Journal of the Neurological Sciences 407 (2019) 116533

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Human leukocyte antigens class II in CIDP spectrum neuropathies

Stefano Cotti Piccinelli[a], Graziella Carella[b], Micol Frassi[c], Filomena Caria[a], Serena Gallo Cassarino[a], Enrico Baldelli[a], Mirella Marini[b], Angela Tincani[c], Alessandro Padovani[a], Massimiliano Filosto[a,*]

[a] Center for Neuromuscular Diseases, Unit of Neurology, ASST "Spedali Civili" and University of Brescia, Italy
[b] Laboratorio Istocompatibilità, Servizio di Immunoematologia e Medicina Trasfusionale SIMT, ASST "Spedali Civili", Brescia, Italy
[c] Unit of Rheumatology and Clinical Immunology, ASST "Spedali Civili" and University of Brescia, Italy

ARTICLE INFO

Keywords:
CIDP
Chronic inflammatory demyelinating polyradiculoneuropathy
HLA
DR3
DR3/DQ2

ABSTRACT

CIDP spectrum encompasses several clinical variants and the reasons of the heterogeneous clinical expression and the variable response to therapy are scarcely known.

HLA associations are common in dysimmune conditions. In CIDP, few studies reported no associations or HLA-DR13/DQ6 association in some populations but, to date, a clear confirmed association is lacking.

We analyzed expression of HLA-DR and DQ haplotypes in 24 CIDP patients and 216 healthy subject.

HLA-DR3 and DR3/DQ2 were significantly more frequent in CIDP patients than in the control group. The DR3 and DR3/DQ2 positive patients present with more frequent relapsing course, worse response to IVIg, higher inflammatory neuropathy sensory sumscore (ISS) and Rotterdam Inflammatory Neuropathy Cause and Treatment Scale (INCAT) than negative patients.

1. Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an autoimmune disease mediated by humoral and cellular immunity against Schwann cell and/or myelin antigen [14].

The estimated overall prevalence of the disease is 4,77 per 100,000 (95% confidence interval 3.49–6.37) [26].

The main clinical features of classical CIDP are symmetrical distal sensory symptoms, including paresthesia or pain, and muscle weakness with a proximal progression [28]. While CIDP symptoms usually develop gradually over > 8 weeks, about 16% of patients can experience acute deterioration (acute CIDP, A-CIDP) and some patients may present with a subacute onset (SIDP) [24,29].

The clinical spectrum encompasses several different variants including an asymmetrical form (multifocal acquired demyelinating sensory and motor neuropathy - MADSAM), focal CIDP, distal acquired demyelinating symmetrical (DADS) neuropathy, sensory CIDP and motor CIDP [5]. Clinical progression could vary from a progressive to a relapsing form [36]. To date, diagnosis is usually based on the EFNS/PNS electrophyisiological and clinical criteria [11].

CIDP pathogenesis is still not completely understood. A putative antigen target is the non-compact myelin located at the nodal and paranodal region which is extremely important in the processes of myelin-axon interaction. Disruption of these regions may result in early conduction block. The current view suggests an immune cell activation in the blood following putative antigen processing by antigen-presenting cells such as macrophages [3]. Subsequent steps are clonal expansion of T cells, upregulation of adhesion molecules on endothelial cells and transmigration of T cells across the blood-nerve barrier to the myelin sheath. T cells chemokine and cytokine release activates resident macrophages which by invading myelin cause a macrophage-mediated demyelination [4].

Abbreviations: CIDP, Chronic inflammatory demyelinating polyradiculoneuropathy; HLA, Human Leucocyte Antigen; MADSAM, Multifocal acquired demyelinating sensory and motor neuropathy; DADS, Distal acquired demyelinating symmetrical; EFNS/PNS, European Federation of Neurological Societies/Peripheral Nerve Society; FcR, Fc receptor; MHC, Major histocompatibility complex; CSF, Cerebrospinal fluid; ENG, Electroneurography; EMG, Electromyography; MAG, Myelin-associated-glycoprotein; GM, GQ, Anti-ganglioside antibodies; CNT1, Anti-contactin 1; NF155, Anti-neurofascin 155; INCAT, Inflammatory Neuropathy Cause and Treatment disability score; ISS, Inflammatory neuropathy sensory score); MRC, Medical Research Council score; IVIg, Intravenous Immunoglobulins; scIg, Subcutaneous Immunoglobulins; SSP, Sequence Specific Primers; PCR, Polymerase chain reaction; SPSS, Statistical Package for Social Science

* Corresponding author at: Center of Neuromuscular Diseases, Unit of Neurology, ASST Spedali Civili and University of Brescia, Pz.le Spedali Civili 1, 25100 Brescia, Italy.

E-mail address: massimiliano.filosto@unibs.it (M. Filosto).

https://doi.org/10.1016/j.jns.2019.116533
Received 25 June 2019; Received in revised form 11 October 2019; Accepted 14 October 2019
Available online 23 October 2019
0022-510X/

A role of humoral factors in pathogenic process is likely. Cytokines and chemokines may activate B cells which produce antibodies which recognize antigens on the myelin by fixing complement or by binding to the Fc receptors on macrophages [3,17].

Autoantibodies targeting nodal and paranodal antigens, i.e. Neurofascin, Contactin1 and contactin-associated protein 1 have been recently identified in about 10% of the patients [37]. Their dominant isotype is IgG4 which has several different features from the other IgG subtypes such as no capacity to effectively cross-link target antigens, no capacity to activate complement and little FcR binding capacity [37].

Antigen presentation and T cell activation appear to be key processes for triggering an autoimmune response. Antigens are internalized via antigen presenting cells (APC) and are bound by Human Leucocyte Antigen (HLA) class II molecules which are synthesized in the rough endoplasmic reticulum. The HLA peptide complex is then transported to the cell surface for recognition by CD4+ Th cells [38].

HLA represents a set of gene-encoding loci for some antigens involved in regulating the immune response and which collectively assume in humans the name of major histocompatibility complex (MHC). Class I HLA molecules (A, B and C) are expressed on most, but not all, the nucleated cells in the body at basal conditions, including peripheral nerve myelin cells ([13,31]. Class II HLA molecules (DP, DQ and DR) are weakly expressed in Schwann cell cultures under basal conditions [19]. Schwann cells increased expression of HLA Class I and II molecules under inflammatory conditions [19].

HLA class II molecules traditionally present exogenous antigens and class I present endogenous antigens such as those derived from viruses and intracellular bacteria, but this rule is not rigid and presentation of endogenous antigens by class II and exogenous antigens by class I has been also observed (*Simmonds* et al., *2007*).

Several HLA polymorphisms have been implicated in a number of autoimmune disorders and the presence of a specific HLA association can be one of the criteria for diagnosing autoimmune diseases [10,27], i.e. in ankylosing spondylitis (HLA-B27:02, HLA-B27:05), narcolepsia (HLA-DQ6), seropositive rheumatoid arthritis (DRB1–04:01, DRB1–04:04, DRB1–04:05, DRB1–01:01) [20]. Some HLA associations may predispose to specific diseases as HLA-DR1 and DR4 (rheumatoid arthritis, type 1 diabetes, and systemic lupus erythematosus), DR2 which confers susceptibility to multiple sclerosis and DQ2 and DQ8 which predispose to celiac disease [9,12].

Several hypotheses have been suggested to explain how variation in HLA genes could trigger or predispose to autoimmunity. HLA class II molecule polymorphisms in binding sites could lead to preferential presentation of only a specific limited set of self-peptides, could alter the Th and Treg cell repertoire or could cause changes in how the antigen is recognized in the periphery (*Simmonds* et al., *2007*). Viral/bacterial antigens presented by HLA class I molecules may trigger autoimmunity through molecular mimicry and via acting as superantigens, producing a strong non-specific immune response that then cross reacts attacking other tissues (*Simmonds* et al., *2007*). HLA class I molecules can also act by inhibiting NK cell activity (*Simmonds* et al., *2007*).

The role of HLA polymorphisms in influencing clinical expression of CIDP has been already investigated [18,21]. HLA II has been mainly studied because of its decisive role in presenting antigenic peptides from predominantly extracellular sources to CD4+ T cells and in mediating the thymic selection of helper T cells [34].

However, discordant results have been obtained and different HLA associations, including HLA DR13, DR2 or D3, have been reported in different studies [18,21,22].

In this study we aimed to explore HLA II haplotype in an Italian cohort of CIDP patients in order to better define the relations between specific haplotypes and the disease. Moreover we aim to explore a possible HLA II role in determining clinical variability and therapeutic response, by taking in account eventual relations between some specific haplotypes and different clinical presentations, course and response to therapy.

2. Patients and methods

2.1. Patients

We analyzed lymphocytic expression of HLA DR and DQ haplotypes of 23 Italian patients and 1 Asian patient diagnosed with CIDP at our Center between 2010 and 2016.

All patients had a defined CIDP according to EFNS/PNS criteria [11].

Diagnostic work-up include cerebrospinal fluid (CSF) analysis, electroneurography (ENG), electromyography (EMG) and antibody profile against myelin-associated antigen (anti-MAG, anti-gangliosides [anti-GM and GQ], anti-Contactin-1 [CNT1] and anti-Neurofascin [anti-NF155]). For each patient INCAT (Rotterdam Inflammatory Neuropathy Cause and Treatment Scale), ISS (inflammatory neuropathy sensory sumscore), MRC (Medical Research Council) sumscore and Quality of Life (Score) score were calculated.

The mean age of onset was 53,8 ± 16,7 years, ranging from 18 to 76.

Twenty-one patients had classical form, 2 had pure sensory CIDP, 1 had DADS.

Sixteen patients had a chronic form, while 8 presented a relapsing-remitting course.

Out of the 24 patients studied, 5 (20,8%) showed response to the first treatment line, 13 (54,2%) received two different treatment, 5 (20,8%) requires three treatment lines and only 1(4,2%) four.

Twenty-one subjects were treated with IVIg and 18 (85,7%) showed clinical benefits. Three of these patients then switched to treatment with SCIg, all showing a positive response.

Twenty-one patients were treated at least once with corticosteroids, but only 13 (61,9%) showed a satisfactory response. Of the 15 patients treated with both corticosteroids and IVIg, 10 showed benefit in both cases, 2 only with IVIg treatment, and 3 with neither of the two therapies.

Plasmapheresis was used in 3 cases but showed effectiveness in only 1 (33%) subject, which previously had no benefit from IVIg and corticosteroid therapy.

Immunosuppressants were used in 2 cases but showed no clinical benefits.

Two hundred sixteen healthy samples from Brescia Bone Marrow Donor Registry were random selected as the control group.

2.2. Methods

HLA analysis was performed by SSP, a PCR-based method that uses Sequence Specific Primers (SSPs) for molecular tissue typing. The kits for typing are composed of mixtures of primers, wherein each mixture contains one or more pairs of primers specific for an allele and/or an allelic group, in addition to a pair of control primers for conserved sequences in the sample. The pair of control primers has the internal control function of the PCR and therefore amplifies efficiency verification. The method is based on the principle that a primer perfectly matching the allele sequence is used more efficiently in the PCR reaction than a primer with one or more mismatch at end 3′. The specificity of the typing is within the amplification phase and the processing of the results occurs after an electrophoresis on agarose gel. The amplified fragments are then separated by electrophoresis on agarose gel in the presence of specific dye, exposed to ultraviolet light and photographed. Each pair of primers identifies two polymorphic sites [7,25]. Haplotype analysis was performed by determining the association of alleles presents on each of the subjects' chromosomes [15].

Table 1
HLA-DR and HLA-DQ alleles frequency in healthy controls compared to CIDP patients.

HLA class II	% allele in healthy controls (18n = 432)	% allele in CIDP (2n = 48)	P value
DRB1*01	11%	10,40%	1
DRB1*03	***4,00%***	***12,50%***	***0,042***
DRB1*04	14,10%	8,30%	0,373
DRB1*07	13,20%	6,30%	0,248
DRB1*08	4,40%	0%	0,241
DRB1*10	***0%***	***4,20%***	***0,01***
DRB1*11	25,70%	31,30%	0,393
DRB1*13	12,50%	14,60%	0,65
DRB1*14	3,70%	4,20%	0,699
DRB1*15	5,60%	4,20%	1
DRB1*16	4,40%	4,20%	1
DRQ1*02	16,90%	16,70%	1
DRQ1*03	45,40%	41,70%	0,65
DRQ1*04	3,70%	0%	0,389
DRQ1*05	19,20%	25%	0,342
DRQ1*06	14,60%	16,70%	0,67

Bold indicates statistically significant values.

2.3. Statistical analyses

The statistical analysis was carried out using SPSS software (RRID:SCR_002865), version 20. The clinical, pathological and immunological characteristics of patients with CIDP were analyzed by $\chi 2$ or Student's *t*-tests for independent variables, depending on the appropriateness. We used the Bonferroni correction for multiple comparisons. A $p < .05$ was considered statistically significant.

3. Results

3.1. Relation between HLA haplotypes and CIDP

HLA-DR3 results to be significantly more frequent in the cohort of patients with CIDP (six patients, 25%) than in the controls (18 controls, 8%) with a $p < 0,05$. Single HLA-DR and HLA-DQ frequency in patients and controls are shown in Table 1.

All CIDP patients carrying HLA-DR3 were also HLA-DR3/DQ2 positive.

HLA-DR3/DQ2 results to be significantly more frequent in the cohort of patients with CIDP (six patients, 25%) than in the controls (16 controls, 7.4%) with a statistically significant difference ($p < 0,05$) (Table 2).

Three CIDP patients harbored HLA DQ2 without HLA DR3.

No one of the patients neither healthy controls were homozygous for alleles HLA DR3, HLA DQ2 and for DR3/DQ2 haplotype.

HLA haplotype DR10/DQ5 was found only in the Asian CIDP subject and in none of the control group subjects (4,2% vs 0%, $p < 0,01$).

Table 2
HLA-DR/DQ haplotypes frequency in healthy controls compared to CIDP patients.

Aplotipo DRB1*/ DQB1*	% Healthy controls (18n = 432)	% CIDP patients (2n = 48)	P value
DR03/DQ02	***3,70%***	***12.5%***	***0,038***
DR04/DQ03	10,60%	6,30%	0,455
DR07/DQ02	7,60%	2,10%	0,234
DR07/DQ03	4,20%	4,20%	1
DR10/DQ05	***0%***	***4,20%***	***0,01***
DR11/DQ03	20,80%	22,90%	0,711
DR13/DQ06	9,50%	14,60%	0,306
DR15/DQ06	4,60%	2,10%	0,71

Bold indicates statistically significant values.

3.2. Relation between HLA haplotypes and CIDP variants

All the patients harboring HLA-DR3/DQ2 haplotype present with a classical CIDP. The other 15 classic patients and the three subjects having a non-classical variant were DR3 and DR3/DQ2 negative.

3.3. Relation between HLA haplotypes and clinical aspects

Although following findings did not reach statistical significance, DR3/DQ2 positive patients present more frequently relapsing-remitting course, a more frequent upper limb distal sensory and cranial nerve involvement and higher ISS and INCAT scores than DR3 and DR3/DQ2 negative patients.

Specifically, 50% of the HLA-DR3/DQ2 positive patients have a relapsing-remitting course versus 27% of the HLA-DR3/DQ2 negative ones (*p* value 0.36).

Eighty-three per cent of the HLA-DR3/DQ2 positive patients present with a severe distal sensory impairment and 17% with cranial nerve involvement versus 50% and 5,6% respectively of the HLA-DR3/DQ2 negative subjects (p value respectively of 0,34 and 0,44).

No significant differences about pain (66,7% vs 50%) and tremor (33,3% vs 27,8%) were found between HLA-DR3/DQ2 positive and negative subjects.

The results of both ISS (7,17 vs 5,7) and INCAT scores (3,83 vs 2,72) were slightly higher in patients with HLA-DR3/DQ2, while MRC score (52,5 vs 53) and Quality of life score (8,17 vs 7,83) showed no differences (Table 3).

3.4. Relation between HLA haplotypes and therapy

All the DR3/DQ2 positive patients were treated with IVIg, showing a good response in 4 (66,7%) cases, while corticosteroids where used in 4 cases as second line treatment, showing effectiveness in half of the cases. In two patients a plasma-exchange cycle was used, but, given the lack of response, we returned to IVIg therapy.

HLA-DR3/DQ2 positive patients showed a worse response to IVIg than HLA-DR3/DQ2 negative CIDP subjects, (66,7% vs 78%), while the rate of response to corticosteroids was similar (50% vs 55,6%).

4. Discussion

Several putative risk factors, such as previous infections or vaccinations, have been investigated for a long time in CIDP but their role in the disease pathogenesis has not been completely clarified so far [6]. Recently, Doneddu et al. reported antecedent events before CIDP onset in 15.5% of the patients, including infections in 12% and vaccinations in 1.5% [6].

Also a number of candidate genes possibly involved in CIDP pathogenesis have been investigated [2]. Specifically, two genes have been implicated in CIDP susceptibility: *SH2D2A* (a gene encoding for a T-cell-specific adapter protein involved in controlling early T-cell activation) and the M3 allele of alpha-1 antitrypsin [23,32].

HLA haplotype association with CIDP has been already studied in the past with discordant and not definitive results [2]. Generally, no attempt to relate HLA haplotype to different clinical characteristics of the disease was done.

In late '70, patients with chronic relapsing polyneuritis were reported to show an association with HLA-AW30 and AW31 and probable associations with HLA-B8, HLA-DW3 [30].

Adams et al. reported possible disease susceptibility gene associated with the HLA-A1, −B8, −DRw3, and –Dw3 haplotype in 14 cases diagnosed as recurrent or chronic relapsing idiopathic inflammatory polyneuropathy [1]. They did not find associations with HLA-AW30 and AW31 [25].

In 1990, HLA-A3, −B7, −DR2 associations and concomitant decreased frequency of HLA-B44 and DR7 were found in 71 CIDP patients,

Table 3
MRC, ISS, INCAT and QOL score of DR3-DQ2 positive CIDP patients compared with DR3-DQ2 negative.

	DRB1 03	N	Average	Standard deviation	Standard error average	P value
MRC SCORE	No	18	53	8275	1,95	0,89
	Yes	6	52,5	5431	2217	
ISS SCORE	No	18	5,72	2886	0,68	0,3
	Yes	6	7,17	3061	1249	
INCAT SCORE upper limbs	No	18	0,89	0,9	0,212	0,2
	Yes	6	1,5	1225	0,5	
INCAT SCORE lower limbs	No	18	1,83	1,15	0,271	0,41
	Yes	6	2,33	1633	0,667	
Total INCAT (ONLS)	No	18	2,72	1674	0,394	0,24
	Yes	6	3,83	2787	1138	
QoL SCORE	No	18	7,83	2333	0,55	0,74
	Yes	6	8,17	1472	0,601	

while previous observed associations were not confirmed [8].

In the same year, a different study confirmed a mild association with HLA-B8 and identify a stronger association with HLA-Cw7 [35].

The only attempt to evaluate the MHC associations with CIDP on the bases of specific clinical parameters was made in 1991 when van Doorn et al. studied HLA in CIDP patients divided for the presence or absence of anti-neural antibodies or improving or not improving after intravenous immunoglobulin [33]. However, they found no significant associations with any of the HLA-A, B, C, DR or DQ antigens [33].

In 2006, McCombe et al. showed that the gene frequency and the frequency of CIDP individuals positive for HLA-DR2 were greater in female patients than female controls, although this was statistically significant only for the gene frequency [18].

In 2013, association with the HLA-DR13 allele was found in a cohort of 36 Tunisian patients; moreover, the haplotypes DR13/DQ6 and DR7/DQ3 were found to confer a susceptibility to disease [21].

More recently, DR15 alleles were found to be a strong risk factor associated to anti-NF155 associated CIDP, providing further evidence that this subset of patients constitute a specific entity within the CIDP spectrum diseases [16].

In a way, our study further complicates the picture. We found an association between HLA-DR3 and DR3/DQ2 and CIDP in a cohort of Italian patients. HLA haplotype DR10/DQ5 was found only in the Asian patient and in none of the other patients or control group subjects.

The allelic analysis of the class II DR and DQ HLA genes showed a statistically significant prevalence of the alleles DR3 ($p = .042$) and DR10 ($p = .01$) in the affected subjects compared to the healthy control population. Haplotype analysis showed that haplotypes DR3/DQ2 and DR10/DQ5 are more statistically present in disease subjects than healthy controls.

These results are, again, different from previous studies and, in particular, did not show any association with DR2 and DR13 alleles. None of our patients was anti NF155 positive.

Regarding the relation HLA haplotype/clinical characteristics, in our cohort the DR3 and DR3/DQ2 patients represent a subset of our CIDP population which present more frequently with a relapsing-remitting course, an upper limb distal sensory and cranial nerve involvement, higher VAS, ISS and INCAT scores and worse response to Ig IV treatment than DR3 and DR3/DQ2 negative subjects.

Unfortunately, the number of our non-classic patients is too small to have adequate evaluations on HLA haplotype differences between classic and non-classic variants. However, on the light of our results this last aspect deserves further studies on a larger population.

Our results (statistically significant although the relatively small patient population) support a role for HLA haplotype association in the pathogenic mechanisms of CIDP.

As for the recent evidence of a specific association between DR15 alleles and the NF155-linked subset CIDP patients, our findings identify some prevalent clinical characteristics in DR3 and DR3/DQ2 positive patients respect to the negative ones, therefore reinforcing the idea that different subsets of patients both from a clinical and immunological point of view do exist in this disease [16].

The differences between the results of the various studies performed on HLA involvement in CIDP remain hardly explainable but we believe that a major bias could be the “uncorrect” selection of the patients, which means that we really don't know the real boundaries of CIDP and whether it should be considered a single disease with some variants or, more likely, a group of diseases that may differ in their clinical presentation, pathogenesis and therapeutic response [22]. Especially, it is unclear if a single immune mechanism underlies CIDP or different pathogenic mechanisms may be more likely involved and which possibly may explain different clinical presentations [22].

Further studies on HLA and other genetic susceptibility factors will be useful to achieve these responses and better understand the real range of the CIDP spectrum diseases.

Author contribution

Stefano Cotti Piccinelli: Conception or design of the work, Data collection, Data analysis and interpretation, Drafting the article.

Graziella Carella: Data collection, Data analysis and interpretation.

Micol Frassi, Filomena Caria, Serena Gallo Cassarino, Enrico Baldelli: Data collection.

Mirella Marini, Angela Tincani, Alessandro Padovani: Critical revision of the article.

Massimiliano Filosto: Conception or design of the work, Data analysis and interpretation, Critical revision of the article.

Declaration of Competing Interest

None

Acknowledgements

We thank Prof. E. Nobile Orazio and his staff for anti-NF155 and anti-CN2 auto-antibodies analysis.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] D. Adams, H. Festenstein, J.D. Gibson, R.A. Hughes, J. Jaraquemada, C. Papasteriadis, J. Sachs, P.K. Thomas, HLA antigens in chronic relapsing idiopathic inflammatory polyneuropathy, J. Neurol. Neurosurg. Psychiatry 42 (1979) 184–186, https://doi.org/10.1136/jnnp.42.2.184.

[2] S. Blum, P.A. McCombe, Genetics of Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): current knowledge and future directions, J. Peripher. Nerv. Syst. 19 (2014) 88–103, https://doi.org/10.1111/jns5.12074.

[3] M.C. Dalakas, Medscape, Advances in the diagnosis, pathogenesis and treatment of CIDP, Nat. Rev. Neurol. 7 (2011) 507–517, https://doi.org/10.1038/nrneurol.2011.121.

[4] M.C. Dalakas, Pathogenesis of immune-mediated neuropathies, Biochim. Biophys. Acta 1852 (2015) 658–666, https://doi.org/10.1016/j.bbadis.2014.06.013.

[5] P.E. Doneddu, D. Cocito, F. Manganelli, R. Fazio, C. Briani, M. Filosto, L. Benedetti, A. Mazzeo, G.A. Marfia, A. Cortese, B. Fierro, S. Jann, E. Beghi, A.M. Clerici, M. Carpo, A. Schenone, M. Luigetti, G. Lauria, G. Antonini, T. Rosso, G. Siciliano, G. Cavaletti, G. Liberatore, L. Santoro, E. Peci, S. Tronci, M. Ruiz, S. Cotti Piccinelli, A. Toscano, G. Mataluni, L. Piccolo, G. Cosentino, M. Sabatelli, E. Nobile-Orazio, Italian CIDP Database Study Group, Atypical CIDP: diagnostic criteria, progression and treatment response. Data from the Italian CIDP database, J. Neurol. Neurosurg. Psychiatry 90 (2019) 125–132, https://doi.org/10.1136/jnnp-2018-318714.

[6] P.E. Doneddu, E. Bianchi, D. Cocito, F. Manganelli, R. Fazio, M. Filosto, A. Mazzeo, G. Cosentino, A. Cortese, S. Jann, A.M. Clerici, G. Antonini, G. Siciliano, M. Luigetti, G.A. Marfia, C. Briani, G. Lauria, T. Rosso, G. Cavaletti, M. Carpo, L. Benedetti, E. Beghi, G. Liberatore, L. Santoro, E. Peci, S. Tronci, S. Cotti Piccinelli, A. Toscano, L. Piccolo, E.P. Verrengia, L. Leonardi, E. Schirinzi, G. Mataluni, M. Ruiz, P. Dacci, E. Nobile-Orazio, Italian CIDP Database Study Group, Risk factors for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): antecedent events, lifestyle and dietary habits. Data from the Italian CIDP database, Eur. J. Neurol. (2019 Jul) (2019) 20, https://doi.org/10.1111/ene.14044.

[7] M.E. Fasano, M. Berrino, G. Mazzola, E. Dametto, M. Tacconella, F. Brancatello, F. Marin, E.S. Curtoni, Metodologia di approccio alla tipizzazione HLADRB mediante analisi del DNA, La trasfusione del sangue. 46 (2001) 81–95.

[8] D.J. Feeney, J.D. Pollard, J.G. McLeod, G.J. Stewart, T.J. Doran, HLA antigens in chronic inflammatory demyelinating polyneuropathy, J. Neurol. Neurosurg. Psychiatry 53 (1990) 170–172, https://doi.org/10.1136/jnnp.53.2.170.

[9] M.M. Fernando, C.R. Stevens, E.C. Walsh, P.L. De Jager, P. Goyette, R.M. Plenge, T.J. Vyse, J.D. Rioux, Defining the role of the MHC in autoimmunity: a review and pooled analysis, PLoS Genet. 4 (2008) 1000024, , https://doi.org/10.1371/journal.pgen.1000024.

[10] S.C. Gough, M.J. Simmonds, The HLA region and autoimmune disease: associations and mechanisms of action, Curr. Genom. 8 (2007) 453–465, https://doi.org/10.2174/138920207783591690.

[11] Joint Task Force of the EFNS and the PNS, European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society–First Revision, J. Peripher. Nerv. Syst. 15 (2010) 1–9, https://doi.org/10.1111/j.1529-8027.2010.00245.x.

[12] E.Y. Jones, L. Fugger, J.L. Strominger, C. Siebold, MHC class II proteins and disease: a structural perspective, Nat. Rev. Immunol. 6 (2006) 271–282, https://doi.org/10.1038/nri1805.

[13] M.A. Khan, A. Mathieu, R. Sorrentino, N. Akkoc, The pathogenetic role of HLA-B27 and its subtypes, Autoimmun. Rev. 6 (2007) 183–189, https://doi.org/10.1016/j.autrev.2006.11.003.

[14] H. Köller, B.C. Kieseier, S. Jander, H.P. Hartung, Chronic inflammatory demyelinating polyneuropathy, N. Engl. J. Med. 352 (2005) 1343–1356, https://doi.org/10.1056/NEJMra041347.

[15] S.G. Marsh, E.D. Albert, W.F. Bodmer, R.E. Bontrop, B. Dupont, H.A. Erlich, D.E. Geraghty, J.A. Hansen, C.K. Hurley, B. Mach, W.R. Mayr, P. Parham, E.W. Petersdorf, T. Sasazuki, G.M. Schreuder, J.L. Strominger, A. Svejgaard, P.I. Terasaki, J. Trowsdale, Nomenclature for factors of the HLA system, Int. J. Immunogenet. 32 (2005) 107–159, https://doi.org/10.1111/j.1744-313X.2005.00509.x.

[16] L. Martinez-Martinez, M.C. Lleixà, G. Boera-Carnicero, A. Cortese, J. Devaux, A. Siles, Y. Rajabally, A. Martinez-Piñeiro, A. Carvajal, J. Pardo, E. Delmont, S. Attarian, J. Diaz-Manera, I. Callegari, E. Marchioni, D. Franciotta, L. Benedetti, G. Lauria, O. de la Calle Martin, C. Juárez, I. Illa, L. Querol, Anti-NF155 chronic inflammatory demyelinating polyradiculoneuropathy strongly associates to HLA-DRB15, J. Neuroinflammation 14 (2017) 224, https://doi.org/10.1186/s12974-017-0996-1.

[17] E.K. Mathey, S.B. Park, R.A. Hughes, J.D. Pollard, P.J. Armati, M.H. Barnett, B.V. Taylor, P.J. Dyck, M.C. Kiernan, C.S. Lin, Chronic inflammatory demyelinating polyradiculoneuropathy: from pathology to phenotype, J. Neurol. Neurosurg. Psychiatry 86 (2015) 973–985, https://doi.org/10.1136/jnnp-2014-309697.

[18] P.A. McCombe, P.A. Csurhes, J.M. Greer, Studies of HLA associations in male and female patients with Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), J. Neuroimmunol. 180 (2006) 172–177, https://doi.org/10.1016/j.jneuroim.2006.07.017.

[19] G. Meyer Zu Horste, H. Heidenreich, H.C. Lehmann, S. Ferrone, H.P. Hartung, H. Wiendl, B.C. Kieseier, Expression of antigen processing and presenting molecules by Schwann cells in inflammatory neuropathies, Glia. 58 (2010) 80–92, https://doi.org/10.1002/glia.20903.

[20] Y.M. Mosaad, Clinical role of human leukocyte antigen in health and disease, Scand. J. Immunol. 82 (2015) 283–306, https://doi.org/10.1111/sji.12329.

[21] M. Mrad, N. Fekih-Mrissa, M. Mansour, A. Seyah, A. Riahi, N. Gritli, R. Mrissa, Association of HLA-DR/DQ polymorphism with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in Tunisian patients, Transfus. Apher. Sci. 49 (2013) 623–626, https://doi.org/10.1016/j.transci.2013.07.024.

[22] E. Nobile-Orazio, Chronic inflammatory demyelinating polyradiculoneuropathy and variants: where we are and where we should go, J. Peripher. Nerv. Syst. 19 (2014) 2–13, https://doi.org/10.1111/jns5.12053.

[23] F. Notturno, M. Pace, M.V. De Angelis, C.M. Caporale, A. Giovannini, A. Uncini, Susceptibility to chronic inflammatory demyelinating polyradiculoneuropathy is associated to polymorphic GA repeat in the SH2D2A gene, J. Neuroimmunol. 197 (2008) 124–127, https://doi.org/10.1016/j.jneuroim.2008.04.003.

[24] S.J. Oh, K. Kurokawa, D.F. de Almeida, H.F. Ryan Jr., G.C. Claussen, Subacute inflammatory demyelinating polyneuropathy, Neurology 61 (2003) 1507–1512, https://doi.org/10.1212/01.wnl.0000096166.28131.4c.

[25] O. Olerup, H. Zetterquist, HLA-DR typing by PCR amplification with sequence-specific primers (PCR-SSP) in 2 hours: an alternative to serological DR typing in clinical practice including donor-recipient matching in cadaveric transplantation, Tissue Antigens 39 (1992) 225–235, https://doi.org/10.1111/j.1399-0039.1992.tb01940.x.

[26] Y.A. Rajabally, B.S. Simpson, S. Beri, J. Bankart, J.A. Gosalakkal, Epidemiologic variability of chronic inflammatory demyelinating Polinueropathy with different diagnostic criteria: study of a UK population, Muscle Nerve 39 (2009) 432–438, https://doi.org/10.1002/mus.21206.

[27] N.R. Rose, C. Bona, Defining criteria for autoimmune diseases (Witebsky's postulates revisited), Immunol. Today 14 (1993) 426–430, https://doi.org/10.1016/0167-5699(93)90244-F.

[28] G. Said, Chronic inflammatory demyelinating polyneuropathy, Neuromuscul. Disord. 16 (2006) 293–303, https://doi.org/10.1016/j.nmd.2006.02.008.

[29] J.Y. Sung, J. Tani, S.B. Park, M.C. Kiernan, C. Shin-Yi, Early identification of 'acute-onset' chronic inflammatory demyelinating polyneuropathy, Brain 137 (2014) 2155–2163, https://doi.org/10.1093/brain/awu158.

[30] G. Stewart, J.D. Pollard, J.G. McLeod, C.M. Wolnizer, HLA antigens in the Landry-Guillain-Barré syndrome and chronic relapsing polyneuritis, Ann. Neurol. 4 (1978) 285–289, https://doi.org/10.1002/ana.410040317.

[31] J. Trowsdale, J.C. Knight, Major histocompatibility complex genomics and human disease, Annu. Rev. Genomics Hum. Genet. 14 (2013) 301–323, https://doi.org/10.1146/annurev-genom-091212-153455.

[32] A. Uncini, F. Notturno, M. Pace, C.M. Caporale, Polymorphism of CD1 and SH2D2A genes in inflammatory neuropathies, J. Peripher. Nerv. Syst. 16 (Suppl. 1) (2011) 48–51, https://doi.org/10.1111/j.1529-8027.2011.00307.x.

[33] P.A. van Doorn, G.M. Schreuder, M. Vermeulen, J. d'Amaro, A. Brand, HLA antigens in patients with chronic inflammatory demyelinating polyneuropathy, J. Neuroimmunol. 32 (1991) 133–139, https://doi.org/10.1016/0165-5728(91)90005-r.

[34] M. van Lith, R.M. McEwen-Smith, A.M. Benham, HLA-DP, HLA-DQ, and HLA-DR have different requirements for invariant chain and HLA-DM, J. Biol. Chem. 285 (2010) 40800–40808, https://doi.org/10.1074/jbc.M110.148155.

[35] R.W. Vaughan, A.M. Adam, I.A. Gray, R.A. Hughes, E.A. Sanders, M. van Dam, K.I. Welsh, Major histocompatibility complex class I and class II polymorphism in chronic idiopathic demyelinating polyradiculoneuropathy, J. Neuroimmunol. 27 (1990) 149–153, https://doi.org/10.1016/0165-5728(90)90064-t.

[36] K. Viala, T. Maisonobe, T. Stojkovic, R. Koutlidis, X. Ayrignac, L. Musset, E. Fournier, J.M. Léger, P. Bouche, A current view of the diagnosis, clinical variants, response to treatment and prognosis of chronic inflammatory demyelinating polyradiculoneuropathy, J. Peripher. Nerv. Syst. 15 (2010) 50–56, https://doi.org/10.1111/j.1529-8027.2010.00251.x.

[37] A. Vural, K. Doppler, E. Meinl, Autoantibodies against the node of Ranvier in seropositive chronic inflammatory demyelinating polyneuropathy: diagnostic, pathogenic, and therapeutic relevance, Front. Immunol. 9 (2018) 1029, https://doi.org/10.3389/fimmu.2018.01029.

[38] M.J. Simmonds, J.M. Howson, J.M. Heward, J. Carr-Smith, J.A. Franklyn, J.A. Todd, S.C. Gough, A novel and major association of HLA-C in Graves' disease that eclipses the classical HLA-DRB1 effect, Hum. Mol. Genet. 16 (2007) 2149–2153.