Childhood onset of narcolepsy-cataplexy syndrome in Turkey: clinical and genetic study

Zerrin Pelin, Melda Bozluolcay, Derya Kaynak, Hakan Kaynak

Department of Neurology, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

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Narcolepsy is a disabling sleep disorder characterized by excessive daytime sleepiness and abnormal manifestations of rapid eye movement (REM) sleep including cataplexy, sleep paralysis and hypnagogic hallucinations. It is known to be complex disorder in which both genetic predisposition and environmental factors play a role. In humans, susceptibility to narcolepsy is tightly associated with a specific HLA allele, DQB1*0602. In this report, we took advantage of the ongoing genetic study in Turkish narcoleptic patients to document clinical and genetic data of eight patients whose onset of symptoms were in the childhood period.

*Key words: narcolepsy-cataplexy syndrome, HLA DQB1*0602, excessive daytime sleepiness.*

Narcolepsy-cataplexy syndrome is among the leading causes of excessive daytime sleepiness (EDS) and is the most common neurologic cause. Despite a prevalence similar to that of multiple sclerosis, a socio-economic impact that may be as high as that of epilepsy, and the availability of effective treatments, knowledge about narcolepsy often remains limited even among neurologists[1].

Excessive daytime sleepiness, cataplexy, sleep paralysis, hypnagogic hallucinations and disturbed nocturnal sleep are the five cardinal symptoms of the narcolepsy-cataplexy syndrome. These symptoms vary greatly in severity and occurrence in narcoleptic patients. Daytime sleepiness is usually the most disabling symptom of the narcolepsy syndrome. Patients with narcolepsy report a continuous sleepiness that fluctuates and episodically becomes irresistible, with involuntary sleep attacks occurring in such unusual circumstances as talking, eating, standing and even walking. Sleepiness alone has a poor diagnostic value, because it is difficult to differentiate from that observed in other sleep disorders, as in obstructive sleep apneas, especially in adults. However, cataplexy, the second most disabling symptom, is almost pathognomonic for the syndrome. Cataplexy is defined as brief episodes of muscle weakness provoked by strong emotions. Typically laughter, happiness or anger produces brief attacks of knee buckling, head dropping, and/or jaw sagging that may escalate in total paralysis with collapse to the floor. The severity of cataplexy is variable and may range from unnoticeable loss of muscle tone in the legs to a complete episode of muscle paralysis. In most patients, cataplexy lasts for one minute or less (usually for just a few seconds) and consciousness is maintained during the episode. Isolated cataplexy without associated sleepiness is an exceptional occurrence that is most often observed in young narcoleptic subjects still developing the full-blown disorder. Sleep paralysis and hypnagogic hallucinations are not specific for narcolepsy and their diagnostic values are very poor. Sleep paralysis (SP) is seen in 60-80% of narcolepsy patients and is characterized by an inability to move at sleep onset or upon awakening. Hypnagogic hallucinations are reported in 40-60% of patients with narcolepsy and are the expression of the changing state of consciousness in which, as opposed to dreaming, elements of the normal awake mentation are still present. Such hallucinations may be simple (e.g., unformed sensations, geometric figures) or complex (e.g., faces, animals) and may involve one or more senses[1].

The diagnosis of narcolepsy is facilitated by the availability of an established diagnostic test, the multiple sleep latency test (MSLT)[2]. In this test, patients first undergo nocturnal polysomnography to eliminate other causes of daytime sleepiness such as obstructive sleep apnea. The following day, sleep is also recorded during five successive 20 minute naps separated by two-hour intervals. Latency to falling asleep and possible occurrence of rapid eye movement (REM) sleep episodes are then noted for each nap. Normally, MSLT sleep latency is more than 10 minutes and at most one REM sleep period (sleep onset REM period or SOREMP) is observed after an efficient night-time sleep. In contrast, narcoleptic patients have poor night-time sleep efficiency (% asleep/total bed time), a very short mean sleep latency (≤8 min) and multiple SOREMPs (≥2 in 5 naps).

Human narcolepsy-cataplexy is associated with centrally mediated hypocretin deficiency that has a tight association with HLA DQB1*0602[3]. Narcoleptic patients with well defined cataplexy appear to represent an etiologically pure nosological entity with a very high (85-100%) degree of association with HLA DQA1*0102 and DQB1*0602, mostly in the context of the DRB1*15, DQA1*0102, DQB1*0602 haplotype[4,5]. Also, significantly higher relative risk was reported for heterozygote combinations including DQB1*0301, DQA1*06, DRB1*04, DRB1*08, DRB1*11 and DRB1*12[3]. Three alleles, DQB1*0501 and DQA1*01 (non-DQA1*0102), were revealed to be protective[3].

Although considerable attention has been directed toward understanding narcolepsy in adults, few investigators have focused on childhood narcolepsy. Limited reports have emphasized that narcolepsy symptoms may begin in childhood. Retrospective studies suggest that about half of the adults with narcolepsy report experiencing symptoms during childhood or early adolescence[6]. Childhood narcolepsy is emerging as a significant clinical entity for several reasons. This disorder if frequently underrecognized and undiagnosed, leading to years of untreated symptoms during the important childhood years.

In this report, we took advantage of the ongoing genetic study of narcolepsy-cataplexy syndrome in Turkey to describe the onset of symptoms, and diagnostic and genetic data of narcoleptic patients whose narcoleptic symptoms manifested before puberty.

Material and Methods

All subjects reported here were seen prospectively at İstanbul University, Cerrahpaşa Medical School, Neurology Department, Sleep Disorders Unit between 1996 and 1999. The data of eight narcoleptic patients (5 female, 3 male) who were selected from 25 narcoleptic patients, with the inclusion criteria of onset of symptoms before the age of 16, were documented.

At the initial visit, the clinical evaluation included a complete history, general physical examination, complete neurological examination, administration of a sleep questionnaire and a narcolepsy inventory. The sleep questionnaire used was the Epworth Sleepiness Scale[7]. These were completed by a physician and the patients were to answer the questions with their close relatives when needed. The Epworth Sleepiness Scale is a questionnaire that asks patients to rate their sleepiness in each of eight different situations on a scale from 0 (never) to 3 (high chance)[7]. The total score in the Epworth scale can range from 0 to 24. The range from 0 to 7 was accepted as normal and above the score of 7 as an indicator of pathologic degree of sleepiness[7]. The narcolepsy inventory (Stanford Center for Narcolepsy Sleep Inventory) is a validated, 146-item questionnaire requesting details and specific examples for all narcolepsy symptoms experienced, with special emphasis on cataplexy[5].

All patients were studied with the same nocturnal polygraphic parameters. These recordings included electroencephalography (EEG) (C3/A2, C4/A1 of the international 10-20 electrode replacement system); chin electromyography (EMG); right and left electro-oculogram (EOG); nasal-oral airflow and oxygen saturation. The polysomnograms were scored using the standard international recommendations of Rechtschaffen and Kales[8]. These recordings were always performed after the patients were free of medication for at least 10 days.

MSLT was obtained following a nocturnal polysomnography. The MSLT recording included EEG as above, chin EMG, and right and left EOGs. For each MSLT, we recorded the mean sleep latency and the number of SOREMPs. Sleep latency was defined as the time in minutes from lights out to the first epoch (30 sec) of sleep. Sleep-onset REM sleep was scored when REM sleep occurred within 15 minutes of the first epoch of sleep.

HLA typing of all patients was performed with the great support of Emmanuel Mignot at Stanford University, Center for Narcolepsy. Inclusion criteria for HLMA typing: a) recurrent daytime naps or lapses into sleep occurring almost daily for three months, b) sudden bilateral loss of postural muscle tone in association with intense emotion (cataplexy) and c) less than 8 minutes sleep latency on a 5 nap MSLT. These patients also had to have ≥2 SOREMPs during MSLT and polysomnography combined. Blood drawings were performed from the patients and when possible their parents and controls. All subjects gave informed consent for blood drawings for HLA typing. Blood samples were sent to Stanford University at the same day of blood drawing, together with the data of polysomnography, MSLT and narcolepsy inventory.

Serological HLA typing was performed at the Stanford University Blood Center (Palo Alto, CA, U.S.A.) HLA DQB1 and DRB1 subtypes were determined using group-specific polymerase chain reaction (PCR) amplification and Sequence Specific Oligonucleotide (SSO) hybridisation as previously described by Mignot et al.[4].

The results were given as mean ± standard deviation.

Results

Narcolepsy-cataplexy syndrome was diagnosed in these eight patients (5 female, 3 male) based on the complaint of daytime sleepiness, the presence of cataplexy and their MSLT results. Their mean age on admission was 21±6.2 years. The age range was 12 to 28 years. The age of symptom onset was 12.9±3.3 years (range: 6 to 16).

Excessive daytime sleepiness was the first symptom in four patients. School-related complaints like inability to follow the lesson due to lack of attention and learning disabilities were more pronounced by these patients after the onset of symptoms.

Cataplectic attacks were the initial complaint in four patients. The emotional conditions that triggered cataplectic attacks are shown in Table I.

Table I. Emotional Conditions Triggering Cataplectic Attacks

Emotional Conditions	Patients* (n=8)
Laughter	8
Anger	5
Excitement	8
Surprise	8
Embarrassment	4
Stress	4
Being startled	4
Tension	2
Telling or hearing a joke	6

* The number of patients who had the emotion triggering cataplexy.

Three patients described hypnagogic hallucinations and only one patient had had both sleep paralysis and hypnagogic hallucinations during the childhood period. These symptoms appeared after the onset of the main symptoms, either excessive daytime sleepiness or cataplexy.

Epworth sleepiness score of patients was 21.5±1.9 (range: 18 to 23). The mean sleep latency of MSLTs was found to be 0.96±0.85 minutes (range: 0.5 to 3 minutes). Three patients had sleep onset REM period in each 5 nap MSLT. Three other patients had 4 SOREMPs in 5 naps. The remaining two patients had 3 and 2 SOREMPs, respectively.

The HLA analysis demonstrated that all patients were heterozygous for HLA DRB1*1501, DQB1*0602 except one. All HLA results of patients, their parents (if present) and their controls are given in Table II.

Discussion

This report is the first preliminary genetic and clinical data of narcolepsy-cataplexy syndrome in Turkey. The aim of this study was to focus

Table II. HLA DRB1 and DQB1 Subtypes in Narcoleptic Patients, Parents and Their Controls

Patient Number	Patient DRB1-DQB1	Father DRB1-DQB1	Mother DRB1-DQB1	Control DRB1-DQB1
1	0402/1501-0302/0602	0402/1104-0301/0302	1201/1501-0301/0602	0701/1601-0201/0502
2	1401/1501-0503/0602	0402/1501-0302/0602	1104/1401-0301/0503	0101/0101-0501/0301
3	0701/- -0201/-			0402/0701-0302/0303
4	1201/1501-0301/0602	1501/1502-0601/0602	0401/1201-0301/-	1101/1502-0301/0601
5	1301/1501-0602/0604	1501/1103-0301/0602	1301/1302-0603/0604	0701/0901-0203/0302
6	1101/1501-0301/0602			0101/0701-0501/0201
7	1104/1501-0301/0602			0403/1103-0305/0301
8	1104/1501-0301/0602			0101/1202-0501/0301

on the presenting features that are unique to childhood narcolepsy and provide especially the genetic information about Turkish narcoleptics. Studies of childhood narcolepsy in the medical literature are sparse. In 1960, Yoss and Daly[1] reported that 59% of 85 consecutive adults with narcolepsy experienced symptom onset by the age of 15. They reported 16 subjects with symptom onset before 15 years of age, including three children with onset by the age of three. In a retrospective review, Nevelet et al.[6] reported that excessive sleepiness presented before 15 years of age in 49% of adults with narcolepsy. In our patient population, 32% of narcoleptic patients had the first experience of narcoleptic symptoms before the age of 16, and the earliest onset of symptoms was found to be at the age of six. This lower percentage may be due to underrecognition of symptoms by both patients and their families before puberty.

In 1998, Gulleminault et al.[9] reported that cataplexy was an obvious symptom and clearly preceded observance of daytime sleepiness in several of his cases. They defined laughter as always being reported as a trigger af cataplexy. Of our cases, 50% had cataplexy as an initial symptom. Moreover, laughter, excitement and surprising conditions were common reports of our patients as causes of cataplectic attacks. Although these results are similar to the literature, study of a larger number of patients is still necessary in order to comment on Turkish narcoleptics. The early presence of cataplexy and frequency of complete association of HLA DR15 and DQB1*0602 must be emphasized in children with early onset of the disease[4,5]. The Turkish results confirm the positive association of the HLA DRB1*1501 and DQB1*0602. In Turkey a similar association was found in patients with multiple sclerosis in that myelin degeneration led to this disease, while in narcolepsy-cataplexy syndrome[11], degeneration in hypocretin neurons was present.

In 1988, Young et al.[12] analyzed clinical and polysomnographic data in patients with narcolepsy, comparing eight children at the age of 15 or younger with a comparable adult group. The pediatric group showed greater daytime sleepiness and a higher frequency of SOREMPs than the adult group, as measured by MSLT. The results of MSLT and Epworth score revealed greater daytime sleepiness in our patient population.

Even though the overwhelming majority of the adult cases of narcolepsy and cataplexy are idiopathic, narcolepsy has occasionally been shown to be associated with brain tumors and various other brain lesions, mostly around the third ventricle[13] and in the pons[14]. The situation is more complex in children, especially those younger than six to eight years of age. In an analysis of 97 reported cases of childhood narcolepsy by Challamel et al.[15], a significant proportion of very young children with narcolepsy and cataplexy had other associated disorders. Niemann-Pick disease type C and D and diencephalic tumors were diagnosed in this group. Therefore, narcolepsy-cataplexy syndrome carries greater importance when symptoms begin during childhood.

In conclusion, narcolepsy-cataplexy syndrome is only recently beginning to be recognized in Turkey. The increasing number of Turkish patients will provide new insights into our patient population and help to generate various medical and psychological treatment approaches in narcoleptic children as well as in adults.

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