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Invited review

Clinical aspects and pathophysiology of narcolepsy

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Abstract

Narcolepsy is a chronic debilitating sleep disorder first described in the late 19th century. It is characterized by two major symptoms, excessive daytime sleepiness and cataplexy, and two so-called auxiliary symptoms, hypnagogic hallucinations and sleep paralysis. The final diagnosis relies on polysomnography showing the presence of sleep onset rapid eye movement periods (SOREMPs) during the multiple sleep latency test. The presence of HLA DQA1*0102–DQB1*0602 is supportive of the diagnosis. The pathophysiology of the disorder is still unknown but an imbalance between monoamines and acetylcholine is generally accepted. Recent findings in narcoleptic dogs, a natural model of narcolepsy, and in knockout mice revealed that a mutation of type 2 hypocretin receptor plays a major role in the etiology of narcolepsy. Up to now, no mutation has been found in humans except a case of early onset and atypical narcolepsy. However, a marked reduction of hypocretin type 1 has been found in the cerebrospinal fluid (CSF) of a majority of patients and a global loss of hypocretins was noted in post-mortem brain tissue of narcoleptic subjects. Conversely, no hypocretin neuron degeneration has been observed in the genetic form of narcolepsy in dogs but no trace of hypocretin was seen in the brain or the CSF in cases of sporadic canine narcolepsy. This suggests that different hypocretinergic mechanisms are involved in sporadic and genetic forms of canine narcolepsy. Treatment has not evolved significantly over the last few years. However, new drugs, such as hypocretin agonists, are currently being developed.

Significance: After the discovery of the type 2 hypocretin receptor mutation in canine narcolepsy and the finding of a CSF hypocretin-1 deficiency in human narcolepsy, the major stream of research has involved the hypocretinergic system. However, other lines of research deserve to be pursued simultaneously, in view of comprehensive advancements in the understanding of narcolepsy.

Keywords: Narcolepsy; Cataplexy; Sleep onset REM periods; HLA; Hypocretin (Orexin)

1. Introduction

Narcolepsy has been extensively studied despite its low prevalence in the general population. Today narcolepsy continues to retain the attention of scientists more than a hundred years after its initial description by Westphal (1877) and Gelineau (1880). After a number of milestones such as the finding of sleep onset rapid eye movement periods (SOREMPs; Vogel, 1960), the discovery of a natural animal model (Knecht et al., 1973; Mitler et al., 1975), the evidence of an imbalance between monoaminergic and cholinergic mechanisms (refer to Nishino and Mignot, 1997), and the association with HLA DR2 (Juji et al., 1984), a mutation of the type 2 hypocretin receptor has been found in canine narcolepsy (Lin et al., 1999), a phenotype strikingly similar to human narcolepsy in orexin/hypocretin mice (Chemelli et al., 1999), and a hypocretin-1 deficiency in human narcolepsy (Nishino et al., 2000). However, there are still a number of pending issues. From a clinical point of view, the spectrum of narcolepsy is still far from being clearly delimited. Diagnostic procedures used in narcolepsy, the multiple sleep latency test (MSLT) and HLA typing have been once considered as specific tools of diagnosis until it was shown that typical narcolepsy could be observed without SOREMPs or HLA association. Thus, the specificity of the newly developed cerebrospinal fluid (CSF) hypocretin measurement has to be well evaluated. Major progresses have been made in the neuropharmacology and neurochemistry of acetylcholine and monoamines in narcolepsy. Yet the role of serotonin is less clear than that of noradrenaline and dopamine. The involvement of the HLA system in narcolepsy has suggested that narcolepsy

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is an autoimmune disease. Unfortunately, almost all attempts to prove it have been negative. It is generally accepted that in addition to genetic factors, environmental factors are necessary, but the search for such factors is far beyond the efforts put in genetics. The discovery of the role of hypocretin in narcolepsy has immediately raised the question of the functional link between hypocretin and the cholinergic/monoaminergic imbalance. Finally, the finding of low CSF hypocretin levels in humans has opened the door for new treatments.

2. Epidemiology

A number of prevalence studies have been reported, some based on questionnaires only and some based on questionnaires and polysomnography. Solomon (1945) studied United States naval recruits and found two narcoleptics with cataplexy out of 10 000 blacks (20/100 000). Roth (1962), working on his patient material, estimated the frequency of narcolepsy in Czechoslovakia to 20–30/100 000, of which 13–20/100 000 had the 'polysymptomatic' (with cataplexy) form. Dement et al. (1972, 1973) made two surveys, the first one based on responses to a newspaper advertisement in the San Francisco bay area and the second on responses to a television broadcast in the Los Angeles Metropolitan area. They found prevalences of 50 and 67/100 000. The highest prevalency (160/100 000) is reported in Japan, based on a questionnaire and short personal interview with 478 teenagers (Honda, 1979) and the lowest in Israel (0.23/100 000) based on 7 narcoleptics found among 1800 polysomnographically examined excessive daytime sleepiness (EDS) patients (2/3 Jews and 1/3 Arabs approximately) (Lavie and Peled, 1987). Finally, a recent study based on a telephone interview (using the Sleep Eval expert system) of 18 980 randomly selected subjects in 5 European countries, found a prevalence of 47/100 000 (Ohayon et al., 2002).

The second group of studies was founded on questionnaires and sleep studies. In a study conducted on a cohort of 8000 twins from Finland, 0.026% of subjects had daily irresistible sleep episodes and at least one episode of muscular weakness per week (Hublin et al., 1994a). Similar results (0.021%) were found in the South of France (Ondzé et al., 1998). More recently, a prevalence of 34/100 000 was found in Hong Kong (Wing et al., 2002) and 56.3/100 000 on Olmsted County, Minnesota (35.8/100 000 for patients with narcolepsy and cataplexy) (Silber et al., 2002). In the latter study, incidence was considered for the first time and found to be 1.37/100 000 per year (1.72 for men and 1.05 for women). The incidence rate was highest in the second decade, followed in descending order by the third, fourth and first decades.

The age of onset varies, from early childhood to the 1950s, with two peaks, a larger one that occurs at around 15 years of age and a smaller peak at approximately 36 years of age (Dauvilliers et al., 2001a) (Fig. 1). Similar results were found in two different populations but the reasons for this bimodal distribution remain obscure.

Several factors may be associated with the onset of symptoms such as major psychological stress, abrupt modification of bedtime and rising time, trauma, pregnancy, etc. In more than half of the cases, these factors are found in the days or weeks preceding the onset of symptoms (Billiard et al., 1983; Orellana et al., 1994). The delay between the appearance of the first symptom(s) and the diagnosis has been reported to last on average more than 10 years (Alaila, 1992) but this delay shortened in recent years when physicians and the public became more informed on narcolepsy.

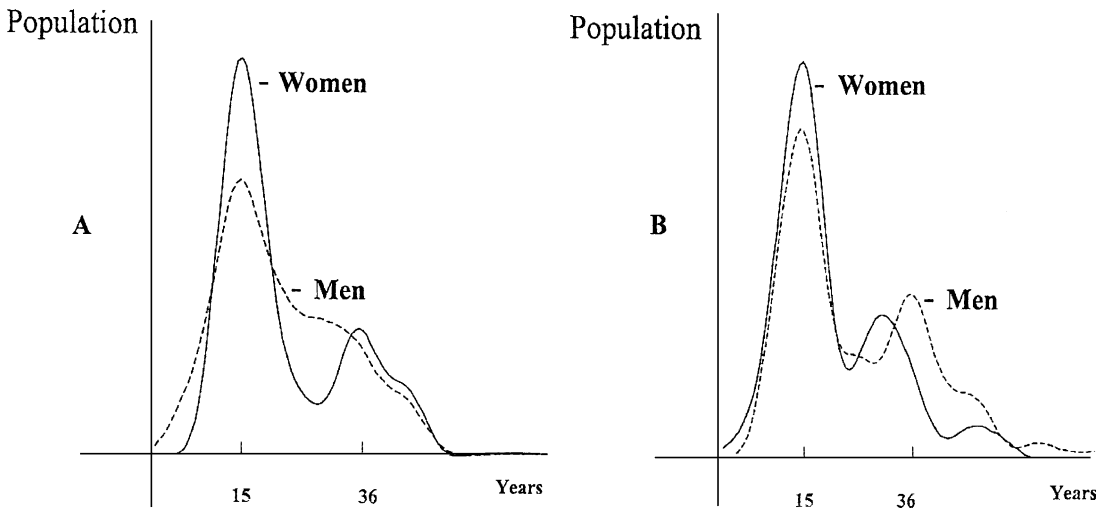

Fig. 1. Density curves of age at onset distribution for male and female in narcoleptic populations from Montpellier, France (A) and Montreal, Canada (B) (reprinted from Neurology, Vol. 57, Dauvilliers et al., Age at onset of narcolepsy in two large populations of patients in France and Quebec. Page 2031, Copyright (2001), with permission from Neurology).