HLA genetic variants such as *IL2RA* also influence the risk of developing MS, which is central for expansion, differentiation, and apoptosis of Th cells. The *IL2RA* variant (rs2104286) increases the frequency of granulocyte/macrophage colony-stimulating factor (GM–CSF)–producing Th cells. GM-CSF expression is associated with MS severity [23]. *IL7RA* is critical to the VDJ recombination process during lymphocyte development. Furthermore, IL7/IL7R interaction is very important in proliferation and differentiation of $CD4^+$ T cells. *IL7RA* rs3194051, rs987107, and rs11567686 variants contribute to the genetic susceptibility of this disease [24]. The *CD226* gene encodes a glycoprotein expressed in NK cells and in some T cell subsets that control NK cell cytotoxicity. In MS, the *CD226* variant rs76336 that reduces CD226 expression is associated with a higher threshold for NK-cell activation [25]. The rs11129295 variant of the eomesodermin gene, which encodes for several transcription factors that are important for defending against viral infections, is reduced in MS patients [26]. Nuclear factor κB (NF-κB) is a crucial transcription factor in inflammation since it induces the expression of pro-inflammatory genes. The *NFκB1* rs228614-G variant is associated with an increase in p50 NFκB expression and diminished negative regulators of NFκB signaling in MS [27].

Concerning GBS, the genetic contribution to this disease has been modestly studied and only in small cohorts of patients. It is usually preceded by infectious agents, and little is known about its genetic component [28]. Several studies have shown that *HLA-DQB1*03* and *HLA-DQB1*060x* polymorphisms are associated with the risk of GBS development [29]. In addition, Sinha et al. [29], identified *HLA-DRB1*0701* as a novel risk factor in individuals with evidence of recent infections. Moreover, *HLA-DRB1* and *HLA-DQB1* alleles of patients from northern China were differentially distributed in AIDP and AMAN subtypes respectively [30]. This was extensively reviewed in Rodríguez et al. [31]. Furthermore, a meta-analysis evaluated the contribution of polymorphisms in *TNFα*, *FCγrIII*, *CD1*, Toll-like receptor (*TLR)* 4, and immunoglobulin *KM* genes to GBS susceptibility. In this analysis, genetic polymorphisms and the risk of GBS were inconclusive. Only a moderate association with the *TNFα-308* (G/A) polymorphism was identified [32]. This is a pro-inflammatory cytokine mainly produced by monocyte-macrophages, and its variant correlated with augmented levels of TNF-α in Japanese [33], Chinese [34] and Indian patients [35]. Heterozygous genotype *TNFα-308* (G/A) had an association with AMAN, and the homozygous genotype (A/A) was related to AMAN and acute motor sensory axonal neuropathy (AMSAN). In addition, the *TNFα-857* (C/T) polymorphism has been associated with AMAN [35]. The *TNFα-863* allele was also found to be a potential genetic factor associated with GBS development [36]. Moreover, polymorphisms in the *FcγR* gene are related to increased risk of GBS in British and Dutch patients. Specifically, *FcγRIIIA* and *FcγRIIIB* seem to play a role as mild disease modifying factors in GBS [37]. Finally, an Italian study demonstrated that *CD1A* and *CD1E* polymorphisms in *CD1*, a gene that encodes a glycoprotein involved in the presentation of lipids to T cells, were associated with susceptibility to GBS apart from any recent *C. jejuni* infection or the presence of ganglioside autoantibodies [38].

Like other NADs, genetic susceptibility in MG is mainly attributable to HLA alleles. The ancestral haplotype 8.1 (*A1-B8-DR3-DQ2*), a common haplotype in Caucasians, is associated with early-onset of MG (EOMG) [39]. Studying a Chinese cohort, Zhu et al. [40], found that *HLA-DQA1/DQB1* haplotypes were strongly related to the onset of ocular MG in children. Particularly, *HLA-DQA1*03:02/DQB1*03:03:02* (*DQ9*) was significantly associated with this disease, and its association was not related to the AChR antibody production. Furthermore, other studies in Norwegian and Italian patients associated *HLA-DRB1*15:01*, *HLA-DRB1*16* and *HLA-DQB1*05:02* with an increased risk of late-onset MG (LOMG) [41,42]. In addition to HLA, there are non-HLA genes associated with MG. One of the most relevant susceptibility genes is *PTPN22*, which has a protein that participates in the inhibition of T-cell activation [13]. The *PTPN22* R620W variant may produce a hyper-response in allele-specific T cells that could result in individuals developing autoimmunity [43]. Moreover, a functional single-nucleotide polymorphism (SNP) in the *TNFα*-308 is associated with higher levels of TNF expression and a more severe MG outcome [44]. Polymorphisms of *IL4RA* gene were found to be associated with adult thymoma and the presence of anti-AChR antibodies in MG patients [45]. Other gene variations associated with a minor or moderate risk of MG have been identified. Polymorphisms at the *CTLA4* gene, which encodes for a negative regulator of T cells, may cause aberrant splicing and T-cell abnormalities, thus contributing to MG pathogenicity [13]. *AChR* gene subunit *CHRND*, encodes a protein that shows epitopes to T and B cells. Polymorphisms in this gene (i.e. rs1004432, rs1550093, and rs2767) disrupt a transcription binding motif [46]. The frequency of the variant *FcγRIIα-R/R131* is higher in MG patients, and it modifies B-cell activation and clears ineffectively small AChR IgG complexes [47]. *IL1β Taq I* polymorphism allele 2 is associated with IL-1β high-secretor phenotype in MG, thus maintaining the inflammatory environment [48]. *IL-10.G* allele 134 is located between −1193 and −1150 in the promoter region of *IL-10* and contributes to the increase in IL-10, B-cell expansion, and production of nAChR autoantibodies [49]. Finally, STAT4 is activated after IL-12 stimulation and mediates the differentiation of naïve $CD4^+$ T cells to Th1 cells. In addition, IL-12Rβ2 contributes to the recruitment and activation of STAT4. In EOMG, *STAT4* variant rs7574865 possibly influences Th1 activation, whereas *IL12Rβ2* variant rs6679356 is associated with LOMG [50].

Finally, several HLA-I and HLA-II alleles have been studied in NMO genetic susceptibility. Canadian aboriginals with *DRB1* and *DQB1* alleles showed an association with demyelinated lesions in the optic nerve and cervical spinal cord [51]. Additionally, Brazilian afro-descendant, Caucasian, and Mestizo patients presented the *HLA-DRB1*03:01* allele which was associated with NMOSD regardless of anti-AQP4 status [52]. Other *HLA-DRB1* alleles reported to be associated with the risk for NMO are *HLA-DRB1*04:04* and *HLA-DRB1*10:01* in Muslim Arabs [53], *HLA-DRB1*04:02* in Danish Caucasians [54], *HLA-DPB1*05:01* in African-American and Latino populations [55] and *HLA-DRB1*16:02* in the Chinese population [56]. Wei et al. [57], also showed that 3′ UTR of

AQP4 has several polymorphic sites that may affect protein and contribute to NMO pathogenesis. In addition, four *STAT4* SNPs revealed a significant association with an increased risk of NMOSD [58]. Other non-HLA genes exert an increase in relative risk for NMO/NMOSD pathogeneses that range from modest to high. This is the case for *CYP7A1* that is associated with alterations in transcriptional regulation [59], *IL17* which produces high levels of IL-17 [60], *CD226* that affects T-cell signaling [61], *PD1* that interferes in T-cell activation [54], *CD40* that produces alterations in the TNFR family [62], and *CD58* that is involved in cell adhesion [63]. Table 1 summarizes the presence of genetic variants associated with other NADs.

4. Epigenetic factors

Epigenetics refers to alterations in gene expression apart from DNA sequence. DNA methylation, histone modifications, and non-coding RNAs are epigenetic mechanisms that influence the regulation of gene transcription and genomic stability [64]. In addition to genetic factors, epigenetic factors are regulators of the immune response. In the last decade, researchers have shown that epigenetics is crucial in autoimmune processes and neuronal development in neurological disorders [65].

4.1. DNA methylation

DNA methylation is the adjunction of a methyl group at the 5′-carbon position of a cytosine in a pyrimidine ring. Two processes regulate the level of methylation: 1. DNA methylation by DNA methyltransferases (DNMT) such as DNMT1, DNMT3a, and DNMT3b which are active mediators of gene transcription silencing [66]. 2. DNA demethylation is mediated by deaminases, glycosylases, and ten-eleven-translocation (TET) enzymes (i.e. TET1, TET2, and TET3) [67]. DNA methylation at CpG sites or within gene promoters produces the silencing of gene expression. In contrast, DNA demethylation in gene promoters leads to transcriptional activation and gene expression [68].

In MS, it has been shown that DNA methylation within gene promoters or CpG sites plays a central role in the onset and progression of this disease. Epigenome-wide association studies (EWAS) describe differentially methylated CpG positions (DMP), including the *HLA-DRB1* locus. This methylation mediates the effect of the MS risk variant *HLA-DRB1*15:01* [69]. Another EWAS done by Baranzini et al. [70], in MS-discordant monozygotic (MZ) twins detected only 2 out of 176 changes in the methylation of 2 million CpG dinucleotides between twins. However, a recent study of a larger cohort of 45 MZ twins observed changes in DNA methylation. Indeed, DMPs *ZBTB16*, and *TMEM232* are related to long-standing MS [71]. A study done of 51 MS patients and 137 healthy individuals found a hypermethylation in repetitive elements (i.e. Alu, SAT-α, and LINE-1) associated with disease

Table 1
Genetic factors in neurological autoimmune diseases.

Neurological autoimmune disease	Gene variant	Alteration-Mechanism	Reference
Autoimmune ataxia	*CACNA1A*	Mutation in intron 39 (c5843-14G>A) play an essential role in calcium channels.	[227]
	ITPR1 c.7721T>C(p.V2574A)	Alteration in IP3 signaling by disrupting the calcium influx.	[228]
Autoimmune epilepsy	*LGI1*	Modulation of Voltage-Gated Potassium Channel activity.	[229]
Neuro-Behçet's disease	Linkage disequilibrium between *HLA-B*51* and *MIC-A009*	Alteration in antigen presentation.	[230]
	IFI16 SNP rs6940	Alteration in the levels of this molecule leading to over-expression of type I IFN.	[231]
	Intergenic region between *IL23R* and *IL12RB2* SNP rs12119179	Increase of Th17 cell proliferation and inflammatory cytokine release.	[232]
	IL-10 rs1518111	Low expression of IL-10.	[233]
	STAT4 rs7574070 in intron 3	High expression of STAT4.	[234]
	ERAP1p.Asp575Asn and p.Arg725Gln rs17482078	Alteration of peptide trimming and antigen presentation by MHC I.	[234]
Chronic inflammatory demyelinating polyneuropathy	*TAG−1 rs2275697*	Disruption of juxtaparanodal molecules, which alter the distribution of Kv channels.	[235]
	*HLA- DRB1*13, HLA-DRB1*10, DRB1*07/ DQB1*03*	Alteration in antigen presentation.	[236]
	SH2D2A genotype GA13-16 homozygote	Defective control and elimination of autoreactive T-cells.	[237]
Lambert-Eaton syndrome	*HLA-B8, HLA-DR3* and *HLA-DQ2*	Alteration in peptide presentation.	[238]
Myopathies (PS/DM)	*HLA-DRB1*03:01, HLA-DQA1*05:01, HLA-DQB1 *02:01*	Alteration in peptide binding and genetic susceptibility to anti-Jo1.	[239]
	TNFα −308 and −1031T alleles	Induction of high circulating levels of TNF-α in serum.	[240]
	IL1α +4845TT/*IL1β*+3953T	Overexpression of these pro-inflammatory cytokines.	[241]
	MBL2 (Asp54 allele, Glu57 allele)	Low serum levels of MBL leading to alterations in clearance of apoptotic cells and control of pro-inflammatory cytokines.	[242]
	PTPN22 R620W rs2476601	Dephosphorylation of signaling proteins, increasing circulation of autoreactive T cells.	[243]
	STAT4 rs7574865	Increase and/or prolong STAT4 protein activity.	[244]
	TNFAIP3 rs2230926, rs5029939	Decrease of A20 expression that inhibits the activation of *NF-κB* signaling pathways.	[245]
	IRF5 rs4728142	Participation in type I IFN signaling pathway.	[245]
Narcolepsy	*HLA DQB1*06:02, HLA-DRB1*15:01*	Activation of cross-reactive T cells, destruction of hypocretin-producing neurons.	[246]
	TNFSF4 rs7553711	Dysregulation in co-stimulation of T cells.	[247]
	CTSH rs2289702, rs34593439	Modification of the MHC II-peptide repertoire presented to T cells.	[247]
	P2RY11 rs2305795	Decrease expression in LT $CD8^+$ and NK cells.	[248]

CACNA1A: calcium voltage-gated channel subunit alpha1 A, *ITPR1*: inositol 1,4,5-trisphosphate receptor type 1, *LGI1*: leucine-rich glioma inactivated 1, *HLA*: human leukocyte antigen complex, *IFI16*: interferon gamma inducible protein 16, *IL23R*: interleukin 23 Receptor, *IL12RB2*: interleukin 12 Receptor Subunit Beta 2, *IL10*: interleukin 10, *STAT4*: signal transducer and activator of transcription 4, *ERAP1*: endoplasmic reticulum aminopeptidase 1, *TAG1*: transient axonal glycoprotein-1, *SH2D2A*: SH2 Domain Containing 2 A, DM: dermatomyositis, PM: polymyositis, *TNF*: tumor necrosis factor, *IL1:* Interleukin 1, *MBL2*: Mannose binding lectin, *PTPN22*: protein tyrosine phosphatase non-receptor type 22, *TNFAIP*: TNF alpha induced protein, *IRF5*: interferon regulatory factor 5, *TNFSF4*: TNF superfamily member 4; *CTSH*: cathepsin H, *P2RY11:* purinergic receptor subtype 2Y11.

severity [72]. A study of cell-free plasma DNA from patients at relapsing-remitting MS (RRMS) found differences in the methylation of 15 gene promoters, especially in the cyclin dependent kinase inhibitor 2B [73]. Calabrese et al. [74] described modifications in the methylation level of *TET2* and *DNMT1* gene promoters in peripheral blood mononuclear cells (PBMCs) from MS patients. These alterations led to downregulation of DNMT1 and TET2 levels. Furthermore, downregulation of *TET3* genes in secondary progressive MS patients has also been reported [75].

DNA demethylation has been demonstrated in genes involved in the immune response and T-cell differentiation such as *FOXP3*, *IFNG*, *IL17*, and *IL13* [76]. In contrast, leukocytes from MS patients have hypermethylation in the promoter region of *SHP1*, a negative regulator of the pro-inflammatory response [77]. Another EWAS identified modifications in the overall DNA methylation in $CD4^+$ and $CD8^+$ T cells [78]. Furthermore, this study demonstrated that CpG of $CD8^+$ T cells from MS patients are hypermethylated in promoter regions [78]. Graves et al. [79], showed differences in the methylation of *HLA-DRB1* in $CD4^+$ T cells, whereas Ewing et al. [80], showed more methylation changes in B cells and monocytes than in T cells. Additionally, there is evidence in the brain of MS patients of changes in DNA methylation such as hypomethylation in peptidyl arginine deaminases (PADI) 2, an enzyme involved in the citrullination of the myelin basic protein (MBP), which favors the breakdown of myelin in MS patients. In fact, the white matter from postmortem brains of MS patients disclosed low methylation patterns in the *PADI2* promoter [81]. In addition, in brains from MS patients there was hypermethylation of oligodendrocyte survival genes such as *NDRG1* and *BCL2L2*. In contrast, *LGMN* and *CTSZ* genes associated with proteolytic processing were hypomethylated [82].

In MG, few studies have evaluated DNA methylation as the culprit of the disease. Mamrut et al. [83], evaluated the methylome of peripheral monocytes in MZ twins. More than 1800 methylated CpGs were different between MG patients and controls, which seems to contribute to the development of the disease. Research has shown an association between the genetic predisposition of *CTLA4* and MG development. Fang et al. [84], showed that *CTLA4* methylation is lower in MS patients than in controls. This methylation pattern is associated with thymus status. Moreover, *in vitro* inhibition of *CTLA4* methylation suppresses the expression of AChR-Ab, IL-2, IL-10, TGF-β, and IFN-γ as well as reducing E-AChE activity and the percentage of Treg cells.

4.2. Histone post-translational modifications

Histones are essential proteins in the conformation of chromatin and regulation of gene expression. Modifications in the histone tails can alter the structure of chromatin by either activating or suppressing gene expression. These modifications are acetylation, methylation, or citrullination by enzymes such as acetyltransferases, histone deacetylases (HDAC), methyltransferases, demethylases, and deaminases [85].

In the case of MS, Singhal et al. [86], found reductions in histone H3 methylation associated with mitochondrial defects in postmortem gray matter from MS patients. PAD4 nuclear translocation resulting from an increase in histone H3 citrullination induces apoptosis of oligodendrocytes in MS patients [87]. In the experimental autoimmune encephalomyelitis (EAE) model, it was demonstrated that an increase in lysine acetylation on MBP is associated with the neurological disability seen in this model [88]. Moreover, MS patients have greater HDAC3 expression, thus increasing resistance to T cell apoptosis and favoring autoimmunity [89]. HDAC inhibitors have immunosuppressive functions in MS. These inhibitors change the Th1/Th2 balance and reduce the production of pro-demyelinating cytokines such as IL-12, IL-6, and TNF-α [90]. Pedre et al. [91], demonstrated changes in histone acetylation related to high levels of inhibitors of oligodendrocyte differentiation in the white matter. The authors also concluded that early MS lesions have high oligodendroglial histone deacetylations. Martin et al. [92] reported a decreased expression of SIRT1 in MS patients during relapses. SIRT1 is a histone deacetylase that induces chromatin silencing. Therefore, SIRT could be considered a therapy for neurodegenerative disorders of CNS [93].

4.3. MicroRNA

MicroRNA (miRNA) are small noncoding single-stranded RNAs that regulate gene expression at the post-transcriptional and post-translational level. miRNAs bind to complementary sequences within the 3′ UTR of a transcript. This is how miRNAs inhibit transcription activity, reduce mRNA stability, and regulate protein expression [94]. The deregulation of miRNAs leads to diverse NADs. In MS, miRNAs induce Th17 and Th1 cells, thus leading to a deleterious activation of microglia. In comparisons of MS patients and healthy individuals, numerous studies have observed changes in the expression profile of miRNAs. Keller et al. [95], found more than 165 different miRNAs with hsa-miR-145 being the most discrepant between groups. Other miRNAs such as hsa-miR-326, hsa-miR-155, hsa-miR-146a, and hsa-miR-142-3p are overexpressed in RRMS patients [96]. hsa-miR-326 and hsa-miR-155 are related to Th17 differentiation and inflammatory demyelination [97]. Moreover, miR-155 is involved in the permeability of the blood-brain barrier (BBB) and neurodegeneration [98]. hsa-miR-146a and hsa-miR-142-3p regulate T cell activation [99], while miR-125a-3p controls oligodendroglial maturation. MS patients with active demyelinating lesions have high levels of miR-125a-3p in the cerebrospinal fluid (CSF) [100].

White matter in MS patients has a different miRNA profile. This post-transcriptional deregulation made it possible to identify altered CNS signaling pathways as mitogen-activated protein kinase (MAPK) [101].

Several miRNAs have been associated with MG development. These miRNAs regulate genes involved in the MAPK signaling pathway such as *MAPK1*, *RAF1*, *PGF*, *PDGFR*A, *EP300*, and *PPP1CC* [102]. In MG patients, miR-320a is downregulated, and this modulates the production of inflammatory cytokines through the expression of COX-2 and MAPK1 [103]. miR-146a is involved in the regulation of AChR specific B cells and in the development of MG. Transfection with the miR-146a inhibitor decreases the expression of miR-146a, CD80, CD40, NF-κB, and TLR4 in AChR specific B cells [104]. Increased expression of miR-15a reduces the expression of CXCL10 and abnormally activates T cells, but this miR is reduced in MG patients [105]. miR-20b is reduced in the serum of MG patients and negatively correlates with quantitative MG scores in the pretreatment stage [106]. miR-181c binds to the 3′ UTR of IL-7 and downregulates the secretion of IL-7 and IL-17 in MG [107]. Furthermore, a feature of EOMG is thymic hyperplasia with ectopic germinal centers (GC). One study described the role of two miRNAs in the thymic changes related to EOMG. miR-7 regulates CCL21, which is important for the development of GC, and is downregulated in MG. In contrast, miR-125a is upregulated in MG, which controls FoxP3 and regulates inflammatory pathways [108]. In addition, miR-139-5p and miR-452-5p negatively regulate the expression of RGS13, which at the same time regulates ectopic GC [109]. Xin et al. [110], demonstrated the role of miR-20b in the progress of thymoma-associated MG, particularly in the activation and proliferation of T cells. The tumor suppressive function of miR-20b is due to the inhibition of NFAT signaling caused by blocking NFAT5 and CAMTA1.

Regarding NMO, the accumulation of altered miRNAs in neutrophils and eosinophils demonstrates the role of these cells in the pathophysiology of the disease [111]. A recent study detected multiple downregulated miRNAs (i.e. miR-22b-5p, miR-30b-5p, and miR-126-5p) in NMO patients without a known function [112]. A study done by Vaknin-Dembinsky et al. [113], analyzed the miRNA profile of rituximab-treated NMO patients before and after therapy. The findings of this study showed that after therapy, the expression levels of 10 out of 17 miRNAs returned to the levels seen in controls. Of these 10 miRNAs, 6 were specific to the brain, which suggests the impairment of the CNS during this disease. Table 2 summarizes the presence of epigenetic modifications in other less studied NADs.

Table 2
Epigenetic mechanisms in neurological autoimmune diseases.

Neurological autoimmune Disease	Related epigenetic mechanism	Observed change	Reference
Narcolepsy	DNA methylation	Genes associated with narcolepsy present more DMP. Methylation in the ccr3 region.	[249]
	miRNA	miR-30c, let-7f and miR-26a are overexpressed in type 1 narcolepsy.	[250]
		miR-155 and miR-125b are increased in drug-naïve patients, mediating an inflammatory mechanism of T cells.	[251]
Vogt-Koyanagi-Harada disease	DNA methylation	Hypermethylation in the promoter of *GATA3, IRF8, IL4*, and *TGFβ*.	[252]
	miRNA	miR-20a-5p suppresses the production of IL-17 through the genes oncostatin M and CCL1.	[253]
Autoimmune encephalomyelitis	miRNA	miR-129-5p inhibits the progress of epilepsy related to autoimmune encephalomyelitis by inhibiting HMGB1 expression and TLR4/NF-κB pathway.	[254]
Behçet's disease	miRNA	miR-185 levels are decreased in the disease. There is a moderate inverse correlation between the levels of CPLX1 and miR-185.	[255]
GBS	miRNA	has-miR-4717-5p and has-miR-642b-5p were upregulated in patients with GBS. It is possible that dysregulation affects cell survival and axonal growth.	[256]
Myositis	Histone modification	Decrease in SIRT1 deacetylase activity in sporadic inclusion-body myositis patients.	[257]
	miRNA	Plasma levels of hsa-miR-4442 in active PM and DM are very high.	[258]
		miR-206 is decreased in DM patients. It is necessary for differentiation and maintenance of adult skeletal muscle.	[259]
		MiR-146a controls inflammatory infiltration through TRAF6 and IL-17/ICAM-1 in PM and DM.	[260]

CCL1: chemokine (C–C motif) ligand 1, CPLX1: complexin 1, DM: dermatomyositis, DMP: differentially methylated position, DNA: desoxyribose nucleic acid, GATA3: GATA Binding Protein 3, GBS: Guillain-Barré syndrome, ICAM-1: intercellular adhesion molecule 1, IL: interleukin, IRF8: interferon regulatory factor 8, NFkB: Nuclear factor kappa B, PM: polymiosytis, RNA: ribonucleic acid, SIRT1: sirtuin 1, TGF: transforming growth factor, TLR: Toll-like receptor, TRAF6: TNF receptor associated factor 6.

5. Environmental factors

5.1. Infections

The immune system represents a barricade against microbial infections, but it is not a fail-safe. Microorganisms provoke robust immune responses which are mostly specific for their programmed antigens. Nevertheless, microbial agents can trigger responses against self-antigens, leading to activation and clonal expansion of autoreactive T and B cells, which is the hallmark of autoimmunity. That is the reason microbial infections have been considered the main environmental culprits for some autoimmune processes (Fig. 1). The mechanisms by which a post infectious agent can lead to an autoreactive process have been assessed mainly in animal models, and these concepts, together with their applicability to human diseases, are under discussion and still controversial [114]. They include autoimmunity driven by molecular mimicry [115], epitope spreading [116], bystander activation [117], and superantigens [118]. These pathogenetic mechanisms are not selective and are important at specific stages of disease development. For example, molecular mimicry can trigger activation of autoreactive T lymphocytes while superantigens can reboot autoreactive T cells, thus inducing relapses [114]. Of all NADs, the ones studied the most in terms of infectious

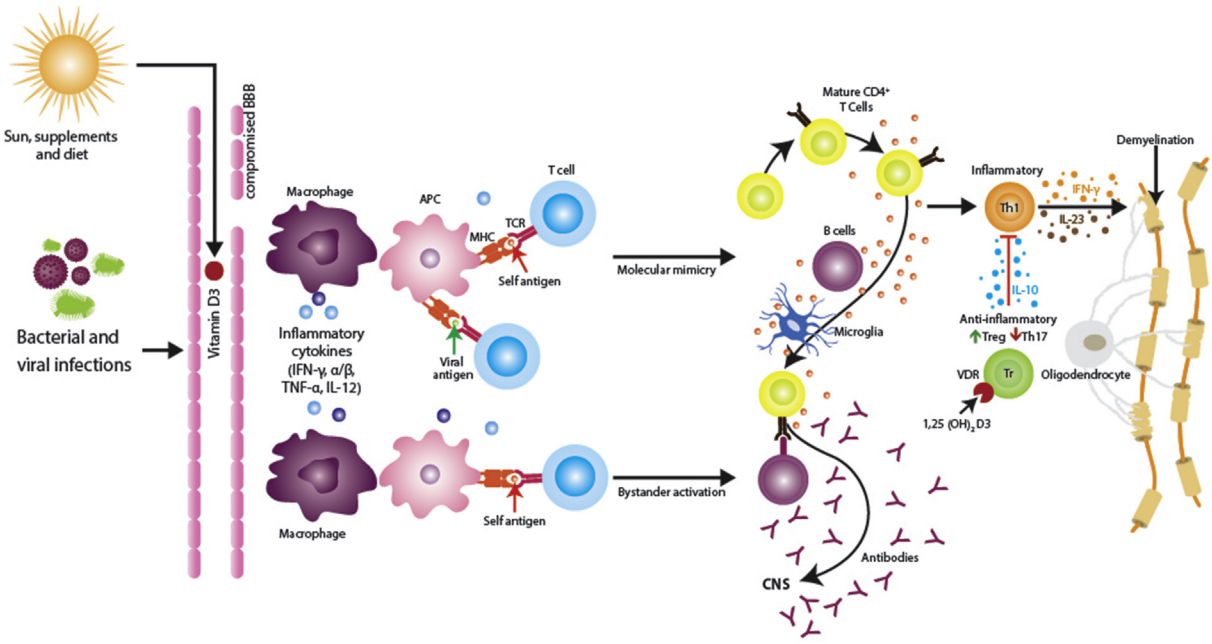

Fig. 1. Effects of environmental factors on the development of NADs. During infectious processes, virus and/or bacteria capable of disrupting the BBB, produce an immune response that is perpetuated by the continuous production of cytokines and chemokines and thus constitute an inflammatory milieu. These infectious agents can induce an autoimmune response through several mechanisms such as molecular mimicry and bystander activation which lead to demyelination. Vitamin D3 appears to regulate the inflammatory response induced by infectious agents by increasing Treg and reducing Th17 cells. APC: antigen-presenting cell, CNS: central nervous system, IFN: interferon, IL: interleukin, MHC: major histocompatibility complex, TCR: T cell receptor, Th: T helper cells, TNF: tumor necrosis factor, Tr: Type of regulatory T cells, Treg: regulatory T cells, VDR: vitamin D receptor.

etiology are MS, GBS, MG, and NMO.

5.1.1. Viral infections

The viral infection most associated with MS to date is EBV [119]. EBV is a double stranded DNA virus primarily transmitted by saliva. Infection in early life is normally asymptomatic, but when delayed to adulthood, it is responsible for infectious mononucleosis. EBV infection at late age is a risk factor for MS. In a cohort of EBV-negative young adults, MS developed only in those who had seroconverted before disease onset [120]. Moreover, high titres of IgG antibodies against EBV nuclear antigen 1 (EBNA1) are prognostic for MS development in the future [121]. EBV is found in B- and plasma cells in MS brains with pathological damage. EBV has the ability to confer B cell survival advantages for antibody secretion and presentation of antigens to pathogenic T cells [119]. There is genetic and molecular evidence suggesting the pathogenic role of viral interaction between EBV and Human Herpes Virus-6A (HHV-6A) in MS. HHV-6A is a neurotropic virus that infects astrocytes in MS patients [122]. HHV-6A activates latent EBV in B cells present in MS brains, which leads to intrathecal B-cell transformation. Furthermore, HHV-6A and EBV induce the expression of the human endogenous retrovirus HERK-K18 superantigen, which is a risk factor for MS [123].

EBV has also been found in tumor-infiltrating B cells in patients with MG thymomas which suggests the involvement of EBV in B cell dysregulation and the disruption of tolerance in MG patients. In contrast to healthy individuals, MG patients have hyperplastic and involuted thymuses infiltrated with EBV B- and plasma cells. This suggests that the virus could be implicated in the autoimmune process within intra-thymic MG, possibly by the activation and perpetuation of autoreactive B cells and the stimulation of pathogenic TLR7 and TLR9 signaling [124]. In a study done in Japan, researchers found that antibodies against EBV early antigen IgG (anti-EA) was significantly elevated in the serum of NMO patients in comparison to MS patients and controls. These results support the postulate that persistent, active EBV replication is frequent in NMO [125].

Another virus that has recently gained attention is the Zika virus (ZIKV), which is among the Flaviviruses. From December 2015 to July 2016, hundreds of cases of ZIKV-related GBS were reported [126]. This led the World Health Organization to name Zika a worldwide public health emergency, mainly due to its viral neurotropism that was causing microcephaly, GBS, and other neurological disorders [127]. ZIKV infection can produce a characteristic post-infectious GBS, together with a concurrent para-infection of the nervous system heightened by pre-existing arboviral and herpesvirus immunity [126]. Nevertheless, the mechanisms underlying the host-pathogen neuro-immune interactions remain unknown. Furthermore, GBS has already been associated with preceding dengue virus (DENV) [128] and chikungunya virus (CHIKV) infections [129]. The isolation of virus from brain tissue and CSF as well as the presence of IgM antibodies against DENV suggests direct virus invasion of the nervous system and underlines the probable neurotropism of DENV [128]. In the case of CHIKV, there is epidemiological causality since CHIKV infection contributed to a 2-fold increase in the overall incidence of GBS in the West French Indies [129]. Another pathogen that preceded GBS, is hepatitis E virus (HEV), which has been demonstrated worldwide [12]. In the Netherlands and Bangladesh, case-control studies showed that 5% and 10% of GBS patients had HEV infection prior the onset of GBS respectively [12,130]. Another virus that has been associated with GBS is cytomegalovirus (CMV) [131]. In the largest series study, 12% of GBS patients were serologically positive for CMV infection, and almost 70% of these patients had CMV DNA in serum [132]. Sawai et al. [133], showed that moesin is a possible target molecule for AIDP after CMV infection since serum IgG antibodies of CMV-related GBS were immunoreactive with moesin. Moreover, molecular mimicry between moesin and CMV proteins resulted in six consecutive amino acids. Moesin is a member of the ERM family proteins, which are expressed in the microvilli of Schwann cells, and moesin may have a critical function in myelination.

A recent report demonstrated two patients with anti-AQP4-seropositive NMO occurring in association with DENV for the first time [134].

Hepatitis B and C, herpes simplex, and human immunodeficiency virus are examples of viral infections affecting MG [135]. Herpes simplex virus has been associated with MG by molecular mimicry since an auto-antigenic site of the AChR alpha-subunit responds immunochemically to herpes simplex virus [136]. Recently, six MG patients who had had West Nile virus infection were described 3–7 months afterward [137] and two MG patients who had had ZIKV infection were described 8–10 weeks afterward [138].

5.1.2. Bacterial infections

Chlamydia pneumoniae (*C. pneumoniae*) is one of the bacterium that has been most investigated in MS. Up to 70% of the adult population has antibodies to this intracellular bacterium [139]. There is a dispute as to whether *C. pneumoniae* triggers MS or just co-exists with this NAD [140]. Some MS patients have IgG antibodies against *C. pneumoniae* in CSF regardless of disease severity and presence of oligoclonal IgG [141]. Moreover, some studies have found *C. pneumoniae*-specific intrathecal IgG production in MS and other inflammatory disorders, thus showing that humoral response to *C. pneumoniae* is not restricted to MS [142]. Nonetheless, other studies showed that 24% of patients with MS synthesized intrathecal IgG antibodies against this bacterium in contrast to only 5% of patients with other non-inflammatory and inflammatory disorders [143]. Data in EAE are more consistent. Mice that were immunized with myelin oligodendrocyte glycoprotein (MOG) 35–55 peptide, which induces an autoimmune process resembling many features of MS, were subsequently infected with *C. pneumoniae* and showed an increase in the severity of EAE [144].

Another bacterium implicated in MS is *Streptococcus pneumoniae* (*S. pneumoniae*), which contains important virulence factors in its cell wall such as lipoteichoic acid (LTA), teichoic acid (TA) and peptidoglycan [145]. Anti-LTA and anti-peptidoglycan antibodies have been detected in the CSF and serum of MS patients [146]. Since macrophages are unable to digest peptidoglycan completely, persistence of these peptides may induce or exacerbate MS [147]. Peptidoglycans were detected within APCs in the brains of MS patients [146]. Moreover, *S. pneumoniae* infection aggravates EAE through TLR2, thus causing a rise in TNF-α and IL-6 [148]. All these data together suggest that *S. pneumoniae* might trigger MS through bystander activation.

C. jejuni has been identified as the infection that most frequently precedes GBS and appears in approximately 25% of patients [149]. Nevertheless, despite the robust association between Campylobacter enteritis and GBS, the risk of this post-infectious complication developing is only one in 1000–5000 patients in the 2 months following the infection [150]. The hallmark of induced GBS-*C. jejuni* is the production of antibodies that mimic the carbohydrate fraction of gangliosides that are present in peripheral nerves. However, cross-reactive lipo-oligosaccharides are only present in some *C. jejuni* strains [151]. The production of these ganglioside-mimicking carbohydrate moieties varies according to a set of polymorphic genes and enzymes characteristic of each *C. jejuni* strain [152]. Furthermore, the production of cross-reactive antibodies is exclusively induced in genetically predisposed individuals [153]. The specificity of these antibodies is closely related to particular GBS subtypes and other neurological syndromes [12].

The second most frequent bacterial agent associated with GBS is *Mycoplasma pneumoniae* (*M. pneumoniae*), which causes atypical pneumonia. *M. pneumoniae* seropositivity in GBS patients ranges meaningfully (1–25%) but is also common in controls [154]. In a cross-sectional study of 57 pediatric GBS patients, 20% exhibited IgM antibodies against *M. pneumoniae* compared to 14% of controls [155]. In our case-control study [156], sera from 82.76% of the GBS-ZIKV patients showed IgG antibodies against *M. pneumoniae* as compared to 54.05% of the control subjects (OR: 3.95; 95% CI 1.44–13.01; $p = 0.006$). Perception of pneumonia did not correlate with a previous *M. pneumoniae* infection.

Moreover, antibodies against galactocerebroside, a main component of the peripheral nerve myelin, have been identified in some patients with GBS following infection with *M. pneumoniae* [157].

5.2. Gut microbiota

Intestinal microbiota have gained attention due to their association with maturation and activation of the immune system through the production of compounds derived from themselves, the host, or the bacterial metabolism of components consumed in the diet. Gut-associated lymphoid tissue can control pro- and anti-inflammatory responses through Th17 and Treg cells. These cellular subsets are regulated by interaction between microbiota and dietary components [158]. Additionally, integrity of the gut is essential in the maintenance of the mucosal barrier, therefore, when it is lost, microbes may enter the lamina propia and blood circulation, thus leading to alterations in the homeostasis and systemic immune over-activation [159]. Several studies have highlighted the relationship between altered microbiota and the onset of NADs [160] (Fig. 2). Indeed, gut microbiota can have a bidirectional communication with the brain through the vagus nerve and release of neurotransmitters. Moreover, it can control BBB permeability, activate microglia, limit astrocyte pathogenicity, and express myelin genes [161]. Berer et al. [162], showed that stimulation of the microbiota with MOG in a mouse model leads to autoimmune demyelination by auto-reactive T and B cells. Concerning MS, its prevalence has risen, especially in Mediterranean areas and in Japan. This increase can be attributed to microbiota alterations due to changes in eating habits [163]. A significant reduction in *Clostridium* XIVa and IV clusters affect clostridial butyrate producers, which are related to MS pathogenesis [164]. In addition, Jangi et al. [165], showed an increase in *Methanobrevibactea*, *Akkermansia* and a reduction in *Butyricimonas* both of which correlated with altered pathways in MS. Furthermore, fecal microbiome analyses showed that MS patients had a higher abundance of *Pseudomonas, Mycoplana*, *Haemophilus*, *Blautia*, and *Dorea,* thus indicating a gut microbial imbalance in MS [166]. In addition, an MS pediatric study demonstrated that *Bacteroidetes* were inversely associated with Th17 cells [167]. Anti-epsilon toxin (*Clostridium perfringens*) antibodies were detected in 10% of MS patients. This toxin can alter BBB and bind to oligodendrocyte-myelin, thus making it attractive as a potential MS trigger [168]. Moreover, *Prevotella copri* was lower in MS patients [169]. Cekanaviciute et al. [170], demonstrated that microbiota transplantation from MS patients into germ-free mice was able to induce EAE. Finally, changes in gut microbiota composition can lead to differences in the susceptibility to EAE and variability in the clinical course of the disease in animal models.

Up to now, an association between the microbiota and the risk of developing GBS has not been demonstrated.

Gut microbiota may be a triggering factor for MG in susceptible populations. Qiu et al. [171], observed a sharp decrease in microbial diversity and significantly low levels of short chain fatty acids in MG

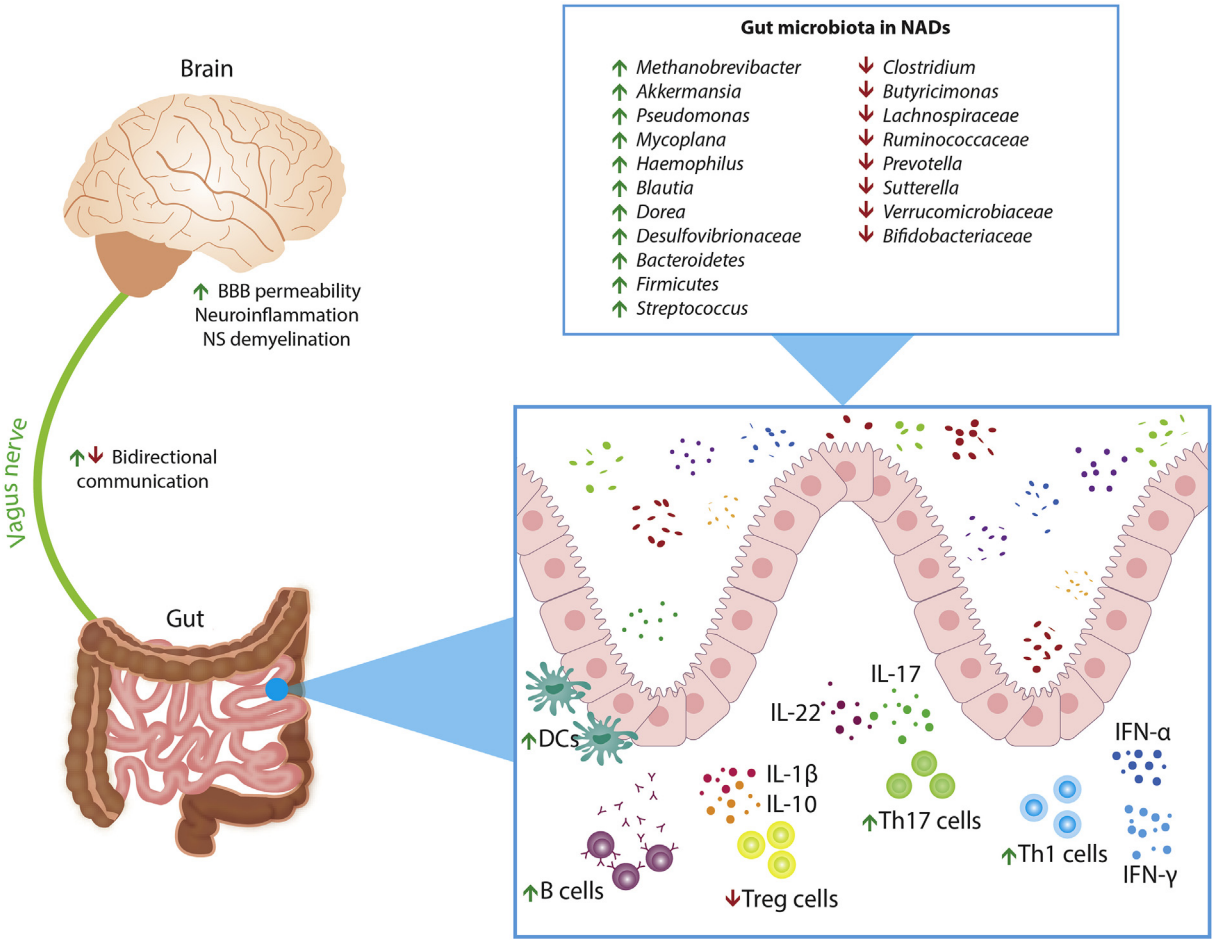

Fig. 2. Gut microbiota dysbiosis in NADs. The interaction between gut and brain is bidirectional mainly through the vagus nerve and neurotransmitters. Under healthy conditions, the microbiota control the maturation and activation of the immune system, but an imbalance in its relative abundance can be associated with the risk of NADs. Neurological alterations include increased BBB permeability, neuroinflammation, and destruction of myelin in the nervous system. Disruption of homeostasis in gut microbiota leads to pro-inflammatory cytokine release, autoantibody production as well as an increase in DCs, B cells, Th1, and Th17 cells. However, it causes a reduction in Treg cells. BBB: blood brain barrier, NS: nervous system, DCs: dendritic cells, IL: interleukin, Th: T helper cells, Treg: regulatory T cells, IFN: interferon.

patients. The ratio of *Firmicutes-Bacteroidetes* was significantly lower in MG patients than in controls, thus leading to a pro-inflammatory environment that damaged the intestinal epithelium. *Clostridium* is depleted in MG patients, and this affects the differentiation, frequency, and TCR repertoire of Treg cells through the expression of TGF-β1 and 2,3-dioxygenase. In addition, alterations in Treg and B cells are related to AChR autoantibodies. In addition, fecal sample analysis showed decreased proportions of *Verrucomicrobiaceae* and *Bifidobacteriaceae*, but increased percentages of *Desulfovibrionaceae,* thus showing a strong dysbiosis in the gut microbiota of MG patients [172].

The second most frequent taxon in the microbiota of NMO patients is *Clostridium perfringens* [173]. The adenosine triphosphate binding cassette transporter from *Clostridium perfringens* has been seen to induce a cross-reactive response together with the homologous sequence of AQP4 by molecular mimicry [163]. Therefore, dysbiosis in microbiota by *Clostridium* species influences pro-inflammatory Th17 responses, which is the central core in NMO pathogenesis [174]. A recent study showed that *Streptococcus*, *Shigella*, and *Faecalibacterium* were the bacteria differential distributed among NMOSD patients and controls . Interestingly, a significant increase in *Streptococcus* in NMOSD patients was correlated with disease severity [175].

5.3. Smoking

A smoking habit influences the development of NADs as well as the activity and progression of these conditions. The impact of smoking on the immune system includes an increase in the inflammatory response and susceptibility to infections. Smoking is one of the most studied risk factors for MS. A case-control study showed that smoking was associated with a 40–80% risk of developing the disease [176]. Smoking increases the risk of MS regardless of the age at exposure. However, its effects are reduced only after 5 years of not smoking. In the Swedish population, the risk of developing MS rises in moderate smokers [177]. Surprisingly, in another Swedish study, tobacco consumption for more than 15 years reduced the risk of developing MS. In fact, this tobacco, called snus, is free of smoke and contains only nicotine. Therefore, it is less probable that nicotine is the culprit behind MS development [178]. However, smoking does affect the clinical course of MS. The disease progresses rapidly in smokers compared to non-smokers. Correale et al. [179], established that smoking decreases antimicrobial activity in respiratory infections, thus facilitating the relapse of MS. Another study has shown that the activity of indoleamine 2,3-dioxygenase is reduced in smoking patients, thus increasing IL-6 and IL-13 production. Expression and activity of the renin-angiotensin system is also high in smoking patients, thus increasing IL-17, IL-22, CCL2, CCL3, and CXCL10 production. Finally, both pathways decrease the number of Treg cells [180]. In smokers with RRMS, T cells increase the expression of the G protein-coupled receptor 15 and adopt a Th17 phenotype [181].

In addition to the above mentioned studies, a study in UK showed higher mortality in current smokers with MS compared with never- or ex-smokers [182].

The effect of smoking on MG has not been well studied. However, Gratton et al. [183], found an association between cigarette smoking and the severity of ocular MG symptoms. In a Norwegian population, there was a higher consumption of tobacco in patients with EOMG compared to the general population [184]. The immunopathological role of smoking in NADs is described in Fig. 3.

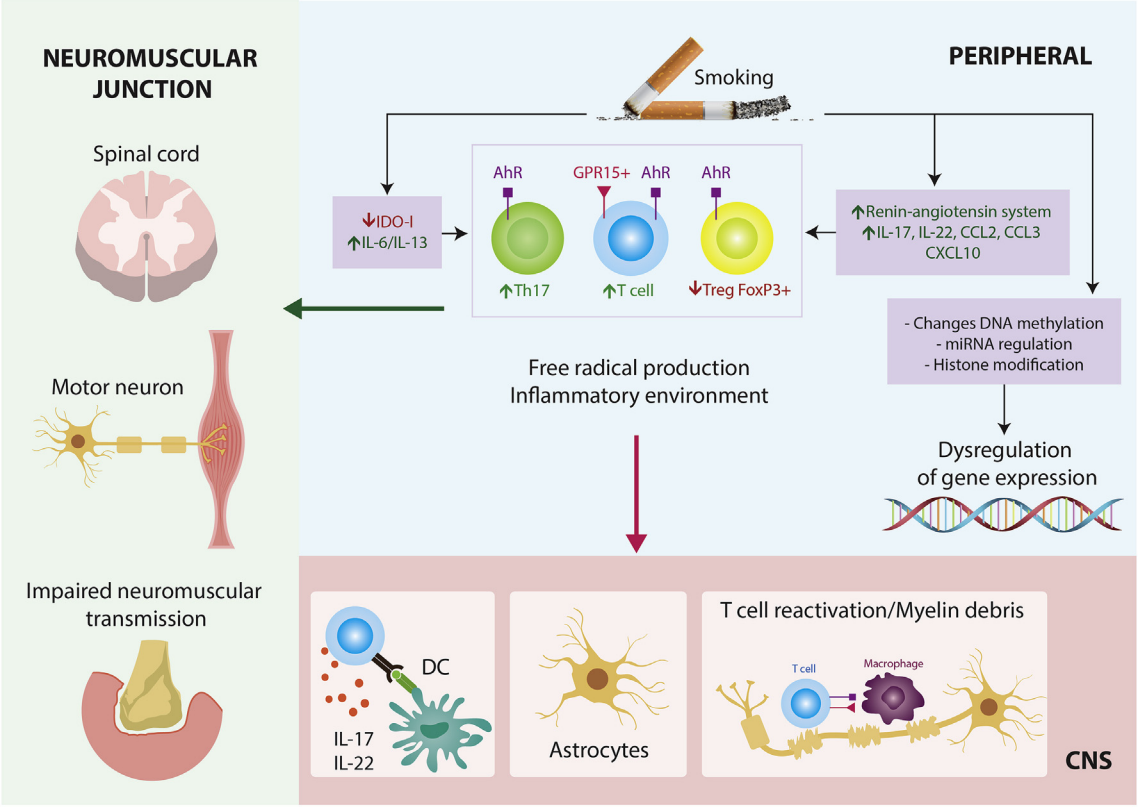

Fig. 3. Possible mechanisms underlying NADs due to smoking. Smoking can induce NADs mainly through two different pathways: 1. The reduction of IDO-1 enzymatic activity increases IL-6 and IL-13 production. 2. The upregulation of the renin-angiotensin system increases IL-17, IL-22, CCL2, CCL3, and CXCL10. Both pathways favor the increase in Th17 cells and the decrease in Treg cells. Oxidative stress favors the secretion of pro-inflammatory cytokines. The recruitment of inflammatory cells to the CNS and to the neuromuscular junction causes demyelination and the blockade of neuromuscular transmission. The epigenetic changes caused by smoking favor the development and progression of NADs. AhR: aryl hydrocarbon receptor, CCL: chemokine (C–C motif) ligand, CNS: central nervous system, CXCL10: C-X-C motif chemokine 10, DC: dendritic cell, DNA: desoxyribose nucleic acid, FoxP3: forkhead box P3, GRP15: G-proteinecoupled receptor 15 gene, IDO-1: indoleamine 2,3-dioxygenase 1, IL: interleukin, miRNA: microRNA, Treg: regulatory T cells.

5.4. Air pollution

The main source of air pollution includes vehicle exhaust, industry, forest fires, and solid fuel combustion. This particulate matter (PM) is a combination of sulfur dioxide, carbon monoxide, ozone (O3), and nitrogen dioxide (NO2). Air pollutants bind to the aryl hydrocarbon receptor, which regulates Treg and Th17 cells. Oxidative stress favors the secretion of pro-inflammatory cytokines. These cytokines help DCs and B cells to maintain the autoimmune process [185]. Recent evidence showed that air pollution affects the CNS by oxidative stress, neuroinflammation, cerebrovascular damage, microglial stimulation, and changes in the BBB [186].

Exposure to air pollutants initiates pathological processes in MS and leads to cerebral autoimmunity through inflammatory-oxidative cascades, loss of immunological tolerance, and neurodegeneration [187]. NO2, O3, and PM10 are associated with the appearance of MS relapses [188]. In fact, PM10 contributes to MS relapses through oxidative stress mechanisms [189]. In south-western Finland, the risk of relapse was four times higher when the PM10 concentration was in the highest quartile [190]. However, a study done on two prospective cohorts of women did not show any relationship between exposure to air pollution and MS risk [191]. More studies are needed to decipher the role of air pollution in other NADs.

5.5. Vitamins

Exposure to the sun and vitamin D are environmental factors that have been widely associated with MS development and activity [192]. Vitamin D seems to be an intermediary between the two since UVB produces this vitamin under physiological mechanisms [4]. The consumption of vitamin D enriched food appeared to have protective effects later in life for the risk of MS, thus suggesting an epidemiological link between the risk of MS and vitamin D [193]. Moreover, numerous studies showed an inverse relationship between the frequency of relapses, the occurrence of new brain magnetic resonance imaging (MRI) lesions, disability progression, and the levels of vitamin D [194]. Nonetheless, the effect of vitamin D on the activity and development of MS is not yet proven. Vitamin D coming from the skin and food is carried to the liver, where it is transformed into 25(OH)D3 (calcidiol) through hydroxylation. 25(OH)D3 is converted into 1,25(OH)2D3 (calcitriol), the active metabolite, through a second hydroxylation that takes place in the kidneys. Through binding to the intracellular vitamin D receptor (VDR), 1, 25(OH)2D3 exerts its biological effects [192]. All immune cells express VDR, thus vitamin D influences innate and adaptive immunity, mainly shifting the immune response toward an anti-inflammatory one [195]. 1, $25(OH)_2D_3$, in particular, suppresses Th17 by inhibiting the transcription of *IL23R, RORγt, IL22*, and *IL17*. Moreover, this metabolite promotes Treg through the induction of *Foxp3*, *IL10,* and *CTLA4*. $1,25(OH)_2D_3$ also inhibits GM-CSF secretion, which is a MS risk factor. Furthermore, 1, $25(OH)_2D_3$ reduces the expression of CCR6, known as Th17 marker and, at the same time, reduces the number of Th17 cells that migrate to CNS in response to CCL20. In addition, $1,25(OH)_2D_3$ suppresses isolated $CD4^+$ T proliferation and MBP-specific T cells from MS patients *in vitro* [196]. The EAE model has been used to demonstrate the complicated interaction between vitamin D and the immune system, by showing that vitamin D treatment reduced EAE symptoms [197]. Low 25-OH-D serum levels due to abnormalities of *CYP27B1* (enzyme 1α-hydroxylase that controls calcitriol synthesis) and *CYP24A1* (calcitriol degradation) genes also seem to contribute to MS susceptibility [198]. There is a vitamin D responsive element (VDRE) located within the promoter region of *HLA-DRB1*1501*, one of the strongest genetic factors associated with MS [199]. Recent data suggest that vitamin D and EBV infection are not independent risk factors for MS. Rather, they interact closely with each other [200]. Rosjo et al. [201], showed that after 48 weeks of supplementation with vitamin D3, there was a reduction in anti-EBNA1 antibodies in MS but not in the antibody levels against EBV viral capsid antigen, CMV, or Varicella Zoster virus. Vitamin D may be affecting anti-EBNA1 antibody responses by eliminating EBV-infected B cells more efficiently. Since vitamin D increases the percentages of $CD8^+$ T cells, it has been suggested that vitamin D augments the $CD8^+$ T cell reaction to latent EBV-infected B cells. Otherwise, vitamin D might target and weaken EVB viral replication in infected cells. This would explain the evolution of the EBNA3 protein that is capable of blocking the vitamin D receptor. It has been suggested that the anti-viral effects of vitamin D disrupts viral envelopes through cathelicidin [202]. Recently, Kang et al. [203], reported that MG patients had lower 25(OH)D plasma levels than healthy individuals. Moreover, Gao et al. [204] reported that serum levels of 25(OH)D, 25(OH)D2, and 25(OH)D3 were significantly lower in NMO patients as compared to healthy individuals. Thus, the authors suggest that these low levels might represent a risk factor for NMO disease activity.

Vitamin B9 (Folic acid) has also been related to NADs. In a case-control study, Gao et al. [204], reported folate deficiency in 19% of GBS patients in contrast with 2% in the control group. Moreover, the authors showed a significant correlation between folate levels and the duration of disease progression. This association could be explained as deficient folate levels, which are likely to depress the immune response in GBS and slow the disease progression due to their central role in DNA synthesis. Moreover, folate deficiency diminishes immune functions by disturbing T and B cell differentials along with the lymphocyte-proliferation response [204]. Vitamin B12 has also been associated with MS since a study reported low levels of vitamin B12 in the CSF of MS patients with a tendency pointing to low levels in serum. Vitamin B12 deficiency produces defective formation of the myelin sheath due to the incorporation of non-physiologic fatty acids into neuronal lipids. It also points to defective methylation of MBP [205].

5.6. Stress

Stress may be another triggering factor of MS and its exacerbations. Stress was described for the first time in 1946 by Selye, and it is defined as an event where homeostasis is threatened and then restored by the organism through behavioral and physiological mechanisms. Stressors can be physical and psychological, and their importance resides in both the intensity and duration [206]. Stress may affect the onset and exacerbation of diseases by the regulation of the immune response through the hypothalamic-pituitary-adrenal axis (HPA) and sympathicus. In fact, research on MS in EAE, showed interference in communication between the autonomic nervous system and the HPA axis. A low sensitivity immune response to the β-adrenergic and glucocorticoid modulation can lead to strong immune responses [206]. The glucocorticoid receptors in immune cells are reduced by chronic stress, thus becoming less responsive to regulation by cortisol. This glucocorticoid resistance was detected in patients with RRMS during the initial phase of MS. Acute stress also increases the permeability of the BBB, thus increasing MS activity. Moreover, it increases recruitment of mast cells and cytokine secretion by Th1 and Th2 cells [207]. Djelilovic-Vranic et al. [208], showed that, in MS patients with repeated exacerbations, 39% of cases reported prior stressful events frequently related to problems in family and marriage, personal illness besides MS, illness of a family member, problems at work, and job loss. A study of Lebanese RRMS patients during the Israeli Lebanese war showed that the number of relapses was three times higher than before and after the war. These relapses were accompanied by radiological findings that showed more Gd + lesions on MRI [209]. There are studies on the impact of stress on MS development, and most of the evidence agrees that stress is a relevant provoking factor for disease exacerbation [208].

5.7. Vaccination

The relationship between vaccines and autoimmunity is bidirectional. Thus, vaccines prevent infections which could induce autoimmunity, but in contrast, they can induce autoimmunity either by molecular mimicry

or bystander activation [210]. In general terms, there are case-reports of vaccination associated with some NADs. However, the exact mechanisms are not well established. In MS, a study that includes systematic review and meta-analysis found no association between hepatitis B vaccine and central demyelination [211]. Similarly, there is no association between human papillomavirus vaccine and MS [212]. In acute disseminated encephalomyelitis, 5% of the cases are preceded by vaccinations given one month prior to the onset of symptoms. Some case-reports have described severe neurological damage after vaccination such as virosomal seasonal influenza [213], meningococcal [214], pertussis [215], and anti-rabies vaccines [216]. GBS has been reported with vaccines such as hepatitis A [217], influenza [218], human papillomavirus [219], etc. Influenza vaccination is associated with an augmented risk for hospitalization because of GBS [220]. Available evidence suggests that vaccines are not the main culprit of NADs.

5.8. Medications

Multiple associated factors have been described with regards to drug-induced autoimmunity such as genetic susceptibility, concurrent disease, and type of drug. In addition to the culprits described so far, several diseases such as demyelinating polyneuropathy, MG, and myositis have been reported to have been induced by medication. In MG, D-penicillamine may exacerbate the disease and prevent neuromuscular transmission. However, the suspension of the medication generates an immediate recovery [221]. Other medications that induce MG are quinine, quinidine, procainamide and disopyramide, antimalarials (i.e. chloroquine and hydroxychloroquine), and antibiotics (i.e. streptomycin and kanamycin). Quinoline drugs exacerbate the disease by altering the presynaptic and postsynaptic components on neuromuscular transmission [222]. The mechanisms of action have been demonstrated for some medications that induce myopathies. This is the case with glucocorticoids which facilitate the catabolism of proteins. Statins alter intracellular signaling proteins, thus favoring myocyte apoptosis [223].

TNF antagonists have been linked to GBS, MFS, and chronic inflammatory demyelinating polyneuropathy, etc. The inhibition of TNF-α produces an increase in autoreactive T cells, inflammation, and an attack on myelin [224]. Furthermore, TNF antagonists are associated with dermatomyositis and polymyositis in RA patients and thus, induce IFN-γ production [225]. In the case of MS, a case-report showed acute liver failure after treatment with IFN-β [226].

Finally, the role of medications in the occurrence of NADs is insufficiently explored. More studies are warranted to develop an understanding of the neurotoxic and autoimmune mechanisms associated with medications.

5.9. Culprits interplay in NADs

Genetic and environmental factors work together to cause specific diseases. In our daily translational research, we have the opportunity to evaluate patients with NADs. In the particular case of GBS, genetic and epigenetic factors as well as viral infections have been demonstrated to trigger disease [156]. A 49-year old female patient living in an arboviral endemic region presented fever, rash, arthalgias, conjunctivitis, and diahrrea. This patient was clinically diagnosed with ZIKV infection, and 1 month later went to the medical center with areflexia, paresthesia, upper and lower symmetric muscle weakness, tingling or prickling sensations in fingers and toes, dysautonomia, and difficulty in walking steadily. This made a diagnosis of GBS-AIDP subtype possible. The laboratory findings showed a burden of previous infections since IgG antibodies for CMV, EBV, DENV, CHIKV, and *M. pneumoniae* were positive. Considering the fact that GBS-AIDP is mediated by autoantibodies that cross-react with myelin components, the IgM antibodies were evaluated against a panel of 7 gangliosides. Among these, only GM1 and GM2 were positive in this patient thus demonstrating molecular mimicry. These results suggest a potential interplay between a high load of previous infections and GBS development in ZIKV infected patients. Thus, it is necessary to develop novel diagnostic algorithms based on clinical features, laboratory findings, and the culprits reviewed herein in order to ease the clinical management and treatment of NADs.

6. Conclusions

The identification of genetic susceptibility, epigenetic mechanisms, and the environmental triggers of NADs would allow clear opportunities for disease prevention and treatment. There is insufficient information on the mechanisms linking environmental factors to disease mechanisms, genetic predisposition, and the immune system. Furthermore, the acquisition of further insight into the influence of environment and microbiota on immune homeostasis will permit a better understanding of the rising incidence of NADs.

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Conflict of interest

None.

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