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Childhood Onset Narcolepsy Cataplexy—More Than Just a Sleep Disorder

Commentary on Poli et al. High prevalence of precocious puberty and obesity in childhood narcolepsy with cataplexy. SLEEP 2013;36:175-181.

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Childhood onset narcolepsy-cataplexy (NC) is considered a prototypic sleep disorder with well-defined clinical features of profound daytime sleepiness, cataplexy and nocturnal sleep disruption that occur in conjunction with a deficiency of central nervous system hypocretin (orexin). Individuals who possess the histocompatibility antigen DQB1*0602 are more susceptible to developing NC.

Over the past two decades, there have been anecdotal studies linking NC of childhood to obesity and becoming overweight.[1-3] The association between childhood onset NC with obesity has however not been definitively established. In this issue of *SLEEP*, Poli and colleagues present the results of a systematic investigation of a possible link between NC and alterations in neuroendocrine function.[4] They evaluated 42 children with NC (22 boys, mean age 11.4 ± 3.5) and 52 age-matched obese controls. In the NC group, the mean age at onset of the first symptom of excessive sleepiness or cataplexy was 8.7 ± 2.8 years. We do not know the prior medication history in the NC patients or the obese controls that might have impacted weight gain. The diagnosis of NC was, however, unequivocal—it was established on the basis of clinical history combined with nocturnal polysomnogram and the multiple sleep latency test, and low to absent levels of cerebrospinal fluid hypocretin. Obesity was defined as body mass index (BMI) greater than the 97th percentile for age and gender, and overweight as BMI between the 85th and 97th percentile. Normal weight was defined as BMI less than the 85th percentile. Blood samples were collected for lipid profile, C-reactive protein, and oral glucose tolerance test.

The responses of glucose and insulin to the oral glucose load were calculated by Poli et al. using the area under the curve. NC children had presented at onset with a mean BMI of 22.1 ± 4.3. An impressive finding is that at initial presentation, 31/42 (74%) of NC children met criteria for being overweight or obese. In 60% of these subjects, the increase in weight was temporally close to onset of the NC symptoms. A logistic regression analysis was used to compare NC without obesity (N = 11) and NC with obesity (N = 31). The nocturnal polysomnogram and MSLT findings were similar in these two groups. The salient difference, however, was that the age of onset of symptoms occurred significantly earlier in the obese NC patients (mean age 8.2 ± 3.4 years) than in the non-obese NC patients (mean age 11.8 ± 0.5 years; P = 0.03). Adults with NC also show this predisposition to weight gain.[1,5,6]

We do not know precisely why NC children show this tendency for obesity. In health, orexin (hypocretin) stimulates neuropeptide Y, which in turn stimulates appetite.[7] Down-regulation of this pathway should therefore lead to hypophagia. If we were dealing with a straightforward scenario, hypophagia would have been associated with either normal or low BMI. But how do we reconcile *obesity* seen at onset of NC with the underlying hypocretin deficiency? One explanation is that there is decreased basal metabolism in sleepy-sedentary individuals, with decreased overall energy expenditure. This is supported by the fact that transgenic mice with selective ablation of orexin-containing neurons show a phenotype similar to human narcolepsy, along with obesity and decreased locomotor activity.[8] Obesity seems to develop in these mutant mice despite eating 30% less than their wild-type littermates.[8] Another possible explanation might be binge eating, which is common in NC.[2,9] Narcolepsy patients seem to score higher on the Binge Eating Scale as compared to controls.[9] Furthermore, hypocretin deficiency may disrupt activity of the mesolimbic dopaminergic system, which plays a role in the modulation of *wanting food*.[7,10] On the other hand, the pleasurable or hedonic aspects of *liking food* seem to be regulated by the mu-opiate system.[10] One might ask if obese NC children consume more food simply out of a reflexive desire to do so, or do they eat more because they gain pleasure from it. We speculate it is the former mechanism. Limbic dysfunction in the form of emotional dysregulation is also common in childhood narcolepsy.[2] It would be interesting to assess whether children with NC who have more emotional and behavioral problems are more likely to gain excessive weight. We don't also know much about the trajectory of weight gain in childhood NC—does it continue at the same pace over time, or does it level off? Clinical experience would suggest the latter course, but this needs to be established with longitudinal studies.

As BMI in relatives of NC patients seems elevated relative to the general population,[6] it is possible that the obesity in NC patients partially reflects a trait inherent to NC children and relatives. The study by Poli et al.[4] revealed a high prevalence of obesity, type 2 diabetes mellitus, myocardial infarction, and stroke in relatives of NC patients, but did not compare this with relatives of the obese controls. Unlike what has been shown in adults, Poli et al. did not find differences in the fasting glucose, lipids, and glucose and insulin responses to an oral glucose tolerance test between patients with NC and controls. It is possible that the shorter duration of obesity in NC children compared to NC adults may account for this lack of association between NC and metabolic abnormalities in this population. Another feature

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that was not assessed and merits further investigation is the possibility of an association between abdominal obesity and NC during childhood, as has been demonstrated in adults with NC.[5]

Presently, management strategies are similar in NC children who are obese and those who are not. Should they be different? Wu et al.[11] have found that in dogs with narcolepsy-cataplexy, playful motor activity in the yard, but not actual running on a treadmill, led to rise in cerebrospinal fluid hypocretin. They suggest that emotional aspects of play generated by the limbic system influenced the yard play paradigm. Are our children with NC having fun? Might play therapy have a role in the management of childhood NC? Once again, this is an issue begging for study.

The second important finding of the study of Poli et al. is the possible link between childhood NC and precocious puberty (PP). The clinical manifestations of PP include premature breast and pubic/axillary hair development. Onset occurs before the age of 8 years in girls and 9 years in boys. The pubertal status was assessed by Poli et al. using the Tanner visual score that was combined, when appropriate, with serum gonadotropic hormone stimulation curve, X-ray of the non-dominant wrist for determining bone age/chronological age ratio, and head magnetic resonance imaging of the hypothalamus-pituitary region. Seventeen percent of the NC patients showed PP, as compared to only 1.9% of the obese controls. It would have been helpful to learn what proportion of controls had endogenous versus exogenous obesity, because PP is more common in girls with exogenous obesity. The development of PP was predicted by younger age at onset of NC symptoms, but not by obesity/overweight or other factors. It will be helpful to learn whether on longitudinal follow up, NC subjects with PP show a different clinical course from those without PP. The association of childhood NC with precocious puberty merits further investigation into the role of hypocretin in development of puberty.

The key issue is that childhood NC is a complex, multisystem health condition. It is more than just a sleep disorder. Involvement of the general pediatrician, endocrinologist, nutrition specialist, play therapist, and adolescent gynecologist in management also seems indicated for comprehensive management.

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DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.

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