

Short communication

Polymorphisms of CD1 genes in chronic dysimmune neuropathies

Maria Vittoria De Angelis¹, Francesca Notturmo¹, Christina M. Caporale,
Marta Pace, Antonino Uncini*

*Department of Human Motor Sciences University "G. d'Annunzio", Chieti—Pescara, Italy
Institute of Aging (Ce.S.I), Foundation University "G. d'Annunzio", Chieti—Pescara, Italy*

Received 2 January 2007; received in revised form 26 February 2007; accepted 2 March 2007

Abstract

CD1 are MCH-like glycoproteins specialized in capturing and presenting glycolipid to T cells. Expression of CD1 molecules has been observed on endoneurial macrophages in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) and vasculitis and polymorphisms of CD1A and CD1E genes have been associated with susceptibility to develop Guillain–Barré syndrome.

In 46 patients with CIDP, in 13 patients with multifocal motor neuropathy and in 132 controls we genotyped exon 2 of CD1A and CD1E genes.

We found no association between chronic dysimmune neuropathies, with or without anti-ganglioside antibodies, and polymorphisms of CD1A and CD1E genes.

© 2007 Elsevier B.V. All rights reserved.

Keywords: Chronic inflammatory demyelinating polyneuropathy; Multifocal motor neuropathy; CD1 genes polymorphisms; Anti-ganglioside antibodies

1. Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare (1.2 to 7.7 per 100,000) autoimmune disorder in which both T cells and antibodies are involved (Hughes et al., 2006a). Although the immunodominant antigen in CIDP remains unknown antibodies to ganglioside GM1 have been reported in up to 23% of patients (Van Schaik et al., 1994). Multifocal motor neuropathy (MMN) is even rarer than CIDP. MMN is thought to be dysimmune because it is associated with anti-GM1 IgM in 30–80% of patients and usually has a good response to high-dose intravenous immunoglobulins (Nobile-Orazio et al., 2005).

Investigating the immunogenetics of CIDP two studies have suggested trends toward increased frequency of the HLA-DR molecules DR3 (Stewart et al., 1978) and DR2 (Feeney et al., 1990), whereas other studies have not shown any significant association (Vaughan et al., 1990; Van Doorn et al., 1991). The

failure to find an unequivocal association with specific HLA antigens has been ascribed to the small number of patients and the heterogeneity of CIDP. There are no studies on the immunogenetics of MMN. However MHC classes I and II process and present peptides to T lymphocytes thus the HLA system might not have a role in chronic dysimmune neuropathies with auto-antibodies against self-gangliosides.

The CD1 antigen-presenting molecules are a conserved family of MCH-like transmembrane glycoproteins recently shown to be specialized in capturing and presenting a variety of microbial and self-glycolipids to antigen-specific T cells (Porcelli and Modlin, 1999). There are five closely linked CD1 genes in humans located in chromosome 1 (q22–23) and named CD1A, B, C, D, and E (Porcelli and Modlin, 1999). In the peripheral nervous system the expression of CD1a and CD1b molecules has been observed on endoneurial macrophages in CIDP and in vasculitis (Khalili-Shirazi et al., 1998; Van Rhijn et al., 2000) and the susceptibility to develop Guillain–Barré syndrome (GBS) has been recently associated with polymorphisms of CD1E and CD1A genes (Caporale et al., 2006).

The above observations prompted us to investigate the possible role of CD1 genes polymorphisms in the susceptibility to develop a chronic dysimmune neuropathy.

* Corresponding author. Clinica Neurologica, Ospedale "SS. Annunziata", via Dei Vestini, 66013, Chieti, Italy. Tel.: +39 0871 358584; fax: +39 0871 562026.

E-mail address: uncini@unich.it (A. Uncini).

¹ These authors equally contributed to this work.

2. Patients and methods

2.1. Patients and controls

Forty-six CIDP patients (30 males; age: 59.0 years; range 8 to 81) and 13 patients with MMN (8 males; age: 52.8 years; range 34 to 83) were enrolled in the study. According to the diagnostic criteria and categories proposed by the joint task force of the European Federation of Neurological Societies and the Peripheral nerve Society (Hughes et al., 2006b) of the 46 patients with CIDP: 35 patients had definite and 11 probable CIDP. Forty-three patients had the classical proximal more than distal weakness pattern whereas three patients had multifocal acquired demyelinating sensory and motor neuropathy (Saperstein et al., 2001). Ten patients had CIDP with concomitant diabetes and none had paraprotein. Of the 13 patients with MMN eight fulfilled the criteria for definite MMN and five for probable MMN according to the consensus criteria of the American Academy of Electrodiagnostic Medicine (Olney et al., 2003).

One hundred thirty-two unrelated randomly selected healthy subjects from the same geographic area constituted the control group for genetic studies.

A written informed consent was obtained from each subject and the study was approved by the local Ethics Committee.

2.2. Determination of anti-ganglioside antibodies

Serum antibodies (IgG and IgM) to gangliosides GM1, GD1a, GD1b, GM2 were tested by ELISA as described (Caporale et al., 2006). The positivity was assigned at a titer $\geq 1:200$.

2.3. Genetic analysis

All five genes (CD1A, B, C, D and E) have been reported to be polymorphic in exon 2 but the nucleotide substitutions of CD1B and CD1C genes are silent (Han et al., 1999) and CD1D was found to be monomorphic in both controls and GBS patients (Caporale et al., 2006). Therefore, in healthy individuals and patients we studied the exon 2 of CD1A and CD1E genes as previously reported (Caporale et al., 2006).

Table 1
Genotype and allele frequency for CD1A and CD1E in CIDP, MMN and controls

	Genotype			% of allele		% of subjects	
	Number of subjects			Frequency		Positive for allele	
	01/01	01/02	02/02	01	02	01	02
CD1A							
CIDP	0	8 (17)	38 (83)	9	91	17	100
MMN	0	0	13 (100)	0	100	0	100
Controls	0	28 (21)	104 (79)	11	89	21	100
CD1E							
CIDP	19 (42)	20 (43)	7 (15)	63	37	85	59
MMN	7 (54)	5 (38)	1 (8)	73	27	92	46
Controls	47 (36)	70 (53)	15 (11)	62	38	89	44

2.4. Statistical analysis

The association between CD1 genotypes and presence/absence of chronic dysimmune neuropathy (CIDP plus MMN), CD1 genotypes and presence/absence of CIDP or MMN, CD1 genotypes and presence/absence of antibodies anti-GM1, and CD1 genotypes and presence/absence of anti-ganglioside antibodies were evaluated using odds ratio and Fisher's exact test. The frequency of each genotype was compared to the overall frequency of the other genotypes in patients and controls. The Bonferroni adjustment was used to control the type I error in multiple tests. The threshold for statistical significance was assigned as previously described (Caporale et al., 2006). The same method was followed to evaluate the association between genotype combinations and presence/absence of CIDP and/or MMN.

3. Results

Nineteen of 46 (41%) of CIDP patients had antibody to at least one ganglioside with titres ranging from 1:200 to 1:1600. Fifteen patients had IgM and/or IgG anti-GM1, seven patients had IgM and/or IgG anti-GD1a, seven patients had IgM and/or IgG anti-GD1b, and ten patients had IgG and/or IgM anti-GM2. Six of 13 patients (46%) with MMN had IgM anti-GM1 (range 1:800–1:6400).

In Table 1 the frequencies of CD1A, and CD1E alleles and genotypes in patients with CIDP, MMN, and in controls are shown. The CD1A gene is biallelic. The allele 02 is more frequent in both controls and patients. The genotype CD1A*01/01 is not represented in controls and patients. The frequency of genotype CD1A*01/02 is not significantly different in controls and CIDP patients. All MMN patients have the genotype CD1A*02/02 but the frequency is not significantly different compared to controls and CIDP patients. The CD1E gene presents two alleles with approximately the same frequency in controls and patients. The frequency of genotypes CD1E* 01/01, CD1E* 01/02, and CD1E* 02/02 was not significantly different in controls and patients. All CD1A and CD1E genotype combinations are not significantly associated with the presence/absence of CIDP and/or MMN. There are no significant differences in the frequency of CD1A and CD1E genotypes in patients with and without anti-GM1 and anti-gangliosides antibodies.

4. Discussion

The CD1 antigen-presenting molecules are specialized in capturing and presenting a variety of microbial and self-glycolipids to antigen-specific T cells (Porcelli and Modlin, 1999). Within the endoneurium the macrophages do not express constitutively the CD1 family of receptors, but have the capacity to do so because CD1 molecules were seen on endoneurial macrophages in biopsies from patients with CIDP and vasculitis (Khalili-Shirazi et al., 1998; Van Rhijn et al., 2000).

Recently we found that subjects with CD1E*01/01 genotype are 2.5 times more likely to develop GBS (Caporale et al., 2006)

and in an abstract Lee et al. (2006) reported that 14 of 22 CIDP patients (63.6%) were homozygous for the CD1E 01 allele in comparison to 27.3% of controls with a statistical significance ($p < 0.05$). The allele CD1E 02 has respect to allele CD1E 01 a nucleotide substitution in codon 79 changing A to G which causes an aminoacid replacement of an uncharged glutamine to a positively charged arginine in the region flanking the ligand binding groove. This conferring of an increased hydrophobicity to the CD1e molecule, may alter the role of CD1e in processing and favouring the presentation of glycolipids by CD1b (Han et al., 1999; Caporale et al., 2006).

In the hypothesis that immunity to glycolipid antigens and CD1 molecules may play a role in the pathogenesis of CIDP and MMN we investigated the polymorphisms of CD1A and CD1E genes in a quite large population of patients but we did not find any association even when subgroups of patients with anti-GM1 or anti-ganglioside antibodies were considered.

Acknowledgements

We are grateful to all the study participants. This study has been supported by a grant from the Italian Ministry of Health (Ricerca Finalizzata 2004).

References

- Caporale, C.M., Papola, F., Fioroni, M.A., Aureli, A., Giovannini, A., Notturmo, F., Adorno, D., Caporale, V., Uncini, A., 2006. Susceptibility to Guillain-Barré syndrome is associated to polymorphisms of CD1 genes. *J. Neuroimmunol.* 177, 112–118.
- Feeney, D.J., Pollard, J.D., McLeod, J.G., Stewart, G.J., Doran, T.J., 1990. HLA antigens in chronic inflammatory demyelinating polyneuropathy. *J. Neurol. Neurosurg. Psychiatry* 53, 170–172.
- Han, M., Hannick, L.I., DiBrino, M., Robinson, M.A., 1999. Polymorphism of human CD1 genes. *Tissue Antigens* 54, 122–127.
- Hughes, R.A.C., Allen, D.A., Makowska, A., Gregson, A., 2006a. Pathogenesis of chronic inflammatory demyelinating polyradiculoneuropathy. *J. Peripher. Nerv. Syst.* 11, 30–46.
- Hughes, R.A.C., Bouche, P., Comblath, D.R., Evers, E., Hadden, R.D.M., Hahn, A., Illa, I., Kosky, C.L., Leger, J.M., Nobile-Orazio, E., Pollard, J., Sommer, C., Van den Bergh, P., van Doorn, P.A., van Schaik, I.N., 2006b. European Federation of Neurological Sciences/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. *Eur. J. Neurol.* 13, 326–332.
- Khalili-Shirazi, A., Gregson, N.A., Londei, M., Summers, L., Hughes, R.A., 1998. The distribution of CD1 molecules in inflammatory neuropathy. *J. Neurol. Sci.* 158, 154–163.
- Lee, G., Brannagan, T.H., Chin, R.L., Sander, H., Latov, D., Latov, N., 2006. CD1E polymorphism is associated with increased incidence of CIDP. *Neurology* 66 (Suppl 2), A45.
- Nobile-Orazio, E., Cappellari, A., Priori, A., 2005. Multifocal motor neuropathy: current concepts and controversies. *Muscle Nerve* 31, 663–680.
- Olney, R.K., Lewis, R.A., Putnam, T.D., Campellone, J.V., 2003. Consensus criteria for the diagnosis of multifocal motor neuropathy. *Muscle Nerve* 27, 117–121.
- Porcelli, S.A., Modlin, R.L., 1999. The CD1 system: antigen-presenting molecules for T-Cell recognition of lipids and glycolipids. *Annu. Rev. Immunol.* 17, 297–329.
- Saperstein, D.A., Katz, J.S., Amato, A.A., Barohn, R.J., 2001. Clinical spectrum of chronic acquired demyelinating polyneuropathies. *Muscle Nerve* 24, 311–324.
- Stewart, G.J., Pollard, J.D., McLeod, J.G., Wolnizer, C.M., 1978. HLA antigens in the Landry-Guillain-Barré syndrome and chronic relapsing polyneuritis. *Ann. Neurol.* 4, 285–289.
- Van Doorn, P.A., Schreuder, G.M., Vermeulen, M., d'Amaro, J., Brand, A., 1991. HLA antigens in patients with chronic inflammatory demyelinating polyneuropathy. *J. Neuroimmunol.* 32, 133–139.
- Van Rhijn, I., Van den Berg, L.H., Bosboom, W.M., Otten, H.G., Logtenberg, T., 2000. Expression of accessory molecules for T-cell activation in peripheral nerve of patients with CIDP and vasculitic neuropathy. *Brain* 123, 2020–2029.
- Van Schaik, I.N., Vermeulen, M., Van Doorn, P.A., Brand, A., 1994. Anti-GM1 antibodies in patients with Chronic inflammatory demyelinating polyneuropathy (CIDP) treated with intravenous immunoglobulin (IVIg). *J. Neuroimmunol.* 54, 109–115.
- Vaughan, R.W., Adam, A.M., Gray, L.A., Hughes, R.A., Sanders, E.A., van Dam, M., Welsh, K.I., 1990. Major histocompatibility complex class I and class II polymorphism in chronic idiopathic demyelinating polyradiculoneuropathy. *J. Neuroimmunol.* 27, 149–153.