Narcolepsy syndrome: a new view at the beginning of the second millennium

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Introduction and history

The term ‘narcolepsy’ was first coined by Gélineau [1] in 1880 to designate a pathological condition characterized by irresistible episodes of sleep of short duration recurring at close intervals. Although Westphal [2] and Fisher [3] had previously published reports of patients with sleepiness and episodic muscle weakness, Gélineau was the first to characterize narcolepsy as a distinct syndrome. He wrote that attacks were sometimes accompanied by falls, or “astasias”. Henneberg [4] later referred to these attacks as ‘cataplexy’. In the 1930s, Daniels [5] emphasized the association of daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations. Referring to these symptoms as ‘the clinical tetrad’, Yoss and Daly [6] and Vogel [7] reported nocturnal sleep-onset rapid eye movement (REM) periods in narcoleptic patients, a finding confirmed in the following years [8–11]. Participants in the First International Symposium on Narcolepsy, held in France in 1975, defined the syndrome as follows:

The word ‘narcolepsy’ refers to a syndrome of unknown origin that is characterized by abnormal sleep tendencies, including excessive daytime sleepiness and often disturbed nocturnal sleep and pathological manifestations of REM sleep. The REM sleep abnormalities include sleep onset REM periods and the dissociated REM sleep inhibitory processes, cataplexy and sleep paralysis. Excessive daytime sleepiness, cataplexy, and less often sleep paralysis and hypnagogic hallucinations are the major symptoms of the disease [12].

Prevalence, genetics, and environmental factors

In the United States and the United Kingdom, the estimated prevalence of narcolepsy is 1 per 2000 (0.05 %) [13, 14]. The prevalence of narcolepsy ranges from 0.16–0.18 % in Japan to 0.002 % in Israel [15]. There is no gender difference, and age of
onset is usually between 13 and 24 years. In approximately 6% of patients, symptoms start before the age of 10 [16]. Although most cases occur sporadically, some occur in familial clusters. The risk for a first-degree relative of a narcoleptic developing narcolepsy is 10–40 times higher that in the general population [15].

After the report by Fuji et al. in 1984 [17] in Japan of a tight association between narcolepsy and HLA DR2, many studies have been performed on patients with excessive daytime sleepiness (EDS) and with or without cataplexy. Typing evolved from serological to high-resolution determination. It was found that ethnicity and related presence or absence of linkage disequilibrium between specific alleles had an impact on the major susceptibility allele for the presence of narcolepsy with cataplexy. In the Japanese and a high percentage of Caucasians DQ B1-0602 is very tightly associated with DR B1-1502 [18, 19], while in African Americans and in Martinicans, with variable mixtures of African and Caucasian origins [20–22], an absence of linkage disequilibrium was demonstrated. This absence of linkage disequilibrium in that group indicated that DQ B1-0602 was the major HLA susceptibility allele for EDS with cataplexy across ethnic groups [22]. Depending on the series, and independent of ethnicity, 88–98% of patients with clear cataplexy are HLA DQ B1-0602. Further studies on Caucasians with cataplexy and EDS have shown that, when considering susceptibility for cataplexy and EDS, both DQ A1-0102 and DQ B1-0602 are present, suggesting complementation [23], and indicating that these two alleles may be important for disease predisposition. HLA DQ B1-0602 homozygotes have a two to four times higher risk of developing cataplexy with EDS than heterozygotes [24]. Investigations of heterozygosity and different alleles of DQ B1 have shown that some are protective, while others favor narcolepsy-cataplexy. For example, DQB1-0601 is predictive for the appearance of narcolepsy-cataplexy [25], while a higher risk of cataplexy with EDS is seen in heterozygotes also expressing DQ B1-0301.

As mentioned, a large percentage of patients with cataplexy and EDS are DQ B1-0602, and the highest predisposing effect on the appearance of cataplexy associates the three locus haplotypes, i.e., a combination of DR 15-0102, DQ A1-0102, DQ B1-0602. However, 8–10% of patients with cataplexy and EDS will be negative for DQ B1-0602 but a high proportion of these patients will carry the susceptibility allele DQ B1-0301. In contrast, patients with EDS, two or more sleep-onset REM periods but no cataplexy will have a maximum of 40% chance of carrying the major susceptibility allele DQ B1-0602. This indicates that narcolepsy-cataplexy is greatly influenced by the presence/absence of specific HLA susceptibility alleles [26].

Genetic transmission is likely polygenic in most cases, and is tightly associated with the human leukocyte antigen (HLA) allele DQB1*0602, often in combination with HLA DRB1*15 (DR2) [15]. Month of birth is a proposed risk factor for development of narcolepsy (peak incidence in March and trough in September), with the suggestion that environmental factors acting in concert with genetic factors during the fetal or perinatal period may trigger autoimmune processes targeting the hypocretin (HCRT) system [27].

The major pathophysiology of human narcolepsy has been recently elucidated based on the discovery of narcolepsy genes in animals. Using forward (i.e., positional cloning in canine narcolepsy) and reverse (i.e., mouse gene knockout) genetics, the genes involved in the pathogenesis of narcolepsy (HCRT/orexin ligand and its recep-