Narcolepsy-Cataplexy Syndrome Associated with DRB1*0806-DQB1*0602 Haplotype in a Caucasian Patient

Rosa Peraita-Adrados¹, David Ezpeleta¹, Antonio Balas¹ and José-Luis Vicario¹

¹Unidad de Sueño, Hospital Universitario Gregorio Marañón, 28007 Madrid, Spain,
²Servicio de Neurología, Hospital Mútua de Terrassa, Barcelona, Spain and
³Histocompatibilidad, Centro de Transfusión de Madrid, 28009 Madrid, Spain

Narcolepsy-Cataplexy (NC) is a neurological disorder associated with the human leukocyte antigen HLA DR2. This is a prerequisite for the disease in 95 to 98% of Caucasian patients. It has been demonstrated that the HLA DQB1*0602 allele is a better marker for narcolepsy than DRB1*1501 (DR2). We present a DR-negative and DQB1*0602-positive Caucasian Spanish patient with a very unusual genotype. A 20-year-old male was examined with a 12-year history of excessive daytime sleepiness and sudden muscle weakness caused by laughter and disturbed nocturnal sleep. He had never presented hypnagogic hallucinations or sleep paralysis. The family history was negative. Physical and neurological examinations were normal. The Epworth Sleepiness Scale score was 21/24, The Ullanlinna Scale score was 20/40. The polysomnographic recording showed short sleep latency, increased percentage of stage 1 (St 1), increased number of body movements and decreased sleep efficiency index. MSLT data: mean sleep latency of 1 minute and three sleep onset rapid eye movement (REM) periods (SOREMPs). HLA phenotype: A1, A11; Cw5, Cw7; B44, B39; Bw4, Bw6; DR4, DR8; DR53; DQ6, DQ8 and at the gene level: DRB1*0402, DQB1*0302; DRB1*0806, DQB1*0602. The DRB1*0806 and DQB1*0602 genotype is very infrequent in NC and identical to one African-American case in the series by Mignot et al. (1997a), and to a Caucasian case in another series by Mignot et al. (1997b). This indicates the genetic heterogeneity of the NC.

CURRENT CLAIM: Narcolepsy-Cataplexy Syndrome described in an HLA DR2-negative Caucasian patient with DRB1*0806-DQB1*0602 haplotype.

We have been aware of the genetic character of NC since the first and classic observation in 1877 by Westphal whose mother also suffered from this disease. The real research on the genetic aspects of the disease dates from 1975 after the discovery of a model of narcolepsy in dogs. A clear association was demonstrated between NC and HLA (Honda et al., 1983) then between NC and haplotype HLA DR2-DQ1 (Langdon et al., 1984) and finally with the genetic marker HLA DQB1*0602 (Mignot et al., 1994; 1997a).

It has been proven that the allele DQB1*0602 is a more sensitive marker for NC than the DRB1*15 allele group of the DR2 antigen in Caucasian and black Americans (Mignot et al., 1994) and appears to be associated with the presence and severity of cataplexy, although not with the intensity of hypersomnia.

However, to date it has not been demonstrated that NC pathophysiology is similar to that of classic autoimmune diseases, in spite of the fact that these are less associated with HLA than NC. According to Billiard et al. (1994), two non-exclusive hypotheses have been postulated to explain the relationship between NC and its susceptibility haplotype: an autoimmune process restricted to the human brain unproven to date, or a susceptibility provoked by a non-immunologic gene in linkage disequilibrium with the HLA locus.

The etiology of NC is still unknown and it is thought that there are other genetic factors which have nothing to do with the major histocompatibility complex in its pathophysiology as well as environmental factors which determine its phenotypes. The data from the study of family cases strongly support the hypothesis of a multifactorial origin (Guilleminault et al., 1989) with at least two genes involved; one related to HLA and the other independent of the major histocompatibility complex with a strong influence from environmental non-genetic factors (Mignot et al., 1997a).

METHODS

Questionnaires, neurophysiological studies and immunogenetic studies were undertaken. These are described in the Results section.

RESULTS

Case report

A 20-year-old Caucasian Spanish male with a 12-year history of irresistible sleep episodes and subsequent feeling of "weak knees" caused by laughter was studied. He has never had hypnagogic or hypnopompic hallucinations or sleep paralysis. The family history was negative for NC or recurrent daytime naps or lapses into sleep (RENLS). Physical and neurological examinations were normal.
Patient evaluation and results

Questionnaires
1. Epworth Sleepiness Scale score: 21/24.
2. Ullanlinna Narcolepsy Scale score: 20/40.
   2.1 Cataplectic attacks when laughing, becoming glad or angry or in an exciting situation:
       - Knees unlocking: monthly
       - Mouth opening: never
       - Head nodding: never
       - Falling down: never
   2.2 Sleep latency (SL) in the evening: 10-20 minutes
   2.3 Naps during the day: “I want to but cannot sleep”
   2.4 Episodes of daytime naps or lapses into sleep:
       - Reading: several times daily
       - Travelling: several times daily
       - Standing: daily
       - Eating: daily
3. Stanford Cataplexy Questionnaire items 54 to 74:
   The affirmative answers for cataplexy were:
   - 54. When laughing
   - 60. When having to give a quick answer in a game
   - 62. When scolding a child
   - 70. When playing an exciting game
   - 74. Struggling with someone

The typical situation in which our patient experiences cataplectic attacks is when he engages in rough, physical activity (e.g., struggling with someone), and involves unlocking of the knees.

Neurophysiological studies
The routine EEG (by the International 10-20 System) was normal. Polysomnographic recording: EEG (C3, C4, O1, O2) chin EMG, EOG, respiratory effort, airflow at the nose and mouth, and bilateral anterior tibialis EMG with surface electrodes. Oxygen saturation was monitored by pulse oximetry. The recording was scored manually following the Rechtschaffen and Kales criteria.
Sleep parameters:
- Total Recording Time: 435.5 min
- Total Dark Time (TDT): 446 min
- Total Wake Time: 53.5 min
- Wake Time after Sleep Onset: 45 min
- SL: 1.5 min
- Total Sleep Time: 400 min (89.7% of TDT)
- REM Latency: 36.5 min
- Number of shifts stages: 106
- Body movements: 42 (index=10)
- Number of awakenings > 1 min: 14
- St 1: 97 min (24.25%)
- St 2: 96 min (24%)
- St 3: 48.5 (12.12%)
- St 4: 98.5 min (24.62%)
- St REM: 60 min (15%)
- Sleep efficiency index: 89%

A bruxism was recorded in Slow Wave Sleep.

Multiple Sleep Latency Test (MSLT)
- Mean sleep latency: 1 min
- Sleep onset REM periods (SOREMPs): 3

Immunogenetic study
Low resolution typing for HLA class I and class II antigens was carried out by classical two-step serology. High resolution typing was conducted by PCR-SSOP according to the XIIth International Workshop procedures.

Patient's HLA genotype:
- A1 Cw5 B44 W4 DR4 DR53 DQ8
- A11 Cw7 B39 W6 DR8 DQ6
Class II haplotypes at molecular level:
- DRB1*0402-DQB1*0302
- DRB1*0806-DQB1*0602

Patient's father's HLA genotype:
- A1 Cw5 B44 W4 DR4 DR53 DQ8
- A11 Cw4 B35 W6 DR1 DQ5
Class II haplotypes at molecular level:
- DRB1*0402-DQB1*0302
- DRB1*0101-DQB1*0501

Patient's mother's HLA genotype:
- A11 Cw7 B 39 W6 DR8 DQ6
- A11 Cw5 B18 W6 DR17 DR52 DQ2
Class II haplotypes at molecular level:
- DRB1*0806-DQB1*0602
- DRB1*0301-DQB1*0201

DISCUSSION
A small number of Caucasian patients with NC (2-3%) and a large number of African-Americans (40%) are DR2-negative. Molecular studies corroborate this data: only 60% of African Americans are DRB1*1501 or *1503 compared with 96-98% DRB1*1501 of Caucasians (Langdon et al., 1984; Mignot et al., 1994), whereas all are DQB1*0602.
The only authors to find an association between HLA DR2 and NC in 100% of cases are the Japanese. This may be due to the strict controls applied in their protocols. This association decreases if cataplexy is not considered as a mandatory diagnostic criterion but there are also patients with cataplexy who are HLA DR2, DQB1*0602-negative. This means that there may be another susceptibility gene or genes which are different from the alleles known to date.
The frequency of DR2 and DQB1*0602-negative cases increases if one considers, as a reference group, the narcoleptics’ families (Guilleminault et al., 1989). Some families even have positive and negative in the same pedigree and this data supports the possibility that other genes are involved.
According to Mignot et al. (1997a), the fact that NC associated with HLA DQB1*0602 and NC DQB1*0602-negative could be explained by a dual model given that these diseases are phenotypically similar and genotypically different. The clues offered by animal models are very interesting and most attention has been placed on some genes of the immunoglobulins and genes of the dopamine and nicotinic colinergic receptors.
In our case there are two peculiarities. The first one is the absence of the HLA-DR2 marker, an infrequent situation (2-3%) in Caucasian NC patients. In our series (Ezpeleta et al., 1998) of 33 patients, 31 of whom were DR2-positive and two DR2-negative, only one case carried the DRB1*0806 haplotype. The second peculiarity is that the DQB1*0602-DRB1*0806 is an extremely rare genotype, identical to one
African-American case in a series by Mignot et al. (1997a), and to a Caucasian case in another series by Mignot et al. (1997b).

The allelic association DQB1*0602-DRB1*0806 in a Caucasian patient could be explained by the ancestral admixture of the Spanish and North-African populations, since this haplotype has been well recognized in Algerians (Benmamar et al., 1993) as well as in African-Americans. On the other hand, our patient had slight cataplexy in contrast with the strong cataplexy normally associated with DQB1*0602 in African-Americans. Therefore, our case further reflects the clinical and genetic diversity of NC.

ACKNOWLEDGMENTS

We acknowledge the contribution of Thomas O’Boyle in the preparation of this manuscript.

REFERENCES


