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Case Report

Narcolepsy in pediatric age – Experience of a tertiary pediatric hospital

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ABSTRACT

Narcolepsy, a chronic disorder of the sleep–wake cycle of multifactorial etiology, is characterized by excessive daytime sleepiness, often associated with cataplexy, hypnagogic/hypnopompic hallucinations and sleep paralysis. Both early clinical suspicion and therapeutic approach are essential for promotion of cognitive development and social integration of these children. The authors present a descriptive retrospective study of a series of eight children in whom symptoms first started between 6.8 and 10.5 years of age. Diagnostic delay ranged from 4 months to 2 years. One child had H1N1 flu vaccination eight months before the clinical onset. The first multiple sleep latency test was positive in 6 of 8 cases. All cases were treated with methylphenidate, and venlafaxine was associated in 4 of them. In one case the initial therapy was exclusively behavioral. In all cases, symptomatic improvement, better school performance and social integration were achieved after therapeutic adjustment.

1. Introduction

Narcolepsy is a chronic disorder of the central nervous system (CNS) in which there is a disturbance of the regulation of the sleep–wake cycle, with intrusion of REM sleep during periods of the wake state, whose paradigmatic manifestation is cataplexy. Narcolepsy with cataplexy (NC) has a prevalence of 0.02–0.05% in various Caucasian groups [1–4] and a higher value among the Japanese population (0.16%) [2,3]. The prevalence of narcolepsy without cataplexy is unknown [3].

With a peak onset during the second decade of life [2], the initial symptoms are revealed by an excessive daytime sleepiness (EDS) that is later and often associated with cataplexy, hypnagogic/hypnopompic hallucinations and sleep paralysis. Nocturnal sleep disturbance is often also associated, being sometimes interpreted as insomnia [2].

Initially considered a family disease, recent studies have pointed out to a sporadic disease, although with a strong genetic susceptibility [3] marked by the presence of the allele HLA DQB1*06:02. The autoimmune destruction of hypothalamic

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hypocretin-producing cells in individuals with genetic susceptibility has been signaled as the most likely etiological hypothesis [3,5]. Hypocretin plays a key role in regulating the sleep–wake cycle since its decrease leads to a loss of the boundaries between awake, asleep or dreaming states [2]. It is believed that environmental factors such as bacterial (namely streptococcus [3]) or viral infections and some vaccines, might have a triggering role in this process [6–8]. After the flu pandemic caused by the H1N1 influenza virus, namely between September 2009 and August 2010, an increased incidence of this disease was observed especially among the northern European and American countries [9,10]. The disease was much more common after the administration of the vaccine containing the adjuvant ASO3 [11] (onset from 2 weeks to several months) compared to the incidence after the infection by the virus H1N1 itself [3].

The different sleep duration in children, their reactions and difficulty in verbalizing their symptoms make it even more difficult to recognize and value the clinical data at these ages. Excessive sleepiness might be interpreted as a physiological need of napping in a small child, and in turn as a manifestation of laziness in older children. In addition to the excessive sleepiness, memory lapses, concentration problems and automatic behaviors, especially during monotonous activities, are also associated and can result in learning disabilities at school age [1,2,5,12,13]. Repeated difficulty in achieving expected or desired levels of performance might lead to irritability, hyperactivity, aggressiveness or even depression [2].

The hypnagogic or hypnopompic hallucinations sometimes associated with sleep paralysis, might be scary to the child, leading to resistance in going to sleep or be interpreted as nightmares or night terrors. Cataplexy is a sudden and reversible reduction in muscle tone, commonly triggered by a stimulus such as laughter, surprise or fright. It may lead to falls, which in small children may not be taken into consideration and/or be misinterpreted as a simple clumsy gait, or lead to differential diagnosis with atonic convulsive crisis [2,14] or cardiovascular syncope. In children, cataplexy might be limited to facial muscles, giving rise to an apathetic face, open mouth and protruding tongue, with a slow and slurred speech.

Other symptoms that may be associated are obesity and early puberty [13,15]. The weight increase might be related to nocturnal sleep disturbance and consequent change of the feeding pattern [16,17], or with the fact that hypocretin deficiency may have a direct effect on metabolism and lower the basal metabolic needs [5].

The lack of symptom specificity and the other mentioned difficulties make diagnosis of narcolepsy in children a real challenge. Sometimes other diagnosis such as attention deficit hyperactivity disorder, epilepsy, behavioral insomnia, depression or other psychiatric disturbance may be evoked. Therefore, diagnosis may suffer significant delays and it is often only achieved in adolescence or early adulthood. Delays of 10–15 years between clinical presentation and diagnostic confirmation have been described [1,6].

In the pediatric population and in cases of sudden onset or less characteristic evolution, it is important to exclude secondary causes of narcolepsy. These may amount up to 25%, with genetic syndromes and hereditary metabolic diseases being the most predominant causes [10]. In these cases, the symptoms appear at an early age and associated with the underlying pathology [1,6,18]. Cataplexy is highly selective and almost pathognomonic of narcolepsy, but it also constitutes one of the symptoms to be considered in some genetic diseases, such as Niemann-Pick type 3, Norrie and Prader-Willi syndromes, myotonic dystrophy type 1, or in CNS trauma and tumors [2,10]. In narcolepsy, cataplexy often appears months or years after EDS; if it appears isolated or at an early age, the hypothesis of hypothalamic lesion must be considered [2].

The diagnosis is based on the results of polygraphic sleep study (PSG) and on the multiple sleep latency test (MSLT). However, in children, caution should be taken in MSLT interpretation due to the difficulty in establishing the lower age limit for application of the diagnostic criteria. Previously, the lower age limit has been established at 8 years age [6,11], but recent studies point to the possibility of its application since 5 years of age in cases with a strong suspicion of narcolepsy [19]. The MSLT is considered positive if the average sleep latency is less than 8 min and if there is presence of at least 2 sleep onset rapid eye movement periods (SOREMPs) [19]. PSG must be made the night before the MSLT in order to exclude the existence of another pathology, such as an obstructive sleep apnea syndrome, which might justify the EDS.

HLA DQB1*06:02 is the marker with highest specificity for narcolepsy in all ethnic groups [3], and this relation is particularly strong in the cases where cataplexy is present [3]. This allele is present in 90% of the narcolepsy cases, but it is also present in 12–38% of people without the disease [3,11].

The dosage of hypocretin-1 in the cerebrospinal fluid (CSF) can be useful in complex cases or where there is difficulty in interpreting the results of exams [14]. Its use is not widespread, since it is hardly available and also because it needs an invasive technique.

The therapeutic approach includes both behavioral and pharmacological therapy in order to control the symptoms. Some drugs used in adulthood are not yet approved for children (e.g. modafinil) or are poorly studied in children (e.g. sodium oxybate and immunosuppressant treatment) [2]. The therapeutic monitoring is usually based on clinic symptoms; however, some centers use the Maintenance of Wakefulness Test [20].

2. Material and methods

A retrospective and descriptive analysis of the files of children and teenagers with narcolepsy, diagnosed and followed between 1994 and 2013 at a tertiary pediatric hospital, was performed. Clinical data and all complementary exams were collected. All the children underwent PSG and MSLT. For sleep stages and respiratory classification, we used the Rechtschaffen and Kales rules until 2007, and then after, the *American Academy of Sleep Medicine*'s classification was used. In the PSG, the leg movement index referred to the number of leg movements, regardless of their characteristics, per hour of sleep. MSLT was considered compatible with narcolepsy when the average sleep latency was less than 8 min and when at least 2 SOREMPs were present during the nap time. Hypocretin level below 110 pg/ml was considered a low value [21].

3. Results

The sample consisted of 8 Caucasian children (5 boys). The first symptoms occurred between the ages of 6 and 10 years (median – 8 years). The diagnostic delay (period of time between the onset of symptoms and the diagnostic confirmation by complementary exams) ranged from 4 to 24 months (median – 14 months) (Table 1).

On clinical presentation, all of them had EDS, characterized by the reappearance of naps and frequent episodes of sleepiness in both monotonous situations (car traveling, watching television) and during active tasks (talking, eating). In one case, there were also, since the beginning, suggestive symptoms of cataplexy (jaw fall and hypotony of the limbs triggered by laughter) and hypnagogic and hypnopompic hallucinations. During the clinical evolution, symptoms of partial (loss of the cervical tonus or jaw fall with protrusion of the tongue) or complete cataplexy (hypotony of the limbs and fall) appeared in 4 more cases, as well as hypnagogic hallucinations in 2 cases and sleep paralysis in a single case. There was impact on school performance in 5 cases and psychosocial difficulties in 3 of them. At the first consultation, all children showed body mass index (BMI) $\geq$75th percentile, 5 were overweight (85th percentile$<$BMI$<$95th percentile) and 1 had obesity (BMI $\geq$95th percentile). During the evolution, there was a trend for BMI increasing in 4 cases.

In one case, the anti-influenza H1N1 vaccine (adjuvant SO3) had been administered 8 months before the onset of the symptoms. In 2 of the 8 cases, there was a family record of severe EDS in 1st and 2nd degree relatives with no clear diagnosis.

All children performed PSG with MSLT shortly after diagnostic suspicion (between 7 and 11 years old) – Table 2. In PSG, sleep efficiency below 80% was recorded in 5 patients and the microarousal index ranged between 2.6 and 6.7. Regarding the respiratory parameters, one of the 8 patients snored, the apnea–hypopnea index was always less than 1 and there was no desaturation. The MSLT showed average sleep latencies between 0.1 and 8.5 min, average REM sleep latencies between 1.37 and 4.83 min and 2–4 SOREMPs. The first MSLT was compatible with the diagnosis of narcolepsy in 6 of the 8 cases, while a second test was necessary in the other 2. During the initial MSLTs, these 2 children only slept one nap; one did not have REM sleep and the other had only one SOREMP.

The allele HLA DQB1*06:02 was present in all cases and it was associated with the concomitant presence of allele HLA DRB1*15 in 7 cases. In the 6 most recent cases, we determined the anti-streptolysin-O levels and a high level (324 UI/ml) was present in only one of them.

In one case, due to the diagnostic complexity, hypocretin-1 evaluation in CSF was performed, and its value was low (70 pg/ml).

All children had already been observed in other consultations, where CNS imaging examinations (6) and EEG (6) had been performed.

Both behavioral therapy and nutritional counseling were established in all cases. Behavioral therapy (structured plan with schedule of nocturnal sleep and naps) was used alone at an initial stage of the first case. Regarding pharmacological approach, they were all medicated with methylphenidate. In 4 cases, it was associated with venlafaxine for cataplexy management. The drug dosage was adjusted according to the clinical situation. In the 4 cases with low ferritin level, iron supplementation was prescribed.

In 6 cases, there was a continuous follow-up by the Sleep Psychology Consultation Group and, in two 12 years-old teenagers, it was necessary to add psychiatric support due to behavioral problems and depressive symptomatology. In all cases there was an improvement in school performance and social integration skills.

4. Discussion

The analyzed group of children presents several similarities with the data that have been published in the literature [10,17]. The first symptom in all children was EDS. The reduced initial presence of cataplexy, hallucinations and sleep paralysis may be due to the children's difficulty in reporting information, as described by other authors [14]. The diagnosis delay ranged from 4 to 24 months with a median of 14 months, which represents a lower value than the ones reported by other authors [10,17]. This may be explained by the awareness of the local medical community for sleep disturbances due to the presence of a children's hospital specialized in sleep disorders in the region.

In one quarter of the patients there were 1st and 2nd degree family members with EDS, and although no clear diagnosis was available, there was a case with enough severity to have a fatal outcome while driving. The familial clustering has already been described, with about 8–10% of the patients referring the existence of a relative with narcolepsy/cataplexy or with EDS [3]. First degree family members have a risk of 0.9–2.3% for disease, which, albeit low, represents a 40 times higher risk in comparison with the general population [22,23].

The etiology was considered idiopathic in all cases, based on the high number of complementary exams performed. In the 6 cases in whom the anti-streptolysin-O levels was obtained, only one demonstrated a mildly high level, which does not support the hypothesis of streptococcal infection as a main triggering factor. In the case where the anti-influenza H1N1 vaccination was performed, we can only wonder about its influence since it is not possible to conclude about a correlation favoring a cause and effect relationship [24].

During consultation, all children had BMI $\geq$75th percentile and, despite nutritional advice, there was still a further 50% increase afterwards. The prevalence of obesity/weight gain was similar to the one described by Poli [15], although his study refers only to patients with NC. However, unlike the mentioned study, our work did not show more early-onset weight gain among the patients with NC, which may be due to the small size of the sample. The connection between an increased weight gain and the onset of cataplexy described by Nevsimalova [13] was also verified in our sample.

The sleep study (PSG and MSLT) is crucial for diagnosis and, in doubtful cases, it should be repeated in the presence of a suggestive clinical picture and once other etiologies have been excluded. In 2 of the cases, the initial MSLT was negative, but the diagnostic hypothesis led to its repetition

Table 1 – Clinical characterization and treatment of children with narcolepsy.

Number, gender	Age at first symptoms (years)	Age at Ds (years)/Ds delay (months)	Age at onset (years)				Nocturnal sleep disturbance	HLA test	Initial/ posterior BMI	Treatment after Ds
			Sleepiness	Cataplexy	Hallucinations	Sleep paralysis				
1, F	7	9/24	7	11	17	–	No	DQB1*06:02/ DRB*15	P90–95/P90–95	M
2, F	9	10/8	9	9	9	–	Yes	DQB1*06:02/ DRB*15	P90–95/P95–97	M+V
3, M	8	8/4	8	8	–	9	Yes	DQB1*06:02/ DRB*15	P90–95/P97	M+V
4, M	6	8/14	6	–	–	–	No	DQB1*06:02/ DRB*15	P85–90/P75–85	M
5, M	10	11/9	10	11	–	–	Yes	DQB1*06:02/ DRB*15	P95–97/ P>97	M+V
6, F	6	9/24	6	–	9	–	Yes	DQB1*06:02/ DRB*15	P75/P25–50	M
7, M	10	11/15	10	–	–	–	Yes	DQB1*06:02	P85–90/P75–85	M
8, M	7	9/24	7	9	–	–	Yes	DQB1*06:02/ DRB*15	P75–85/P85	M+V
Total (median)	6–10 (8)	8–11 (9)/4–24(14)	6–10 (8)	8–11 (9)	9–17 (9)					

Ds – diagnosis; BMI – Body Mass Index; M – Methylphenidate; V – Venlafaxine.

Table 2 – Characteristics of polygraphic sleep studies and multiple sleep latency tests.

Number, gender	TST (min)	Polygraphic sleep study			Multiple sleep latency test		
		Efficiency (%)	Arousal index	Mean SpO2 (%)	Mean sleep latency (min)	SOREMP	Mean REM latency (min)
1, F	385	99	ND	96	0.1	2	1.5
2, F	330	76	3.4	94	1.7	4	3.8
3, M	358	66.7	6.7	98	1	3	2
4, M	365	62	2.6	99	8.5	3	4.83
5, M	433	72	9	99	5.2	4	2
6, F	401	81.9	6.1	99	2.37	3	1.67
7, M	438	79.8	5.1	98	2.25	4	1.37
8, M	432	84.7	3.8	98	2.62	4	1.37
Total (median)	330–438 (393)	62–99 (77.9)	2.6-6.7 (5.1)	94–99 (98)	0.1–8.5 (2.3)	2–4 (3.5)	1.37–4.83 (1.83)

TST – Total sleep time; SOREMP – sleep onset rapid eye movement period; ND – data not available.

and the results turned out to be positive. Actually, in one of these cases, symptoms were so suggestive and disturbing, that the therapy was initiated despite the first MSLT non-conclusive result.

The presence of the allele HLA DQB1*06:02 was verified in all cases, confirming the strong association with narcolepsy described for this allele [2,3,24,25], especially when cataplexy is present. About 99% of the patients with NC are HLA DQB1*06:02 positive. Moreover, we confirmed 7 positive HLA DRB1*15 cases. The association of these 2 alleles is present in 75–90% of the Caucasian NC [1,6] and it increases the probability of severe EDS [6]. Three of the cases of our series did not have cataplexy, but it may still manifest itself in the future, as it is a symptom that appears within months to several years after EDS [13].

The hypocretin-1 dosage in the CSF, whose availability is recent in our country, was performed only in one case, and the result was low. Low or undetectable values are usually found in patients with NC [6] or may even precede the onset of cataplexy [13]. Its dosage may be useful in some difficult cases, such as when the MSLT is inconclusive [14].

The medication used is mainly directed to EDS and cataplexy. Currently, one of the first-line treatments of EDS in adults with narcolepsy is modafinil. Its usage in children seems to be safe (though few studies were performed) [10] but it is not approved yet and so it is scarcely used. In all cases, we used methylphenidate and, in 4 of them, venlafaxine was associated for cataplexy control, with a good response. The gradual increase of dosage was determined by the clinical responses. Sodium oxybate, used for the simultaneous control of EDS and cataplexy, is not available in our country yet.

Proper education about the disease is essential, not only for children but also for their educators. This education must be extended also to school, since narcolepsy may have important consequences upon learning performance and social integration. The guidance by the Sleep Psychology Consultation Group proved to be very important in chronic diseases management for both children/teenagers and their parents. It allowed for early identification of behavioral changes observed in 3 of the cases.

Narcolepsy in children is rare and it is one of the most often underdiagnosed diseases [13]. Excessive Daytime Sleepiness is commonly the initial symptom of the disorder and may remain isolated for a long time, although with developmental repercussions. Decreasing diagnostic delay is a primary target for psychosomatic morbidity reduction. A family physician may work his whole life without seeing a single case of narcolepsy and even less in a child. It seems important to increase the awareness of health and educational professional communities for this disease.

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