

ALLERGIES AND DISEASE SEVERITY IN CHILDHOOD NARCOLEPSY

Allergies and Disease Severity in Childhood Narcolepsy: Preliminary Findings

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Introduction: Narcolepsy frequently begins in childhood, and is characterized by excessive daytime sleepiness, with the presence of cataplexy reflecting a more severe phenotype. Narcolepsy may result from genetic predisposition involving deregulation of immune pathways, particularly involving T helper 2 cells (Th2). Increased activation of Th2 cells is usually manifested as allergic conditions such as rhinitis, atopic dermatitis, and asthma. We hypothesized that the presence of allergic conditions indicative of increased Th2 balance may dampen the severity of the phenotype in children with narcolepsy.

Methods: A retrospective chart review of childhood narcolepsy patients was conducted at three major pediatric sleep centers. Patients were divided into those with narcolepsy without cataplexy (NC-) and narcolepsy with cataplexy (NC+). Demographics, polysomnographic and multiple sleep latency test data, and extraction of information on the presence of allergic diseases such as allergic rhinitis, atopic dermatitis, and asthma was performed.

Results: There were 468 children identified, with 193 children in NC- group and 275 patients in the NC+ group. Overall, NC+ children were significantly younger, had higher body mass index, and had shorter mean sleep latencies and increased sleep onset rapid eye movement events. The frequency of allergic conditions, particularly asthma and allergic rhinitis, was markedly lower in NC+ (58/275) compared to NC- patients (94/193; $P < 0.0001$).

Conclusion: Involvement of the immune system plays an important role in the pathophysiology of narcolepsy. Current findings further suggest that an increased shift toward T helper 2 cells, as indicated by the presence of allergic conditions, may modulate the severity of the phenotype in childhood narcolepsy, and reduce the prevalence of cataplexy in these patients.

Keywords: narcolepsy; cataplexy; allergy; asthma; sleep latency

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INTRODUCTION

Narcolepsy is a lifelong condition characterized by excessive daytime sleepiness (EDS), cataplexy, hypnagogic hallucinations, sleep paralysis, and disturbed nocturnal sleep patterns. Narcolepsy frequently begins much earlier than it is clinically recognized, and in retrospect it has become apparent that symptoms typically start during childhood.^{1–3} EDS is almost always the presenting symptom of narcolepsy, and is typically manifest as onset of irresistible sleep episodes and sleep attacks. Cataplexy, which consists of partial or complete loss of skeletal muscle tone except for the respiratory and oculomotor muscles, is the most pathognomonic feature of narcolepsy when it is present. Three clinical types of narcolepsy have been described with different clinical features and underlying pathophysiology, and include narcolepsy with cataplexy (NC+), narcolepsy without cataplexy (NC-), and secondary narcolepsy, usually the result of central nervous system injury such as following head trauma, brain tumors, encephalitis, vascular malformations, and Prader-Willi syndrome.^{3,4}

Primary narcolepsy including narcolepsy with (NC+) and without cataplexy (NC-) is a distinct clinical entity with a

different underlying pathophysiology. This disease is secondary to the specific loss of hypothalamic hypocretin (orexin)-producing neurons in the lateral hypothalamus.^{5–8} In a large proportion of patients, the presence of cataplexy is associated with a more severe clinical phenotype. Pediatric cases sometimes fail to present the classic symptoms, and are frequently unrecognized and only diagnosed several years to even decades later in life.^{3,9–12} Indeed, although narcolepsy usually starts in childhood, and despite the fact that significant advances have been made to recognize the pathophysiology of narcolepsy, the condition is frequently not suspected by the primary care physicians leading to erroneous diagnoses.^{3,9–12} Recent work has shown that primary narcolepsy may result from genetic predisposition involving deregulation of immune pathways, as evidenced by association with a specific HLA allele, HLA-DQB1*0602, and by the presence of Tribbles 2-specific antibodies and T-cell subsets, including T helper 2 (Th2) cells.^{7,13–17} Th2 lymphocytes play an important role in the immune system, particularly in the adaptive immune system,^{18,19} and increased activation of these immune cell populations is usually manifest by an increased prevalence of allergic conditions such as rhinitis, atopic dermatitis, and asthma.^{20–22} We hypothesized that the presence of allergic conditions, indicative of increased Th2 balance, may dampen the severity of the phenotype in children with narcolepsy.

SUBJECTS AND METHODS

A retrospective chart review of childhood narcolepsy pediatric patients was conducted at three major pediatric sleep centers: the University of Chicago in Chicago, IL, USA; Chang Gung Memorial Hospital in Taipei, Taiwan; and

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Table 1—Characteristics of children with narcolepsy with and without cataplexy.

	Narcolepsy with Cataplexy (NC+)	Narcolepsy without Cataplexy (NC-)	P
Number of subjects	275	193	
Chicago	116	64	
Taipei	109	122	
Lyon	50	7	
Age onset (y)	12.3 ± 0.3 (6–18)	14.5 ± 0.6 (7–19)	< 0.05
% males	56.0%	54.9%	
BMI (kg/m ²) [% obese]	24.7 ± 0.9 [65.3%]	21.3 ± 0.7 [38.2%]	< 0.01
MSL (min)	2.9 ± 0.3	5.4 ± 0.4	< 0.001
SOREM (#/5 nap MSLT)	3.7 ± 0.2	2.8 ± 0.3	< 0.01
Asthma (+)	13	39	< 0.0001
Allergic rhinitis (+)	37	69	< 0.0001
Atopic dermatitis (+)	17	23	> 0.05
Allergy total (+)	58	94	< 0.0001
> 1 allergic condition	6	33	< 0.001

BMI, body mass index; MSLT, multiple sleep latency test; SOREM, sleep onset latency rapid eye movement.

Hôpital Femme-Mère-Enfant in Bron, France. The study was approved by the University of Chicago Human Research Committee (Protocol IRB12-1963-CR002), as well as by the Human Research Ethical Committees of both Chang Gung Memorial Hospital and Hôpital Femme-Mère-Enfant. Patients were divided into NC- and NC+. Demographics, polysomnographic and multiple sleep latency test (MSLT) data were extracted from individual medical records, and tabulated into a deidentified database, and subsequently reviewed and analyzed. We should note that only children who had an overnight polysomnographic evaluation followed by a five-nap MSLT were included.²³ In addition, extraction of available medical history information on the presence of allergic diseases, such as allergic rhinitis, atopic dermatitis, and asthma was also performed. If mention of any of the Th2-related clinical diagnoses, such as aforementioned allergic diseases, was not present in the medical record, these conditions were treated as being absent.

Descriptive statistics and χ -square tests, followed by Fisher exact *post hoc* corrections when appropriate, were performed for comparisons of NC- and NC+ cases using MedCalc Statistical Software version 14.10.2 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2014). A P value of < 0.05 was set as representing statistical significance.

RESULTS

A total of 468 pediatric narcolepsy cases were identified, with 193 children in the NC- group and 275 patients in the NC+ group. Mean age at diagnosis varied greatly, but occurred at significantly younger ages in NC+ compared to NC- children (Table 1). Although there were no differences in sex distribution among the two groups, body mass index (BMI) was significantly higher in NC+ affected patients, who also exhibited shorter mean sleep latencies and higher number of sleep onset rapid eye movement (SOREM) events during the MSLT (Table 1). Evidence of increased frequency of allergic conditions indicative of a shift to Th2 balance was present in 48.7% of NC- patients (94/193) when compared to 21.1% of NC+

patients (58/275; $P < 0.0001$). Notably, differences in asthma ($P < 0.0001$) and allergic rhinitis ($P < 0.0001$) emerged, but not for atopic dermatitis (Table 1; $P > 0.05$).

In addition, in children with narcolepsy and cataplexy who had positive responses for the presence of allergies, mean sleep latencies during MSLT were significantly longer (4.0 ± 0.4 min) than in NC+ children without reported allergies (2.7 ± 0.3 min; $P < 0.02$). Similarly, the number of SOREM during a five-nap opportunity MSLT was lower in NC+ patients with allergies (3.1 ± 0.2) when compared to NC+ patients without reported allergies (3.8 ± 0.2 , $P < 0.02$).

DISCUSSION

This retrospective study emanating from three different pediatric sleep centers revealed that the presence of allergic conditions such as allergic rhinitis, atopic dermatitis, and asthma, which are indicative of increased Th2 balance, may dampen the severity of the phenotype in children with narcolepsy, and reduce the prevalence of cataplexy.

Before discussing the potential implications of our findings, some of the limitations inherent to this study merit mention. First and foremost, this was a retrospective study, such that the information of allergic conditions was not systematically investigated, as would be the case in prospective study design. Second, the diagnosis of any of the allergic conditions relied on parental report rather than be based on objective diagnostic criteria. However, it is highly unlikely that reporting of these coexisting conditions would be biased by the presence or absence of narcolepsy, such that the validity of current findings is inferred. Third, there were significant differences in the distribution of NC+ and NC- cases across the three participating centers. Such differences may reflect inhomogeneities in case classification across the centers, or more likely are explained by the absence of consistent and systematic exploration of cerebrospinal fluid hypocretin-1 levels as well as of the HLA DQB1*06:02 allele. Future prospective studies should definitely incorporate such laboratory measures in the classification of narcolepsy subtypes.

Our study confirms and expands on some phenotypic differences that are detectable in NC+ and NC− children. First, and as previously indicated, the presence of cataplexy was more frequent than its absence in this pediatric cohort. Such divergence may indicate true differences in the cataplectic phenotype, or may reflect the earlier referral and diagnosis of more severely affected children. It is also possible that country differences in the prevalence of cataplexy may exist as suggested by the different prevalence rates across the three centers (Table 1). However, systematic exploration of narcolepsy subtypes using laboratory-based attributes will have to guide future studies. Second, significantly elevated BMI and increased prevalence of obesity have been previously noted in children with narcolepsy and cataplexy, further affecting on quality of life, and the current study found similar differences in a much larger cohort.^{24–26} We should remark that in the context of obese children with asthma, higher Th1 expression is anticipated, such that the more prominent propensity toward allergic diseases in the milder condition is intriguing.²⁷ Third, we also identified shorter sleep latencies in NC+ as well as increased frequency of SOREM episodes during the MSLT, thereby attesting to the increased severity of the narcolepsy condition among NC+ children. Notably, even among children with cataplexy, the presence of reported allergies was associated with less severe sleep propensity on MSLT and reduced number of SOREM episodes.

It is now well accepted that an autoimmune basis for hypocretin cell loss is present in narcolepsy in association with selected HLA alleles and T cell receptor (TCR) polymorphisms.^{16–19,28} It is also reported that there is an immunoglobulin (Ig) abnormality in narcolepsy and other hypersomnia patients supporting the immune basis of this disease.²⁹ Several studies have shown that children following exposure to *Streptococcus pyogenes* or H1N1 vaccine may increase rates of narcolepsy onset by activation of T cells leading destruction of hypocretin neurons.^{29–33} Most cytotoxic T cells express TCRs that can recognize a specific antigen produced in viral infections. After the T cells become activated, they have a cytotoxic role within the immune system and have the ability to make some cytokines to damage hypocretin cells.³⁴ T helper cells play an important role in the immune system, particularly in the adaptive immune system. In this context, Th1 cells subserve defense mechanisms aimed against intracellular bacteria and protozoa, and Th1 over activation against autoantigens underlies type 4 delayed-type hypersensitivity, such as that seen in tuberculin reaction or type 1 diabetes. Th2 cellular hyperactivation against autoantigens will cause type I IgE-mediated allergy and hypersensitivity, such as allergic rhinitis, atopic dermatitis, and asthma.^{22–24,35} Increased frequency of allergic conditions indicative of a shift to Th2 balance was clearly present in NC− patients when compared to the NC+ group in our study. We are aware of two previously published studies whereby findings would suggest that a preferentially enhanced Th2 phenotype might alter the clinical phenotype of narcolepsy.^{18,36} Our findings therefore suggest that the underlying presence of an increased shift in the Th1:Th2 balance toward Th2 as indicated by the presence of allergic conditions may modulate the severity of the phenotype in childhood narcolepsy, reduce the prevalence of cataplexy in these patients, and

potentially dampen the severity of the disorder even among those patients with cataplexy. Prospective multicenter studies exploring this immunophenotype, along with potential associations with HLA markers such as DQB1*06:02, appear warranted.

DISCLOSURE STATEMENT

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