Case Report

Narcolepsy with cataplexy in monozygotic twins

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ABSTRACT

Introduction: This paper describes narcolepsy with cataplexy in two monozygotic twin sisters.

Objective: To clinically illustrate the involvement of neurological, genetic and immunologic systems in narcolepsy.

Material and methods: We performed a retrospective study of these patients that were followed in the sleep medicine ambulatory clinic of the Faculdade de Medicina de Ribeirão Preto.

Results: These sisters are two of the few cases in the literature concordant for narcolepsy with cataplexy and without a “positive HLA” for narcolepsy. They had a typical clinical course of narcolepsy with cataplexy and attended all the neurophysiological diagnostic criteria for narcolepsy.

Conclusion: In addition to known possible genetical similarity, this report stresses the role of environmental or unknown genetical factors acting on a specific neuro-imuno-genetical background and resulting in narcolepsy.

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1. Introduction

Narcolepsy is a chronic disturbance that leaves patients incapacitated in most cases; it is characterized by an abnormal sleep pattern that may include excessive daytime sleepiness, sleep architecture alterations, and rapid eye movement (REM) sleep pathological manifestations, including sleep paralysis, hypnagogic hallucinations, sleep onset REM period (SOREMP) and cataplexy [1]. Symptoms typically begin in adolescence or early adulthood and may also emerge in childhood or old age, or even after a central nervous system structural injury [2]. Epidemiologic studies show prevalence ranging from 0.23/100,000 in Israel to 160/100,000 in Japan [3] with 47/100,000 in Europe [4].

The development of human narcolepsy involves environmental factors acting against a specific genetic background. One of the predisposing genetic factors is located in the MHC (Major Histocompatibility Complex) DQ region. Up to 98% (88–98%) of all narcoleptic patients with definite cataplexy share a specific Human Leukocyte Antigen (HLA) allele, HLA DQB1\textsuperscript{\textregistered}0602 (mostly in combination with HLA DR2), compared with 12–38% of the general population, as evaluated in
various ethnic groups. This homozygous presence for the HLA DQB1*0602 allele constitutes a known genetic risk factor for narcolepsy, but more than 99% of the population that have this homozygous allele do not present narcolepsy [5].

Most narcoleptic patients have low levels of hypocretin in their cerebrospinal fluid [6]. Impaired hypocretin neurotransmission, possibly due to an autoimmune mechanism or by a specific lesion, has been seen as having a fundamental role in the pathological process [7].

Thus, the evidence suggests that narcolepsy in humans may emerge when environmental factors act through an immunologic mechanism in a genetic background of predisposition for the disease. Considering that a familial pattern of narcolepsy is rare, mainly in twins, this paper brings the history of two of the few monozygotic twins concordant for narcolepsy and cataplexy known in the scientific literature [8,9].

2. Case reports

These case reports retrospectively cover two monozygotic twin sisters concordant for narcolepsy. They were first attended at the age of 17 by the sleep disorder clinic at the Ribeirão Preto Medical School hospital (Universidade de São Paulo), having been referred directly from a basic health unit in a rural area of the state of São Paulo, where they grew up together in the same home. Their life history is very similar in terms of type and chronology of their narcolepsy symptoms. The twins were born on June 24, 1985 in a premature cesarean childbirth, with water broke lasting for 5 h. There was no familial history of narcolepsy or hypersomnia.

Twin 1 (T1) had no childbirth complications and her neurological, psychological, and motor development was normal. At the age of 9 yo she started to have migraine and fatigue. At the age of 16, she began to show excessive daytime sleepiness that affected social activities, sleep paralysis episodes, and hypnagogic hallucinations, waking up after the first third of the night and hearing a voice ordering her to get up. At 17, she had the first cataplexy episode described as an episode of “loss of strength”, mainly in the legs, causing falls, and triggered by emotions (generally positive ones). Throughout initial clinical follow-up (before treatment had begun), she frequently complained of excessive daytime sleepiness, exhaustion, constant fatigue that could be relieved after brief naps, learning difficulty, and almost daily cataplexy episodes (Table 1). Considering this clinical picture she performed a polysomnography with subsequent multiple sleep latency test – MSLT (Table 2) [10,11].

Further diagnostic assessments, such as determining HLA haplotype (A2, A26, B49, B57, DR1, DR7, DR53, DQ2 and DQ5), were also performed, but the presence of alleles associated with genetic susceptibility to narcolepsy was not detected (Table 1).

Twin 2 (T2), an identical twin, remained in hospital for 38 days after childbirth complications, but her further neurological, psychological and motor development was normal. She started migrane onset at 9 yo. At 14, she reported symptoms directly related to excess sleepiness interfering in her everyday activities. At that time, her parents noticed sleep talk and agitated sleep. She had her first cataplexy episode at the same age as T1, 17 years old. She continuously complained of excessive sleepiness, and excessive irritability. Unlike T1, T2 did not have sleep paralysis or hypnagogic hallucinations, nor were there complaints related to cognitive performance (Table 1). During initial clinical follow-up (before results of the exams) the patient frequently complained of sleepiness during the day, excessive irritability, tiredness, constant fatigue relieved by short naps (30 min) during daytime, and frequent cataplexy episodes. The polysomnography and MSLT endorsed the clinical diagnostic of narcolepsy with cataplexy (Table 2). The determination of HLA haplotype (A2, A26, B49, B57, DR1, DR7, DR53, DQ2 and DQ5) did not show the presence of alleles associated with genetic susceptibility to narcolepsy (Table 1).

Once diagnosis was made, the therapeutical approach was based on intermittent use of methylphenidate, continuous use of tricyclic for cataplexy and programmed naps. With the treatment, they became less sleepy and the frequency of the cataplexy episodes was reduced. The patients also referred better concentration and much less sleepiness, they had resumed normal everyday activities such as school, working and driving with great improvement in their life quality.

3. Discussion

Narcolepsy usually occurs sporadically, but may also show a familiar pattern. Estimates of familial incidence range from 4.3% of all narcolepsy cases in Japan to 9.9% in Canada, and, the risk of a first-degree relative of a patient having narcolepsy–cataplexy is 1–2% (10–40 times higher than the prevalence for the general population) which suggests a genetic etiology. Eight of the 18 monozygotic twin pairs described in the literature were described as concordant for the narcolepsy diagnosis, and only three pairs were considered “positive HLA” [5,12-14]. In other words, most monozygotic twin pairs are discordant for narcolepsy suggesting that nongenetic, and even possible, environmental factors can also be involved in the pathophysiology of human narcolepsy. In the present cases, the presence of alleles associated with a certain kind of genetic susceptibility (HLA) to narcolepsy was not detected. The present paper endorses the hypothesis of the possible involvement of other genes (besides HLA) such

| Table 1 – Clinical/genetic features. |
|-----------------------------|-----------------------------|
|                     | Sleepness onset | Cataplexy onset | REM sleep parasomnias | NREM sleep parasomnia | Fatigue/migrane onset | HLA (DR2/DQB1*0602) |
| T1 16 yo            | 17 yo           | 16 yo           | No                    | 9 yo                  | No                  |
| T2 14 yo            | 17 yo           | No              | 14 yo                 | 9 yo                  | No                  |
as T-cell receptor alpha (TCRA) locus [15] as well as also possible neuro-imuno-genetical interactions with a restricted harmful process involving the neurons controlling hypocretin neurotransmission [16]. Unfortunately, after 2004, the patients described above, could not be found for further evaluations (such as cerebrospinal fluid hypocretin-1 testing).

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REFERENCES