Chapter 6

HLA in Narcolepsy in Canada

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HLA Study in a Patient Population

Introduction

Four years ago we postulated, on the basis of our observations of nearly 100 narcoleptics and those of other researchers, the existence of two types of narcolepsy. Primary narcolepsy was thought to be characterized by an early onset (in adolescence or the 3rd decade), a high prevalence of afflicted individuals in the family, and the absence of precipitating factors associated with the onset of the illness. Secondary narcolepsy was characterized by a late onset of narcoleptic symptoms, the absence of other afflicted members in the family, and the presence of possible precipitating factors like head trauma, CNS infectious diseases, affective disorders, or other factors such as shift work likely to disrupt the sleep-wake cycle.

Because of its polymorphism, the HLA system has been extensively used to search for genetic markers in several diseases (Décair 1981). We therefore thought that it might be an appropriate method to differentiate primary from secondary narcolepsy. Honda et al. (1983) first reported an association between narcolepsy and HLA-Bw35 in Japanese patients and Seignalet et al. (1984) later reported a possible association between this disease and HLA-B7 in French Caucasoids. These conflicting results have been attributed to the different ethnic origins of the populations studied. However, only HLA-A, B, and C were typed in these early studies. We accordingly typed narcoleptics for HLA antigens of loci A, B, C, and DR.

In this chapter, we will summarize our recent findings on HLA antigens in narcoleptics, and in families of patients afflicted with this disease.

Methods

Patient Selection

Several fundamental criteria are needed for a study of the association between HLAs and a disease. First, subjects have to be unrelated and from the same ethnic origin. Second, the clinical population should be as homogeneous as possible with regard to the condition studied.

We investigated 48 unrelated Caucasian narcoleptics. Patients were diagnosed by two independent evaluators unaware of the results of HLA typing. In all cases,
the diagnosis was made on the basis of an unequivocal history of excessive daytime sleepiness (EDS), sleep attacks, and cataplexy. All patients were recorded during at least five consecutive naps [multiple sleep latency test (MSLT) (Richardson et al. 1978; Mitler 1982)] and all had sleep onset rapid eye movement period(s) and short sleep latencies during this procedure. The control group consisted of 158 unrelated Caucasoid subjects. All of them had already been typed for their HLA-A, B, and C, and 150 of them for their HLA-DR antigens during a previous genetic study conducted by the Canadian Red Cross.

**HLA Typing**

Antigens of loci A, B, and C were detected by the standard microlymphototoxicity technique (Terasaki and McClelland 1964). DR antigens were detected using the same technique (Terasaki et al. 1978) after B-cell enrichment performed by rosetting of T cells with sheep red blood cells treated with neuraminidase. National reference laboratory plates (Red Cross Toronto, Canada) were used for all typings. HLA typings were made blind with regard to the clinical and polygraphic findings. The Yate's corrected chi-square with one degree of freedom was used to compare frequencies of each antigen in narcoleptics and controls, and the relative risk was calculated for each antigen. In the case of an antigen frequency of 100%, the relative risk was calculated assuming that the next patient would not carry this antigen.

**Results**

Frequencies of each antigen for narcoleptics and controls are listed in Tables 1 and 2, and significant differences between the two groups are indicated. All narcoleptics were HLA-DR2 positive compared with 22% of controls; 12.50% \( (n=6) \) were possibly homozygotic for HLA-DR2. Frequency of HLA-B7 was also significantly increased in narcoleptics, and there was a non-significant increased frequency of HLA-A3. These two antigens, A3 and B7, are known to be in linkage disequilibrium with HLA-DR2 in Caucasoids (Dausset et al. 1985). HLA-Cw2 frequency was also significantly increased in narcoleptics and HLA-DRw6 and DR7 were decreased in these patients.

In addition to these results, one black narcoleptic woman was typed and found to be HLA-DR2 positive. Five other narcoleptic relatives of those included in the statistics were also typed and found to carry HLA-DR2.

**Atypical Cases**

In the course of this study, two atypical cases of narcolepsy were also investigated. One patient, aged 56 years, had a medical history of head trauma and possibly of encephalitis. Clinically, he had the full narcoleptic tetrad and no family history of this condition. No sleep onset rapid eye movement periods (SOREMPs) were observed during the standard MSLT. He was consequently excluded from the study. His HLA typing showed that he was not HLA-DR2. Further polygraphic investi-