Sleep Medicine xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Narcolepsy–cataplexy and schizophrenia in adolescents

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ARTICLE INFO

Article history:
Received 1 January 2013
Received in revised form 21 September 2013
Accepted 24 September 2013
Available online xxxx

Keywords:
Narcolepsy
Cataplexy
Adolescent
Schizophrenia
HLA
Chinese and HLA DQ B1-03:01

ABSTRACT

Background: Despite advances in the understanding of narcolepsy, little information the on association between narcolepsy and psychosis is available, except for amphetamine-related psychotic reactions. Our case-control study aimed to compare clinical differences and analyze risk factors in children who developed narcolepsy with cataplexy (N–C), schizophrenia, and N–C followed by schizophrenia.

Methods: Three age- and gender-matched groups of children with N–C schizophrenia (study group), N–C (control group 1), and schizophrenia only (control group 2) were investigated. Subjects filled out sleep questionnaires, sleep diaries, and quality of life scales, followed by polysomnography (PSG), multiple sleep latency tests (MSLT), routine blood tests, HLA typing, genetic analysis of genes of interest, and psychiatric evaluation. The risk factors for schizophrenia also were analyzed.

Results: The study group was significantly overweight when measuring body mass index (BMI) ($P = .016$), at narcolepsy onset compared to control group 1, and the study group developed schizophrenia after a mean of 2.55 ± 1.8 years. Compared to control group 2, psychotic symptoms were significantly more severe in the study group, with a higher frequency of depressive symptoms and acute ward hospitalization in 8 out of 10 of the subjects. They also had poorer long-term response to treatment, despite multiple treatment trials targeting their florid psychotic symptoms. All subjects with narcolepsy were HLA DQ B1*0602 positive. The study group had a significantly higher frequency of DQ B1*-03:01/06:02 (70%) than the two other groups, without any significant difference in HLA-DR typing, tumor necrosis factor α (TNF-α) levels, hypocretin (orexin) receptor 1 gene, *HCRTR1*, and the hypocretin (orexin) receptor 2 gene, *HCRTR2*, or blood infectious titers.

Conclusion: BMI and weight at onset of narcolepsy as well as a higher frequency of DQ B1*-03:01/06:02 antigens were the only significant differences in the N–C children with secondary schizophrenia; such an association is a therapeutic challenge with long-term persistence of severe psychotic symptoms.

1. Introduction

Narcolepsy with cataplexy (N–C) [1] is associated with daytime somnolence, disrupted nocturnal sleep, and episodes of abrupt complete or partial loss of muscle tone; the loss of muscle tone is mostly triggered by laughter or abrupt emotional involvement, with the disappearance of deep tendon reflexes during cataplexy. Hypnopompic and hypnagogic hallucinations and sleep paralysis are observed at various frequencies [2]. Nocturnal polysomnography (PSG) may uncover sleep-onset rapid eye movement periods (SOREMPs), though the multiple sleep latency test (MSLT) on the following day shows two or more SOREMPs during the five 20-min naps and less than 8 min mean sleep latency.

N–C is associated with the presence of the HLA DQB1*06:02 allele, independent of ethnicity in at least 92% of the cases [3]; in addition, the cerebrospinal fluid analysis often reveals absence of or pathologically low levels of hypocretin. Presence of the HLA DQB1*06:02 allele has a sensitivity of 89.3% and a specificity of 76%; the presence of two or more SOREMPs at MSLT has a sensitivity of 87.9% and a specificity of 96.9%; and the complete absence of or low levels of hypocretin has a sensitivity of 83.3% and a specificity of 100% in patients with narcolepsy [4].

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http://dx.doi.org/10.1016/j.sleep.2013.09.018

Autopsy material shows destruction of the hypocretin (orexin) neurons that produce peptide hypocretin (orexin) in the lateral hypothalamus [5]. The notion that N–C may be an autoimmune disease has received more and more support due to further genetic analyses [6]. N–C is now frequently recognized in prepubertal and young teenagers due to systematic investigation and the emphasis on recent reports switches to the understanding of the health problems associated with hypocretin deficiency, not limited to sleepiness and cataplexy. Despite previous work indicating an association of narcolepsy in adult schizophrenics and the absence of recognition of narcolepsy syndrome [7–10], we still have little knowledge on the relationship between N–C and schizophrenia to date. The prevalence of N–C combined with schizophrenia has been previously estimated to be in 1–18 cases in a population of 2 million based on independent prevalence rates [11]. Stimulants and amphetamine-like drugs in particular have been used in the treatment of narcolepsy and the development of psychotic disorders in association with drug intake in narcoleptics also has been implicated in the literature [12]. Many studies have emphasized the strong association between narcolepsy and HLA, particularly the HLA-DQ and the HLA-DR protein [3]. In addition, a genetic association between specific HLA-DR genes and schizophrenia also has been shown [6,9,11,13], but the association between HLA alleles and schizophrenia is a field with continuous research efforts [14,15]. The question of a potential interaction between narcolepsy and schizophrenia, especially in children diagnosed with N–C, has mostly been unexplored particularly when looking at the chronologic development of the two syndromes and also questioning if the clinical presentation of the first syndrome gave any clue on occurrence of the second morbidity.

We present the results of a retrospective investigation of our prospectively collected narcoleptic cases. We compared our findings obtained from N–C children who also developed schizophrenia to findings of age-matched children with N–C and age-matched children with schizophrenia only.

2. Methods

2.1. Subjects

Our pediatric sleep center is the only pediatric sleep center for Taiwan (23 million inhabitants) and is the referring center for all children with abnormal sleepiness. The center is responsible for treatment and follow-up of all diagnosed children. During the 4 year prospective study, 151 children fulfilled all the *International Classification of Sleep Disorders*, second edition, criteria for diagnosis of Narcolepsy [16], but only 102 children presented with N–C. The prospectively collected 102 N–C children represented our total clinical initial group. Out of the 102 N–C children, 10 (9.8%) developed schizophrenia. Most of the children were diagnosed with hypersomnia and N–C first and subsequently developed Schneider first-rank symptoms within 3 years' duration (mean time of schizophrenia onset, 2.55 ± 1.8 y).

As shown below, the diagnosis of schizophrenia was based on thorough clinical evaluation by a child psychiatrist and positive testing on different scales. The children with N–C and schizophrenia (n = 10) comprised our study group. We also formed two control groups: control group 1 comprised age- and gender-matched N–C children without schizophrenia (n = 37/92); and control group 2 comprised a group of age- and gender-matched schizophrenic children without N–C (n = 13). In reviewing past teenage schizophrenia cases seen during the last 10 years in our large university pediatric psychiatric clinic, no schizophrenic child developed narcolepsy thereafter. Because the pediatric sleep laboratory and clinic are both part of the pediatric psychiatric division, all of these previous patients received a similar evaluation as those in the study group. Children in the control and study groups completed similar testing procedures.

Study approval was obtained from the Institutional Review Boards of Chang Gung Hospital, Taiwan. Written informed consent was obtained from subjects and their legal representatives following a detailed explanation of the study.

2.2. Diagnostic evaluation

2.2.1. N–C evaluation

All cases underwent a standardized evaluation based on the international recommendations (*International Classification of Sleep Disorders*, second edition) for the diagnosis of N–C and hypersomnia [16]. Children underwent a general pediatric clinical evaluation. Body weight and height of subjects were assessed in a standardized fashion to calculate body mass index (BMI). Complete neurologic evaluation including electroencephalogram (EEG) (while awake and while asleep) and brain magnetic resonance imaging were systematically performed. Routine blood tests (complete blood cell count with differential count and biochemical blood tests [i.e., blood sugar, thyroid-stimulating hormone, thyroxine, liver function, and renal function]) were obtained.

Systematic HLA typing was performed on all children. Blood also was drawn for other potential genetic studies. Parents and children filled out the following sleep questionnaires (validated in Mandarin): the Pediatric Daytime Sleepiness Scale (PDSS) [17], the Epworth Sleepiness Scale (ESS) if the child was old enough to drive [18], sleep diaries for 14 days, and the Stanford Narcolepsy Questionnaire [19]. They also were asked to fill out sleep diaries for a minimum of 14 successive days, with notation of indicators, triggers, and duration of each cataplexy attack; and four daily visual analog scales (VAS) (scored 1–100), which observed excessive daytime sleepiness (EDS), presence of hypnagogic/hypnopompic hallucination, and sleep paralysis. Each patient underwent 14 days of actigraphy tests, which observed the amount of sleep inactivity during the night and during the daytime. Nocturnal PSG also was observed for a minimum of 7 h, with monitoring of the following variables: EEG (C3/A2, C4/A1, Fz/A1–A2, and O1/A2); right and left electrooculogram; chin and legs electromyography; electrocardiography with a modified V2 lead; nasal cannula pressure transducer; mouth thermistor; chest and abdomen inductive plethysmography bands; neck microphone; and finger oximetry, from which oximetry curve and finger plethysmography were extracted and recorded. The following morning, an MSLT was administered to each patient at 2-h intervals consisting of five 20-min naps; mean sleep-latency and presence of SOREMPs were calculated.

After the PSG, patients were submitted to video-monitored challenges reported by family members to trigger cataplectic attacks; such video monitoring allowed the observers to replay the attacks to determining the presence of complete and partial attacks, investigate the segments of the body involved during an "attack," and to affirm the presence of cataplexy. Interaction with family members usually was successful in inducing cataplectic attacks. Attacks provoked in the sleep medicine facilities were witnessed by a physician expert in narcolepsy, and deep tendon reflexes were checked during the attack and just after recovery when the attack was of sufficiently long duration [20].

2.2.2. Schizophrenia evaluation

A structured psychiatric interview was conducted using the Schedule for Affective Disorder and Schizophrenia for school-aged children, adolescent version (K-SADS-E) [21] by experienced child psychiatrists. Schizophrenia was diagnosed based on *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, Text

Please cite this article in press as: Huang Y-S et al. Narcolepsy–cataplexy and schizophrenia in adolescents. Sleep Med (2013), http://dx.doi.org/10.1016/j.sleep.2013.09.018