Anthropometric and endocrine features in children and adolescents with Type 1 Narcolepsy

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Background:
Type 1 narcolepsy (NT1) mainly arises during childhood/adolescence with hypsomnolence and cataplexy as heralding symptoms. Hypocretin deficiency is typical of NT1 and affects not only sleep regulation, but also the neuroendocrine system with abnormalities in energy balance, feeding behavior, glucose metabolism and in the modulation of hypothalamic-pituitary axis. NT1 patients frequently suffer from obesity, type 2 diabetes and central precocious puberty (PP).

Treatment studies for NT1 are lacking in pediatric population and currently the same pharmacological therapies are used both for adults and children (off-label in the latter). Although the association between obesity and NT1 has been observed in pediatric patients, the time gap between NT1 onset and weight gain, as well as the possible effects of treatment on weight loss, have never been addressed.

Methods:

Diagnosis: each patient underwent polysomnography followed by multiple sleep latency test (MSLT), Pediatric Daytime Sleepiness Scale (PDSS), HLA DQB1*06:02 genotyping, brain MRI, and, whenever possible, cerebrospinal fluid hypocretin-1 (CSF hcrt-1) determination.

Assessments: we collected anthropometric (height, body mass index (BMI) z-scores), pubertal (Tanner scores), metabolic (Fasting blood glucose, basal insulin, total/low-density lipoprotein (LDL) cholesterol, triglycerides, oral glucose tolerance test (OGTT), anti-streptolysin O (ASO) titer) and endocrine (TSH, F14, F13, ACTH, Cortisol, stimulated GH peak) data from 72 NT1 patients (35 boys, mean age 11.18 ± 3.13 years) at diagnosis and all premorbid available anthropometric parameters of patients from their pediatrician files (n=30). Central PP was confirmed when: 1) Tanner scale level >2 before the age of 8 years in girls or 9 years in boys; 2) plasma LH levels >5 mIU/ml after GnRH test and 3) normal brain MRI. Treatment: the need for behavioral and off-label pharmacological treatment with Sodium Oxybate monotherapy (as first-line approach chosen to address sleepiness, cataplexy and disrupted nocturnal sleep), or modafinil/± venlafaxine (as second-line approach designated to manage daytime symptoms) were discussed with the family and proposed for each patient. Modafinil was also added if hypsomnolence persisted after SO titration.

Results:

Mean age at first symptom (either somnolence or cataplexy) onset was 8.68±2.50 y, mean delay between NT1 onset and the diagnosis was 5.56 of the sample had previous wrong diagnoses. No thyroid and adrenal hormonal alterations were detected. We detected a high prevalence of overweight (29.2%), obesity (25%), metabolic syndrome (18.8%), and precocious puberty (16.1%), but no signs of linear growth alterations at the diagnosis. Eleven PP children underwent GnRH analogous treatment. Comparing children with and without PP, children with PP received more frequently wrong diagnoses (Table 1). Differences between overweight/obese cases and normal-weight cohort are shown in Table 2. The overweight/obese children showed worse MSLT performances than the ones with normal weight. According to anthropometric records, weight gain started closely after NT1 onset. At 1-year follow-up reasessment sodium oxybate treatment was associated with a significant BMI z-score reduction (-1.29±0.30, p<0.0005) after adjusting parameter for baseline age, sex, and obesity, and BMI (Fig.1). Patients without SO showed comparable BMI z-scores at baseline and at follow-up (Table 3). Correcting for baseline features (Model 1: age, sex, BMI z-score, disease duration), and also for sleepiness level (Model 2; PDSS), only SO monotherapy maintained a significant impact (Table 4, Figure 2).

Conclusions:

◆ Childhood NT1 has been associated with endocrine disorders like obesity and precocious puberty. These comorbidities may challenge the disease, requiring tailored treatments and call for a multidisciplinary approach.◆ Our study not only confirmed the high occurrence of weight and pubertal alterations in NT1, but also showed that clinically significant weight gain begins closely after disease onset thus suggesting that obesity is an ancillary NT1 symptom.◆ At one-year follow-up sodium oxybate therapy reversed weight gain in overweight and obese NT1 children.◆ Circadian profile of hormonal secretion with sleep-wake cycle may be helpful in finding any correlates between hormonal changes, obesity and precocious puberty in NT1.

References and note:


Nothing to disclose.

* The present study has been accepted as original paper in the J Clin Sleep Med, on August 2nd 2016.