Nascer e Crescer - Birth and Growth Medical Journal
2023;32(1):45-49. doi:10.25753/BirthGrowthMJ.v32.i1.24750

CASE REPORTS

Excessive daytime sleepiness. When to think of narcolepsy?

Sonolência diurna excessiva. Quando pensar em narcolepsia?

Inês Rosinha[1], Lea Santos[1], Núria Madureira[2]

ABSTRACT

Narcolepsy is a rare entity that has excessive daytime sleepiness (EDS) as chief complaint. It is a lifelong neurological condition that can be dramatically disabling in the life of a child or adolescent. The classic symptomatic tetrad of EDS – cataplexy, hypnagogic hallucinations, and sleep paralysis – is relatively rare and usually not present in early stages of the disorder, making the diagnosis quite challenging.

The authors describe two clinical cases of adolescents presenting with EDS in which complementary studies culminated in the diagnosis of narcolepsy. Both cases highlight the importance of a high level of suspicion when dealing with EDS since early diagnosis and treatment of narcolepsy are crucial to improve patients' quality of life and minimize the negative impact on school performance and social repercussions.

Keywords: cataplexy; excessive daytime sleepiness; hypocretin-1; narcolepsy

RESUMO

A narcolepsia é uma condição rara que tem a sonolência diurna excessiva (SDE) como principal manifestação clínica. Trata-se de uma situação neurológica cujo impacto a longo prazo na vida de uma criança ou adolescente pode ser extremamente incapacitante. A tétrade sintomática clássica, caracterizada por SDE, cataplexia, alucinações hipnagógicas e paralisia do sono, é relativamente rara e por norma não está presente nos estágios iniciais da doença, tornando o diagnóstico bastante desafiante.

Os autores descrevem dois casos clínicos de adolescentes com SDE, nos quais a investigação complementar culminou no diagnóstico de narcolepsia. Ambos visam destacar a importância de um elevado nível de suspeição clínica perante a SDE, na medida em que o diagnóstico e tratamento precoces da narcolepsia são fundamentais para melhorar a qualidade de vida e minimizar o impacto negativo no desempenho escolar e as repercussões sociais nestes doentes.

Palavras-chave: cataplexia; hipocretina-1; narcolepsia; sonolência diurna excessiva

1. Department of Pediatric, Unidade de Aveiro, Centro Hospitalar do Baixo Vouga. 3810-164, Aveiro, Portugal. inesmendrosinha@gmail.com; lea.santos7@gmail.com
2. Pneumology Unit, Hospital Pediátrico de Coimbra, Centro Hospitalar e Universitário de Coimbra. 3004-561 Coimbra, Portugal. nuriamadureira@gmail.com

INTRODUCTION

Excessive daytime sleepiness (EDS) is a common symptom in adolescents, reported in 16–47% of this age group.[1,2] This subjective sensation of the need to sleep is frequently underdiagnosed and may have a negative impact on the emotional, behavioral, and school achievement domains.[1,2]

According to the third edition of the International Classification of Sleep Disorders (ICSD-3), seven major categories of sleep disorders can be identified: insomnia, sleep-related breathing disorders, central disorders of hypersomnolence (including narcolepsy), circadian rhythm sleep-wake disorders, parasomnias, sleep-related movement disorders, and other uncategorized sleep disorders.[1-3]

Sleep problems can cause EDS in up to 25–40% of children and adolescents, mainly encompassing behavioral, neurological, and respiratory conditions.[2] The leading cause of EDS in adolescents is sleep deprivation, followed by sleep breathing disorders, sleep movement disorders, and circadian rhythm disorders. Nevertheless, other rarer causes of EDS can be present in this population, including depression, brain tumors, drugs, epilepsy, and narcolepsy.[1,2]

Narcolepsy is an uncommon, underdiagnosed lifelong neurological condition, with a variable prevalence of 0.02–0.06% in Europe and the U.S. and 0.16–0.18% in Japan.[3,4] It usually presents between the ages of 10–20 years and is characterized by EDS, cataplexy (type 1 exclusive), hallucinations, and sleep paralysis, although this tetrad is only present in 10–15% of cases.[1,2,4,5]

EDS is by far the most common presenting symptom of narcolepsy and consists of uncontrollable episodes of sleep while talking, eating, or playing sports.[4,6] However, the clinical translation of drowsiness may be quite more subtle in pediatric age, manifesting, for instance, by resuming a nap or falling asleep during classes. Despite its high sensitivity for narcolepsy, EDS lacks specificity.[6]

Conversely, cataplexy is the most specific symptom of narcolepsy. It is present in 60–80% of patients and is characterized by sudden and brief loss of muscle tone, generally in response to strong emotions, like laughter, surprise, or fright.[4,6]

Since 2014, the updated International Classification of Sleep Disorders - third edition (ICSD-3) recognizes two types of narcolepsy: type 1, corresponding to narcolepsy with cataplexy and with hypocretin-1 deficiency in the central nervous system as main pathophysiologic feature; and type 2, corresponding to narcolepsy without cataplexy, currently without an established pathophysiology.[4-8]

This report describes two clinical cases of adolescents presenting with EDS, for whom follow-up and complementary studies lead to the diagnosis of narcolepsy. Both cases highlight the importance of a high level of suspicion in presence of EDS. Early diagnosis and treatment of narcolepsy is paramount to improve the quality of life and minimize negative school performance, risk of accidents, and psychosocial affection in these patients.[1,5,9,10]

Clinical Case 1

A sixteen-year-old female federated football player was referred to pediatric sleep pathology consultation for EDS with one year of evolution. She reported falling asleep in the first morning classes, on the bus, and even during tests, but never while talking, eating, or playing sports. She attended 10th school grade and used to achieve good skills as a student, but a significant decrease in school performance had been noticed during the past year. She had a euthymic mood, but behavioral problems were evident mainly at school. Laughter-related cataplexy episodes and sleep paralysis had also been noticed in the previous six months, together with a subjective perception of 5 Kg weight during the same time. The girl described having a ten-hour night sleep and denied snoring, restless sleep, or nocturnal awakenings.

As personal background, she reported a twin pregnancy and preterm delivery at thirty gestational weeks. Her twin sister had cerebral palsy and quadriplegia and her paternal grandfather had obstructive sleep apnea (OSA).

On physical examination, the girl had a body mass index (BMI) of 22.5 kg/m^2 (standard deviation [SD] +0.58) and drowsy and cataplectic facial appearance consisting of eyelid ptosis, tongue protrusion, and open jaw-dropping, without other major findings.

Complementary study revealed positive human leukocyte antigen (HLA) DRB1*15 and DQB1*06:02, as well as normal thyroid function.

Actigraphy revealed marked sleep schedule irregularity and a median sleep duration of ten hours. Polysomnography (PSG) revealed good sleep efficiency (82%), normal sleep latency (23 minutes, normal range [NR] 22.6±29.8), markedly reduced rapid eye movement (REM) latency (1.5 minutes, NR 132.7±36.4), REM without atonia, elevated microarousals index of 11.4 per hour (NR 2.9-9.1), no relevant respiratory events, and periodic leg movement (PLM) index above 5 per hour (6.2 per hour). Multiple sleep latency test (MSLT) disclosed an average sleep latency of 2.5 minutes (NR ≥8) and four sleep-onset rapid eye movement (SOREM) periods, with a mean REM latency of two minutes (NR >15). The diagnosis of type 1 narcolepsy was established, and treatment with modafinil and venlafaxine was initiated. Due to behavioral difficulties, the girl was referred to Psychology consultation, with good symptomatic control achieved during the four-year follow-up.

Clinical Case 2

A fifteen-year-old girl was referred to pediatric sleep pathology consultation for EDS mostly for the past five years. She attended 9th grade at school, with reasonable performance, but used to fall asleep easily in classes. She also used to fall asleep on the bus and once while having a soaking bath. During weekends, she could spend all day sleeping. No history of cataplexy, hallucinations, or sleep paralysis was reported.

The girl had excessive weight gain for the last three years, particularly evident in the last eighteen months, with an overall weight gain of 30 Kg.

She had an apparently good sleep hygiene, and actigraphy confirmed regular sleep schedules, with a total sleep time of 10–14 hours per night. She reported frequent nightmares and restless sleep, with laughing and somniloquy. Despite having been submitted to adenotonsillectomy at nine years old, the girl still complained of snoring without noticed apnea.

Regarding personal background, she had been diagnosed with epilepsy at the age of five after the beginning of convulsive episodes four months after a head trauma. She had been medicated with sodium valproate for up to ten years, which was later withdrawn due to the absence of recurrent seizures.

Neurological exam was normal, and the main relevant findings during observation were nasobucal breathing, ogivated palate, modified Mallampati grade 3, and BMI of 30.9 kg/m^2 (SD +2.32).

The analytical study revealed positive HLA DRB1*15 and DQB1*06:02 and normal thyroid function.

PSG revealed good sleep efficiency (94%), sleep latency of one minute (NR 22.6±29.8), markedly reduced REM latency (1.5 minutes, NR 132.7±36.4), REM without atonia, elevated microarousals index (10.5 per hour, NR 2.9-9.1), no relevant respiratory events, and normal PLM index of 0.5 per hour (NR ≤5 per hour). MSLT disclosed an average sleep latency of two minutes (NR ≥8) and SOREM periods in four naps. The diagnosis of narcolepsy was established, but due to absence of cataplexy, a lumbar puncture (LP) was planned to measure hypocretin-1 levels in the cerebrospinal fluid. However, LP attempts were unsuccessful, in part due to the girl's obesity. The diagnosis of type 2 narcolepsy was therefore accepted, and the girl initiated treatment with methylphenidate. During the four-year follow-up, she developed hypnagogic hallucinations without evidence of cataplexy so far.

DISCUSSION

EDS is a common presenting symptom in adolescents, with an estimated prevalence of 16–47%.[3] In this age group, its main cause is by far sleep deprivation.[1,2] In 2016, a Portuguese study including 400 adolescents from the ninth to eleventh school grades revealed worrying levels of poor sleep quality.[11] In addition, according to a study from the National Sleep Foundation, only 20% of adolescents sleep as much as necessary in school days.[11,12]

Sleep deprivation and subsequent EDS may lead to attentional and disruptive behavior, mood disturbances, depression, declining academic performance, and multiple safety concerns, namely drowsy driving and automobile crashes, sports-related and unintentional injuries, and increased risk of alcohol and drug abuse.[1,5,9,13]

Since actigraphy is an objective method of estimating patterns of sleep and wakefulness, it is currently considered the gold standard for detecting sleep deprivation.[1,7]

In the present clinical cases, although parents and adolescents reported good sleep hygiene in both, actigraphy was performed as complementary study. In the first case, actigraphy showed markedly irregular sleep schedules and normal median sleep duration.

Regarding primary sleep pathology, sleep-related breathing and movement disorders are two important causes of EDS that should be kept in mind, and a detailed clinical history followed by PSG is crucial to exclude these diagnoses.[1,4,7] The adolescent from the second clinical case had a BMI of 30.9 kg/m^2 and parents had noticed snoring. In turn, PSG showed no respiratory events, excluding OSA as the cause of EDS.[1]

Narcolepsy is a rare entity that is considered an independent central nervous system disturbance, in which EDS is usually the first and most disabling symptom, as observed in both cases in this study.[4] Its onset may be as early as at the age of five, but EDS may not be immediately valued until other manifestations arise.[4] Its severity ranges from waxing and waning drowsiness to irresistible unintended sleep attacks often lasting 30 to 90 minutes, usually but not always followed by a refreshed feeling, but often sufficient to avoid somnolence in the next three to four hours.[1,4] EDS may have an appreciable impact on daytime activities, such as eating or bathing, and in school performance.[1,4] In both cases presented, the adolescents used to regularly fall asleep during classes.

Cataplexy (i.e., episodes of sudden loss of voluntary muscle tone triggered by emotions) is the hallmark of type 1 narcolepsy, but is only present in 60–80% of patients.[4,10] In 5–10% of children, it may be the first symptom and the frequency of episodes is highly variable.[4,6,14,15] It usually develops within five years of the onset of daytime sleepiness, but a delay of several years can also occur.[8,14,15] Cataplexy is the most specific diagnostic sign, despite its possibly atypical features in 50–80% of cases (e.g., facial muscle hypotonia manifested by eyelid ptosis, jaw dropping, tongue protrusion, or thrusting movements and head rolling).[4,6,8,14,16] A cephalocaudal and symmetrical progression of muscular weakness is described, usually arising in response to strong emotions, like laughter, surprise, anger, and anticipation of reward.[4,15] Consciousness is generally preserved, but in some cases may emerge in deep sleep.[4,15]

Cataplexy was one of the clinical manifestations in the first clinical case and, together with MSLT result, allowed to establish the diagnosis of type 1 narcolepsy. In the second case, cataplexy was absent and cerebrospinal fluid examination would have been important to distinguish between the two types of narcolepsy, as cerebrospinal fluid hypocretin-1 levels lower than 110 ng/mL are indicative of type 1 narcolepsy.[4,6,14] However, this important information could not be obtained, and narcolepsy classification in the second case was based essentially on a wait and see approach. Although no cataplexy has been observed after four years of follow-up, it may still manifest in the future.[4,8,12] Until then, type 2 narcolepsy is assumed.[4,8,14]

Sleep paralysis and hypnagogic or hypnopompic hallucinations are present in 50–60% of children and, unlike cataplexy, they are

unspecific, with all these symptoms representing episodic intrusion of fragments of REM sleep onto wakefulness.[4,6,8,15] Sleep paralysis consists in an inability to move the body's striated muscles except for the diaphragm and extrinsic ocular muscles, and results in disability to move or talk. It normally occurs during wakefulness and lasts a few seconds, being often accompanied by paresthesia, as in the first clinical case.[4,6,15]

According to the literature, 50–74% of narcoleptic children are overweight or obese, and this comorbidity is often present as a clinical presentation of narcolepsy.[4,6] This association was evident in the second clinical case. Interestingly, narcolepsy symptoms seem to have an earlier age of onset in obese compared to normal-weight children, as observed in these cases.[4] This seems to be due to abnormal leptin and hypocretin levels, as well as decreased basal metabolism.[6,7]

Regarding diagnosis, MSLT preceded by PSG is used as a standard diagnostic procedure in children older than six years.[1,4,7,9,13,14] Furthermore, some abnormal PSG findings may constitute a valuable clue for the diagnosis of narcolepsy, including SOREM period (REM latency less than 15 minutes), REM sleep without atonia, and increased number of spontaneous arousals per hour.[4,9,13,14,17,18] These findings were evidenced in the present clinical cases.

Regarding MSLT, the presence of at least two SOREM periods and a mean sleep latency less than eight minutes have a high sensitivity and specificity for narcolepsy, despite being inconsistently present in the early stages of the disease.[1,4,9,13-15] Therefore, MSLT results corroborated the diagnosis of narcolepsy in both cases.

The presence of HLA DQB1*06:02 haplotypes is another clue for the diagnosis of type 1 narcolepsy, suggesting a potential immunological explanation for the pathophysiology of the condition.[4,5,7,14] In the present study, these haplotypes were detected in both cases. However, it should be stressed that negativity for these haplotypes does not exclude the diagnosis and positivity is not diagnostic-specific, since the haplotypes can be also be found in the general population.[4,6,14]

According to the literature, the time lag between the onset of symptoms and diagnosis is usually long (15 years in average).[5,8,14] However, in this study, the diagnosis was established faster than reported in the literature (within approximately five years and one year in clinical case 1 and 2, respectively), probably due to the early recognition of daytime sleepiness. The earlier the diagnosis, the better the patient outcomes.

The management of narcolepsy is mainly symptomatic, aiming to improve patients' tolerance and quality of life.[4,6] Most patients eventually require symptomatic treatment aimed at disabling sleep and/or cataplexy.[4,12,14] Pharmacotherapy should be individualized according to the most bothering symptoms and the drugs' side effect profile.[4,6,14,16]

Regarding prognosis, the disease remains stable for several years in most patients, but cases of improvement or worsening can occur.[4,10] The poor night sleep quality and excessive sleepiness persist throughout life, eventually becoming more bearable as time goes by.[4,10] Cataplexy, on the other hand, can be managed with medications and patient education to control their emotions. Sleep paralysis and hallucinations seem to be transient.[4,10,16]

In conclusion, although sleep deprivation is the main cause of EDS, narcolepsy should also be considered. However, the diagnosis is not always straightforward.[6] Regardless of the presence of cataplexy, EDS with great impact in activities of daily life is suggestive of narcolepsy, and the more exuberant the somnolence, the more likely the diagnosis.[1,10] Early referral to a Pediatric tertiary center is imperative to improve the quality of life and minimize the negative outcomes in school or work for these patients.[9] Moreover, patients typically have poor self-esteem and are socially excluded, which should be the object of specialized intervention.[10]

AUTHORSHIP

Inês Rosinha – Conceptualization; Data curation; Investigation; Writing – original draft; Writing – review & editing

Lea Santos - Conceptualization; Investigation

Núria Madureira - Conceptualization; Investigation

REFERENCES

1. Wise MS, Glaze DG. Assessment of sleep disorders in children. May, 2021. (Assessed June 10, 2021). Accessible at: http://www.uptodate.com.
2. Macedo S, Portinha I, Correia Z. Uma criança com narcolepsia. Nascer e Crescer 2014; 23(2): 80-2.
3. Sateia MJ. International classification of sleep disorders – 3rd edition: Highlights and modifications. Chest 2014; 146(5):1387-94. DOI: https://doi.org/10.1378/chest.14-0970.
4. Kotagal S. Narcolepsy in Children. May, 2021. (Assessed June 10, 2021). Accessible at: http://www.uptodate.com.
5. Nevsimalova S. The Diagnosis and Treatment of Pediatric Narcolepsy. Curr Neurol Neurosci Rep 2014; 14: 469. DOI: https://doi.org/10.1007/s11910-014-0469-1.
6. Maski K, Pizza F, Liu S, Steinhart E, Little E, Colclasure A, *et al*. Defining disrupted nighttime sleep and assessing its diagnostic utility for pediatric narcolepsy type 1. SLEEPJ 2020; 1-7. DOI: https://doi.org/10.1093/sleep/zsaa066.
7. Martin JL, Hakim AD. Wrist Actigraphy. Chest 2011; 139(6): 1514-27. DOI: https://doi.org/10.138/chest.10-1872.
8. Maski K, Steinhart E, Williams D, Scammell T, Flygare J, McCleary K, *et al*. Listening to the Patient Voice in Narcolepsy: Diagnostic Delay, Disease Burden, and Treatment Efficacy. J Clin Sleep Med. 2017; 13(3): 419-25.
9. Reiter J, Katz E, Scammell TE, Maski K. Usefulness of a Nocturnal SOREMP for Diagnosing Narcolepsy with Cataplexy in a Pediatric

Population. Sleep 2015; 38(6): 859-65. DOI: https://doi.org/10.5665/sleep.4728.
10. Quaedackers L, Gilst MM, Mierlo P, Lammers G, Dhondt K, Amesz P, *et al*. Impaired social functioning in children with narcolepsy. SLEEPJ 2019; 1-6. DOI: https://doi.org/10.1093/sleep/zsy228.
11. Pinto TR, Pinto JC, Rebelo-Pinto H, Paiva T. O sono em adolescentes portugueses: Proposta de um modelo tridimensional. Análise Psicológica 2016; 4(XXXIV): 339-52.
12. National Sleep Foundation. 2006 Sleep in American Poll – Teens and Sleep. Sleep Health 2015; 1(2):e5.
13. Bin-Hassan S, Videnovic A, Maski K. Nocturnal REM Sleep Without Atonia is a Diagnostic Biomarker of Pediatric Narcolepsy. J Clin Sleep Med. 2018; 14(2): 245-52.
14. Babiker M, Prasad M. Narcolepsy in Children: A Diagnostic and Management Approach. Pediatric Neurology 2015; 52: 557-65. DOI: https://doi.org/10.1016/j.pediatrneurol.2015.02.020.
15. Owens JA, Babcock D, Weiss M. Evaluation and Treatment of Children and Adolescents With Excessive Daytime Sleepiness. Clinical Pediatrics 2020; 59(4-5): 340-51. DOI: https://doi.org/10.1177/0009922820903434.
16. Antelmi E, Pizza F, Vandi S, Neccia G, Ferri R, Oliviero B, *et al*. The spectrum of REM sleep-related episodes in children with type 1 narcolepsy. BRAIN 2017; 140: 1669-79. DOI: https://doi.org/10-1093/brain/awx096.
17. Scholle S, Beyer U, Bernhard M, Eichholz S, Erler T, Graneb P, et al. Normative values of polysomnographic parameters in childhood and adolescence: Quantitative sleep parameters. Sleep Medicine 2011; 12:542-9.
18. Scholle S, Wiater A, Sholle HC. Normative values of polysomnographic parameters in childhood and adolescence: Arousal events. Sleep Medicine 2012; 13:243-51.

CORRESPONDENCE TO

Inês Rosinha
Pediatric Department
Unidade de Aveiro
Centro Hospitalar do Baixo Vouga
Avenida Artur Ravara
3810-164, Aveiro
Email: inesmendrosinha@gmail.com

Received for publication: 10.06.2021
Accepted in revised form: 21.02.2022