INTRODUCTION

Since its very first discovery and disease association studies in early 1970’s, the major histocompatibility complex (MHC) with its polymorphisms has been the “gold standard” and the primer genetic locus in attributing genetic burden for certain autoimmune diseases, like multiple sclerosis (MS). Initial studies, using serological techniques, showed an association of MS with human leukocyte antigen (HLA) class I, especially HLA-A3 and HLA-B7.[1] Multiple recent researches which used current molecular methods (sequence specific oligonucleotide-polymerase chain reaction [PCR], single specific primer-PCR and single-nucleotide polymorphisms, genome-wide association study, etc.)[1] and which were conducted in many MS cohorts, made clear that HLA-DRB1*15:01 is by far the main independent, responsible allele for attributing genetic risk in different MS ethnic groups.[1] In addition, co-existence of certain alleles probably leads to an increase or decrease of the overall risk, via epistatic mechanisms (i.e. HLA-DRB1*15:01 and HLA-DQ1*01:02).[1] Moreover, a Vitamin D response element has been found in the promoter region of HLA-DRB1*15:01, changing the expression of the allele and the risk for the disease. Thus, an environmental factor, the sunlight, via the metabolites of Vitamin D, has been linked to the genome, especially to HLA-DRB1*15:01 and finally to the disease phenotype.[2] The interaction...
between HLA-DRB1*15:01 and Epstein-Barr virus,[25] as well as the estrogen receptor,[4] has also been very well established.

Neuromyelitis optica (NMO) is an autoimmune demyelinating disorder, predominantly characterized by severe optic neuritis (ON) and transverse myelitis (TM).[5] It was considered as a variant of MS, but the discovery that most NMO patients have antibodies against aquaporin-4 (AQP4) or NMO-immunoglobulin G (IgG), dramatically changed our perception of the disease and brought NMO and its spectrum in the center of interest.[6] Researches trying to correlate NMO with specific HLA alleles took place in a limited extend in the last few years, especially in Japanese population, in which NMO appears its greatest frequency. Nevertheless, it has become clear that HLA play a crucial, and maybe the primer role, in the genetic risk of NMO and provide great insight in the profound understanding of its pathogenesis and the differential diagnosis mainly from MS and other demyelinating diseases as well.

In this study, our aim was to summarize in a critical review the results of these researches worldwide and shed light on the contribution of HLA alleles in NMO immunopathogenesis, given the total absence of such a review.

**HISTORICAL NOTES AND EPIDEMIOLOGY**

Neuromyelitis optica was first described in 1870 by Allbutt, who reported an association between myelitis and unilateral optic nerve disorder, but it was in 1894 when the term “neuromyelite optique aigue” (acute optic neuromyelitis) was coined by Devic[7] in order to describe patients who first suffered unilateral or bilateral loss of vision and within weeks developed severe spastic para- or tetraparesis, loss of sensation and sphincter control. In 1999, Wingerchuk et al,[8] proposed the first diagnostic criteria for NMO. Current revised criteria for diagnosing NMO were defined in 2006 by the same group [Table 1],[9] because in 2004, the AQP4 protein was identified for NMO, which was the first molecular target described for any type of demyelinating diseases of the central nervous system (CNS).[8]

Neuromyelitis optica represents < 1% of demyelinating diseases of the CNS in Caucasians[10] and it is certainly more common in Asians. It has been reported to account for up to 30% of West Indian cases of CNS demyelination,[11] 20-30% of Japanese cases,[12] 48% of East Asian cases,[13] 23% of Indian cases[14] and 15% of Afro-Brazilian cases.[15] Japanese patients with opticospinal MS (OSMS) or Asian MS represent a distinct entity from western MS. The equal detection of NMO-IgG in the sera of Japanese patients with OSMS and NMO, as well as the similar clinical and pathological characteristics, indicate that both syndromes may belong to the same clinical entity.[16] NMO is more common in women than men (> 2/3).[17,18] More than 80% present the relapsing form of the disease,[17] while the median age of onset is the late 30s,[18] with few reports of NMO occurrence in children[19] or elderly.[20] Familial cases of NMO are estimated to account for 3% of all NMO cases.[21]

**BASIC CLINICAL FEATURES AND IMMUNOPATHOGENESIS**

Neuromyelitis optica is characterized by ON, which is often bilateral (simultaneously or sequentially), and longitudinally extensive TM with a well-defined sensory level, as well as sphincter dysfunction, pain and tonic spasms of the trunk and extremities.[6] Involvement of the brain stem may cause hiccups, nausea and even respiratory failure,[22] while hypothalamic-pituitary axis dysfunction commonly manifests as hyponatremia, hyperthermia and hyperprolactinemia.[23] Encephalopathy mimicking posterior reversible encephalopathy syndrome has also been described.[24]

Clinical attacks generally progress over days, with variable recovery within months. Most patients endure some residual disability, which accumulates over time.[8]

Even though a review of the complicated mechanisms of pathogenesis of NMO is far from the purpose of our review, in order to explore in which ways HLA may contribute to it, we refer to some important aspects, providing the basics for this purpose. AQP4-antibodies have a decisive role in the pathogenesis of NMO, by complement-mediated astrocyte damage, cascading to leukocyte infiltration, oligodendrocyte death and neuronal cell damage.[25] They are present in up to 80% of NMO cases. AQP4 is highly expressed in astrocytic end-feet in the blood-brain barrier, nodes of Ranvier and neuronal synapses.[25] AQP4 is also expressed in a sub-population of CNS ependymal cells associated with the pia, subfornical organ and...
to a lesser extent in other ependymal cells (not in the choroid plexus), in situ in lipopolysaccharide-activated microglia and on retinal astrocytes (Müller cells). It is abundant in the grey matter of the spinal cord, the periventricular and periaqueductal area. Outside the CNS, it is found on epithelial cells of the kidney collecting ducts, airways, parietal cells of the stomach, skeletal muscle sarcolemma and colon. AQP4-IgG serum levels are found to correlate with NMO disease activity, distinct phenotypic features (gender, course and co-existing autoimmunity), severity and response to treatment. In patients with isolated ON or isolated longitudinally extensive TM, AQP4-antibodies have been shown to predict conversion to NMO. Recent researches have shown that patients’ sera with MS, acute disseminated encephalomyelitis, systemic lupus erythematosus (SLE) and Sjögren syndrome (SS) were negative for AQP4-antibodies. However, Alexopoulos et al. managed to demonstrate that, despite the negativity of the serum in antibodies, 13% of the sera with relapsing-remitting MS reacted with the epitope AQPaa252-275 (NMO-positive sera exhibited reactivity against the intracellular epitope AQPaa252-275 in this study, confirming previous observations).

Additional immunological components participate. NMO lesions contain large numbers of macrophages, eosinophils and neutrophils, on which AQP4-IgG acts by binding to Fc receptors, as well as on B-cells, which produce interleukin (IL)-6. IL-17 and IL-6 are the main pro-inflammatory cytokines which are found to be elevated in the serum and cerebro-spinal fluid of patients with NMO. T-cells, though fewer, are also certainly relevant, as T-helper cells are involved in B-cell isotype switching and affinity maturation. The possible role of natural killer cells and glutationate-mediated excitotoxicity has also been discussed. Of course, it has become clear that NMO is associated with certain HLA alleles, which are extensively described below.

NEUROMYELITIS OPTICA AND OTHER AUTOIMMUNE DISEASES

There is a strong association between NMO and other autoimmune diseases, especially in NMO-IgG positive patients: co-existence with autoimmune thyroid disease, SLE, SS, celiac disease, sarcoidosis, or myasthenia gravis (MG) has been described in a higher frequency than it could be by chance. This co-association could be due to common genetic factors, such as HLA and non-HLA genes, including PTPN22, a tyrosine phosphatase associated with type-1 diabetes, rheumatoid arthritis (RA), SLE, Crohn’s disease and MG, IL-23R, associated with SLE, Crohn’s disease and psoriasis; and finally, TNFAIP3, involved in control of unbiqutination, associated with RA, SLE, Crohn’s disease and psoriasis. As far as MG is concerned, despite of the well-established link between the thymus gland and MG (human thymus tissue has been shown to express AChR, which is widely thought to be a triggering mechanism in early-onset AChR-MG), recent evidence suggests that AQP4 is also expressed in human thymus suggesting a similar and early involvement of the thymus in NMO-spectrum diseases (NMOSD). HLA-DRB1*03 and especially the whole haplotype, HLA A1-B8-DR3-DQ2, is the most commonly attributed to MG in the Caucasians, an haplotype common and in other autoimmune diseases. HLA-DRB1*03 allele is highly frequent in the NMO-IgG positive patients, as we explain in detail below and it could be one of the links between MG and NMO.

NEUROMYELITIS OPTICA ANTICIPATED HUMAN LEUKOCYTE ANTIGEN

According to the results of the researches that have been conducted in Japanese, conventional MS is associated with the HLA-DRB1*15:01 allele, while OSMS, which is now accepted as a component of the NMO spectrum, is associated with the HLA-DPB1*05:01. HLA-DRB1*05:01 is the most common DPB1 allele in Japanese, which may explain the frequent occurrence of anti-AQP4 antibody in Japanese OSMS. Nevertheless, Fukazawa et al. in 2006 came to the conclusion that HLA-DRB1*05:01 plays an important role in the development of MS in general, but not in OSMS. The strong association of HLA-DRB1*05:01 with OSMS may be due to the over-representation of the HLA-DRB1*03:01 allele among individuals in the non-OSMS group, a question that needs further investigation. The observed protective effect of HLA-DRB1*01 in anti-AQP4-negative MS patients is in accordance with findings in Caucasians.

It is also estimated that there is a protective effect of HLA-DRB1*09 in anti-AQP4-negative MS patients, probably by reducing the susceptibility attributed to HLA-DRB1*15, as individuals with a HLA-DRB1*09/HLA-DRB1*15 genotype have a decreased risk of anti-AQP4-negative MS. Recently, HLA-DRB1*09 was also shown to be negatively associated with ulcerative colitis. Thus, it is assumed that HLA-DRB1*09, or some genes in linkage disequilibrium with it, protect against certain autoimmune diseases, at least in Japanese, as it is quite rare in Caucasians. Moreover, a predisposing effect of HLA-DRB1*12 in anti-AQP4-positive MS has been found. Interestingly, HLA-DRB1*12 has been reported to increase the risk of...
allergic disorders, such as asthma, urticaria and food allergy. Finally, HLA-DRB1*04/HLA-DRB1*04, HLA-DRB1*04/HLA-DRB1*14, and HLA-DRB1*04/HLA-DRB1*15 genotypes increase the risk of non-NMO MS, probably by interaction with DRB1*15 allele.

In contrast, researches in Caucasian populations have come to the conclusion that the HLA-DRB1*03 allele is highly frequent in the NMO-IgG positive patients, while DPB1*05:01 is quite rare both in patients and healthy controls. We should also highlight the negative association between HLA-DRB1*15:01 and NMO, which indicates a possible protective role. In this point, the observation that NMO-IgG-positive and negative patients differ mostly in terms of gender and the association of other autoimmune diseases, could imply that HLA-DRB1*03 is associated with the NMO-IgG presence, but not with NMO per se and raise the question of whether NMO-IgG is epiphenomenon or pathogenic. In reply to this, Arellano et al. found that hAQP4281-330 is the dominant linear immunogenic determinant of hAQP4 in the context of HLADRB1*03:01. Within hAQP4281-330 are two dominant immunogenic determinants that induce differential Th phenotypes. In recent times, Asgari et al. reported a high frequency of HLA-DQB1*04:02 in NMO patients, an allele described to be associated with autoimmune diseases such as primary biliary cirrhosis, type-1 diabetes and juvenile idiopathic arthritis, but he didn't show any correlation with HLA-DRB1*03.

In Brazilian cohorts, NMO patients present a high frequency of the HLA-DRB1*03 allele and extremely low frequency of the HLA-DRB1*15. In addition to this, the same study showed that HLA-DRB1*01 allele is associated with NMO and benign MS, a correlation that indicates that this allele may influence the outcome of these demyelinating disorders. We would like to emphasize once more that HLA-DRB1*01 has a protective effect in anti-AQP4-negative MS patients in Japanese and Caucasians. In African-Americans, none OSMS patient carries the HLA-DRB1*1501 allele, while in Afro-Carribeans, NMO has been associated with the HLA-DRB1*03 allele [Table 2].

**DISCUSSION**

To the best of our knowledge, this is the first review aiming at summarizing all the results concerning HLA allelic frequencies in NMO and NMOSD, worldwide. Apart from a detailed description of HLA allelic frequencies in all genotyped NMO ethnic groups, we created a workable table including all this information, for an easier reader’s approach.

As a conclusion, it is clear that quite different HLA-alleles are correlated to NMO/NMOSD compared to MS patients, reflecting different underlying immunopathogenic mechanisms. Particularly, the well-established and most frequent HLA-DRB1*15:01 allele, associated with MS, plays rather a protective role for NMO. In addition, rare alleles, HLA-DRB1*12, like HLA-DRB1*01 and especially HLA-DRB1*09, play a core role in NMO risk or protection respectively and obviously in immunopathogenesis, in some ethnic groups. On the other hand, it is clear that different HLA alleles are associated with different ethnic groups, like Eastern NMO (association with the HLA-DPB1*05:01), which in turn are specifically associated with certain clinical/paraclinical features.

Moreover, the comorbidity of NMO with other autoimmune diseases is still under further investigation, although it seems that so far this comorbidity is highly reflected in HLA profile and anti-AQP4 antibody presence, suggesting common pathways in their immunopathogenesis.

In MS there is also comorbidity with other autoimmune diseases, like SLE, Hashimoto’s thyroiditis, etc., However, this co-existence presumes rarer than in NMO, although more investigation studies are warranted to prove this notion.

In this paper, we tried to focus only on the HLA-immunogenetics of NMO, since the HLA molecule is a core component of the trimolecular complex, which is involved in antigen-presentation, as the first step of the immune response. However, as in MS, similarly in NMO, many non-MHC genes are candidates for the overall genetic burden. First, genes correlated to immune system and immunogenetics, namely IL-7 receptor polymorphisms, IL-2 receptor a chain gene polymorphisms and CD6, interferon regulatory factor 8 and tumor necrosis factor receptor superfamily polymorphisms and secondly, the polymorphisms of the promoter region of cytochrome-P450-7A1 gene and AQP4 genetic variations are involved.

Regarding MS, it has been shown that specific alleles, in particular HLA-DRB1*04:01, HLA-DRB1*04:08 and HLA-DRB1*16:01, are associated with an increased risk of antiinterferon beta antibody development. As a result, the poorer therapeutical outcome highlights the importance of the stratification of patients to responders and nonresponders, according to HLA-genotyping. Similarly, Warabi et al. concluded that patients carrying the NMO-specific HLA allele DPB1*05:01 showed a poor prognosis following interferon beta-1b treatment. The crucial role of the AQP4-antibodies in the pathogenesis of NMO has been
in our consideration for a few years only, in contrast to the 30 years of worldwide research regarding MS and HLA. We expect this to be the new field of extensive future research, in correlation with the accumulated knowledge on the pathogenesis of NMO.

Finally, the HLA profile in a patient with a CNS demyelinating disease tends to highlight different backgrounds in immunopathogenesis and clinical phenotype, components which are very important in the diagnosis and disease therapeutic decision making, which is strongly requested. To this direction and in order to use HLA alleles, as a biomarker, in patients’ early stratification, more HLA-genotyping studies are needed, in different ethnic groups, in order to clarify, replicate or even expand the already existed results.

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