Chapter 5

HLA in Narcolepsy in France

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The genetic aspect of narcolepsy in man has long been considered, with the first report of a positive family history of narcolepsy made by Westphal (1877) even before the term “narcolepsy” was coined by Gelineau (1880). Since then a number of series have been published showing variable rates of probands with a positive family history of narcolepsy and suggesting either an autosomal dominant mode of inheritance with incomplete penetrance (Krabbe and Magnussen 1942; Daly and Yoss 1959; Baraitser and Parkes 1978) or a two-threshold multifactorial system (Nevsimalova-Bruhova and Roth 1972; Kessler 1976; Honda et al. 1983a).

The first report of a significant increased frequency of HLA-B35 and Cw3 and of a significant decreased frequency of HLA-Bw52 and B7 in 56 Japanese narcoleptic subjects was published by Honda et al. (1983b). These results prompted us to investigate HLA antigens in French narcoleptic subjects. We found a significantly increased frequency of B7 and a nonsignificantly increased frequency of A3, an antigen in linkage disequilibrium with B7, in 38 subjects (Seignalet and Billiard 1984). The discrepancy between Honda’s results and ours was not surprising since several associations between HLA and diseases have been found to be different in Mongoloids and Caucasoids. For instance, myasthenia gravis is associated with B12 in Mongoloids and with B8 in Caucasoids, Grave’s disease with B35 in Mongoloids and with B8 in Caucasoids. Later, two reports simultaneously appeared, one in London (Langdon et al. 1984) confirming the increased frequency of B7 in 42 Caucasian English narcoleptic subjects, and revealing a 100% association with HLA-DR2 and DQw1 in 37 Caucasian English narcoleptic subjects. The other study in Tokyo (Juji et al. 1984) confirmed the increased frequency of B35 and the decreased frequency of HLA Bw52, and showed a 100% association with HLA-DR2 and DQw1 in 40 Japanese narcoleptic subjects. Subsequently the 100% association with HLA-DR2 and DQw1 was reaffirmed by the French group (Billiard and Seignalet 1985) and a Canadian group (Poirier et al. 1986). However, there were some reports indicating that a fringe group of typical narcoleptic subjects with cataplexy and sleep onset REM (SOREM) episodes could be HLA-DR2 and DQw1 negative (Andreas-Zietz et al. 1986; Guilleminault 1986; Langdon et al. 1986; Neely et al. 1986; Confavreux et al. 1987).
Subject Population

We performed HLA-DR and DQ typing in a total of 35 unrelated French Caucasian narcoleptic subjects and 110 healthy French control subjects from the southern part of France. All patients had symptoms of fully developed narcolepsy, including excessive daytime somnolence, overwhelming sleep episodes, and attacks of cataplexy, with or without hypnagogic hallucinations and sleep paralysis, and two or more daytime SOREM episodes during 34 h continuous polysomnography beginning at 10:00 p.m. and ending at 8:00 a.m. The age of onset of the first symptom(s) varied from 5 to 45 years, median 16.5 years. Circumstances at onset were clearly identified in 24 of the 35 subjects (68.5%), severe psychological stress in 11, abrupt modification of the sleep-wake schedule in 8, significant medical disease in 3, head traumatism in 1, and pregnancy in 1. Family history was remarkable in five subjects (7%) having one or more relative(s) with excessive daytime somnolence and with either narcolepsy or narcolepsy and excessive daytime somnolence in six subjects (5.8%). We also performed HLA-DR and DQ typing in three further subjects, two of French origin and one of Jewish descent, who had incomplete narcolepsy characterized by excessive daytime somnolence, overwhelming sleep episodes, and two or more SOREM episodes during the 34-h polysomnography, but no history of cataplexy. Ages of onset were 17, 22, and 23 years. A circumstance at onset, namely a modification of the sleep-wake schedule, was found in one subject only.

Methods

Thirty-five HLA, A, B, C antigens were characterized by a standard one-stage lymphocytotoxicity technique, and 12 HLA-DR and DQ antigens also by a standard one-stage lymphocytotoxicity technique, after previous extraction of lymphocytes by differential centrifugation on Ficoll-mitrizoate and separation of B- and T-lymphocytes by the column method (Seignalet 1980).

In addition, HLA-Dw specificities restricted to DR2 subtypes Dw2, Dw12, and FJO were typed with the appropriate homozygous typing cells (Betuel et al. 1983) in 6 of our narcoleptic subjects and 16 from the Department of Neurology, Neurologic Hospital, Lyon.

In the same subjects DNA restriction fragment length polymorphism was analyzed (Marcadet et al. 1985). Genomic DNAs were extracted from the peripheral blood leukocytes (Cohen et al. 1983) and digested with the restriction endonucleases EcoRI and EcoRV. Restriction fragments were separated in agarose gel by electrophoresis, transferred from agarose gel to nitrocellular membranes (Southern 1975), and hybridized with a 32P-labeled HLA-DQ beta cDNA probe (Larhammar et al. 1982).

Finally the transmission of HLA haplotypes was studied in two families with a narcolepsy proband and one or more members with either narcolepsy and excessive daytime somnolence.