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Original article

Clinical features of childhood narcolepsy. Can cataplexy be foretold?

Sona Nevsimalova [a,*], *Cecilia Jara* [b], *Iva Prihodova* [a], *David Kemlink* [a], *Karel Sonka* [a], *Jelena Skibova* [c]

[a] *Department of Neurology, 1st Faculty of Medicine and Teaching Hospital, Charles University, Prague, Czech Republic*
[b] *Sleep Disorder Center, University of Regensburg, Germany*
[c] *Department of Statistics, Institute of Experimental Medicine, Prague, Czech Republic*

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ABSTRACT

Background: Narcolepsy is a life-long disease characterized by abnormal regulation of the sleep–wake cycle and increased penetration of rapid eye movement (REM) sleep. In children, narcolepsy without cataplexy is more frequently seen than in adults. The aim of our study was to evaluate clinical and polysomnographic parameters to verify if cataplexy appearing later in life can be foretold.

Methods: 30 patients (12 boys), who contracted narcolepsy before the age of 18, were enrolled. All underwent clinical examination, nocturnal polysomnography (PSG), multiple sleep latency test (MSLT), HLA-DQB1*0602 testing and, most of them Epworth Sleepiness Scale (ESS) rating. The Mann–Whitney rank and Fisher's tests were used for statistical analysis.

Results: Narcolepsy without cataplexy (NwC) was diagnosed in 40% of the patients. The mean age at the first symptoms was 14.0 ± 3.0, at diagnosis 15.6 ± 3.1 years. Narcolepsy was accompanied by hypnagogic hallucinations in 15 and sleep paralysis in 12 patients. Frequent symptoms were sleep inertia during awakening, REM behavior symptoms, behavioral and serious school problems. BMI was higher in patients with narcolepsy-cataplexy (N-C). A high ESS score was indicative of excessive daytime sleepiness (17.1 ± 2.5). Mean MSLT sleep latency was 4.0 ± 3.1 min with 3.2 ± 1.4 sleep onset REM periods (SOREMs) with no difference between the two study groups. HLA typing revealed no differences either. The N-C group showed a higher degree of wakefulness and superficial non-REM (NREM) stage 1 with a lower NREM stage 3 during PSG.

Conclusion: Narcolepsy in childhood leaves very little scope for the prediction of cataplexy later in life.

* *Corresponding author*. Tel.: +420 224965562, mobile +420 607810139; fax: +420 224922678.
E-mail address: snevsi@LF1.cuni.cz (S. Nevsimalova).

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1. Introduction

Narcolepsy is a life-long disease characterized by abnormal regulation of the sleep–wake cycle and increased penetration of rapid eye movement (REM) sleep due to loss of hypocretin containing neurons located in the lateral hypothalamus.[1] Childhood narcolepsy seems to have a key role in the pathophysiology of the disease. Recently, its autoimmune etiology was proved in narcolepsy-cataplexy (N-C) cases[2] and streptococcal infection as a trigger point of the disease was discovered.[3] Although the first symptoms often appear during childhood and/or adolescence, pediatric narcolepsy is one of the most often underrecognised and underdiagnosed diseases.[4,5] Its prevalence in the adult population varies from 0.05 to 0.02%, in childhood it is unknown.[6]

The main clinical features comprise attacks of excessive daytime sleepiness appearing just at the beginning of the disease and are accompanied and/or followed by attacks of sudden loss of muscle tone evoked by a strong emotion, an event called cataplexy. The clinical picture in some patients may include hypnagogic or hypnopompic hallucinations on falling asleep or on awakening, or attacks of sleep paralysis. Unquiet nocturnal sleep with vivid dreams and frequent periods of wakefulness is often part of the clinical picture, too.[7] Unlike adults, children suffering from narcolepsy often report sleep drunkenness (confusional arousals, sleep inertia) after morning awakening and states of automatic behavior during the day that can imitate attacks of clouded consciousness of epileptic origin. Additional symptoms including personality and behavior changes, school performance worsening, obesity and rarely precocious puberty are also parts of the clinical picture.[8]

According to international classification,[9] three main categories of narcolepsy are distinguished: (i) narcolepsy with cataplexy (N-C) covering in adulthood up to 80% of all idiopathic cases, (ii) narcolepsy without cataplexy (NwC) presenting in adulthood approximately 20% of the idiopathic cases and (iii) narcolepsy due to medical conditions, more frequently seen in childhood than adulthood. However, the exact ratio of N-C to NwC cases in childhood is not known.

The diagnosis of childhood narcolepsy is not easy and specific diagnostic tools should be used. Similarly as in adults, nocturnal video-polysomnography (PSG) is used followed by multiple sleep latency test (MSLT) in school children. Nocturnal PSG helps to eliminate other causes of excessive daytime sleepiness such as sleep disordered breathing and/or periodic limb movements. However, their presence does not rule out the presence of narcolepsy, they can coexist in a significant minority of narcoleptic patients.[10] Overnight polygraphic sleep records also exclude parasomnias as a cause of fragmented and unquiet nocturnal sleep and/or verified REM behavior disorder (RBD) as one of the possible symptoms of narcolepsy.[11] During MSLT, five repeated tests lasting 20 min each, at 2-h intervals, are used in school children as a standard diagnostic method.[12] The mean sleep latency and number of sleep onset REM (SOREM) periods are evaluated. A mean sleep latency of less than 10 min can be assumed as abnormal[13,14] and, similarly as in adults, two or more episodes of SOREM are considered pathological. According to international rules,[9] the same diagnostic criteria are accepted for the diagnosis of N-C as well as NwC; therefore, NwC is a clearly defined entity.

Human leukocyte antigen (HLA) typing is another controversially useful diagnostic tool in children. The presence of the DQB1*0602 haplotype adds a great deal to the diagnostic probability of narcolepsy, particularly N-C, though DQB1*0602 negativity does not exclude it. Particularly, cases of NwC are often DQB1*0602 negative. According to some authors,[13] HLA examinations has a predictive value in children with excessive daytime sleepiness, though currently free from cataplectic attacks.

Cerebrospinal fluid (CSF) hypocretin-1 (Hcrt-1) evaluation is a valuable diagnostic marker in children, especially in N-C cases where the Hcrt-1 level in undetectable.[15] However, diagnostic lumbar puncture is an invasive method and some parents do not accept it. An undetectable Hcrt-1 level can be one of the factors predicting a later appearance of cataplexy, especially in children so far diagnosed only with isolated excessive daytime sleepiness.[8]

The aim of our study was to evaluate clinical and polysomnographic parameters of children and adolescent with narcolepsy, to ascertain the ratio of N-C and NwC patients in the youth, and to verify if cataplexy likely to appear later in the life, can be foretold from the clinical point of view.

2. Patients and methods

Thirty patients (18 girls, 12 boys) participated in this study, in all of them the diagnosis was established before the end of the 18th year of age. The cohort consisted of 26 patients from Prague and 4 cases from Regensburg. They were enrolled during the past 10 years, when diagnosis was established on the same clinical and polysomnographic characteristics.[9] Table 1 illustrates clinical and behavioral characteristics of our sample. N-C was diagnosed in 18 patients, NwC in 12 patients. The age at the first symptoms (14.0 ± 3.0) as well as the age at diagnosis (15.6 ± 3.1) was similar in both groups. Comparing the presence of hypnagogic/hypnopompic hallucinations and sleep paralysis we found no significant differences either.

A clinical face-to face interview was completed using the subjective Epworth Sleepiness Scale (ESS), biochemical examination and HLA typing; most of the patients had neuroimaging examination (CT, MRI) performed to exclude any secondary (symptomatic) narcolepsy. Hcrt-1 level in CSF was measured in only 6 patients. All the patients underwent nocturnal PSG followed by MSLT to verify the diagnosis. Video-PSG records were standardized as regards the time schedule and adapted to childrens' habits (usually 9.30 p.m. up to 6.30 a.m.), and so was the equipment (Schwarzer polygraph). All records comprised electroencephalography (EEG) including C3/A2, C4/A1, O1/A2 and O2/A1 lead, electrooculography (EOG), electromyography (EMG) from the mentalis muscle and anterior tibialis muscle, electrocardiography (ECG) and respiratory parameters. PSG records were evaluated visually according to standardized Rechtschaffen and Kales rules[16] by three sleep specialists (IP, DK, CJ). MSLT – a test of the rapidity with which a subject falls asleep in a standardized, sleep-conducive setting