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 hypersomnolence 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.

Objectives:

In our study we compared the anthropometric, metabolic and endocrine data collected in a large pediatric NT1 cohort before disease onset, at diagnosis, and at 1-year follow-up.

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, weight, body mass index (BMI) z-scores), pubertal (Tanner scores), metabolic (Fasting blood glucose, basal insulin, total/ high-density (HDL)/low-density lipoprotein (LDL) cholesterol, triglycerides, oral glucose tolerance test (OGTT), anti-streptolysin O (ASO) titer) and endocrine (TSH, Ft4, Ft3, 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 hypersomnolence persisted after SO titration.

Table 1

	NT1 with PP (n=12)	NT1 without PP (n=60)	P value
Sex, male %	50	48.3	NS
Age at observation, y	8.68 ± 0.84	11.68 ± 3.18	0.001
Age at onset of first symptom (EDS or cataplexy), y	6.64 ± 1.12	9.09 ± 2.51	0.001
Age at diagnosis, y	8.27 ± 0.84	10.80 ± 2.91	0.001
Disease duration, y	2.18 ± 1.59	2.19 ± 2.38	NS
Diagnostic delay, y	1.62 ± 1.32	1.71 ± 2.27	NS
Patients with wrong diagnosis, %	91.7	49.1	0.007
Medical examination (without diagnosis), n	1.58 ± 1.31	1.04 ± 1.36	NS
Hospital admission (without diagnosis), n	1.17 ± 1.34	0.77 ± 1.15	NS
CSF hypocretin 1, pg/ml (61)	100	93.3	NS
HLA DQB1*06:02, %	16.24 ± 19.99	25.92 ± 30.66	NS
Obesity familial predisposition, %	16.7	26.4	NS
Dyslipidemia familial predisposition, %	16.7	32.1	NS
Type 2 diabetes familial predisposition, %	41.7	28.3	NS
Hypertension familial predisposition,%	41.7	64.2	NS
Onset before PP cut-off, %	100	48.3	0.001
Diagnosis before PP cut-off, %	58.3	21.7	0.01
Overweight/obese, %	41.7/25	26.7/25	NS
Body mass index	21.06 ± 2.87	23.52 ± 5.61	NS
Metabolic syndrome, %	33.3	16.4	NS
Systolic blood pressure, mm Hg	106.86 ± 11.52	108.84 ± 13.32	NS
Diastolic blood pressure, mm Hg	63.43 ± 8.26	66.65 ± 10.60	NS
HDL cholesterol, mg/dL	51.50 ± 13.06	55.43 ± 14.79	NS
LDL cholesterol, mg/dL	103.00 ± 20.07	100.10 ± 28.94	NS
Glucose AUC, mg/dL	13678.50 ± 2041.60	14060.74 ± 2093.13	NS
Insuline AUC, µU/mL	7069.50 ± 3140.02	10205.97 ± 8050.16	NS
Fasting plasma glucose, mg/dL	78.17 ± 6.22	78.28 ± 7.30	NS
Fasting plasma insuline, µU/mL	11.47 ± 5.61	13.38 ± 10.81	NS
Inhaler allergy, %	25	20	NS
Food allergy, %	16.7	10	NS
Atopic dermatitis,%	0	9.3	NS
ASO ≥ 200 IU/ml, %	75	64.7	NS
Positive throat culture for GAS, %	33.3	22.2	NS

Values are indicated as mean ± standard deviation or number/number. ASO, anti-streptolysin O; AUC, area under the curve; CSF, cerebrospinal fluid; GAS, Group A Streptococcus; HLA, human leukocyte antigen; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NT1, Type 1 Narcolepsy; n, number; PP, precocious puberty; y, year.

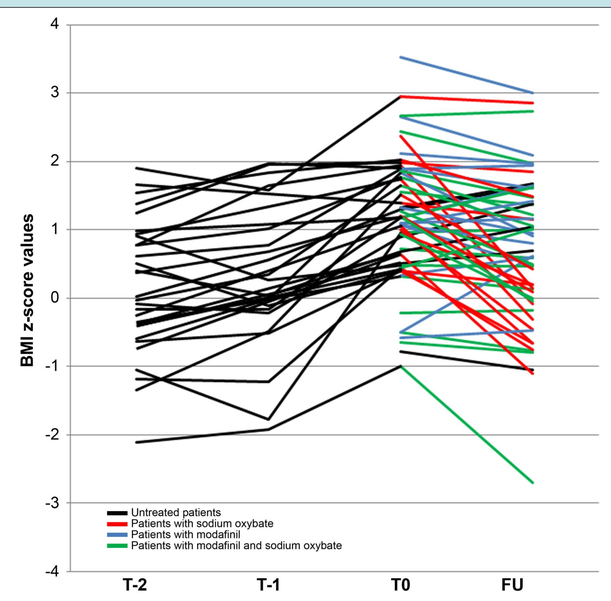

Figure 1: BMI z-score values before NT1 onset and after one year of therapy.
Individual evolution of BMI z scores before diagnosis (T-2, T-1), at diagnosis (T0), and at 1-year follow up (FU). Different treatments (labeled by color codes) were used after diagnosis with sodium oxybate inducing a significant reduction of BMI z score.

Table 2

	NT1 with overweight-obesity (n=39)	NT1 without overweight-obesity (n=33)	P value
Sex, male %	53.8	42.4	NS
Age at observation, Y	11.08 ± 2.98	11.29 ± 3.34	NS
Age at onset of first symptom, y	8.69 ± 2.51	8.66 ± 2.54	NS
Age at diagnosis, y	10.33 ± 2.53	10.44 ± 3.21	NS
Disease duration, y	2.20 ± 2.01	2.18 ± 2.56	NS
Diagnosis delay, y	1.61 ± 1.87	1.80 ± 2.44	NS
Wrong diagnosis, %	57.9	54.8	NS
Medical examination without diagnosis, n	1.27 ± 1.45	0.97 ± 1.25	NS
Hospital admisssion without diagnosis, n	0.76 ± 1.24	0.94 ± 1.12	NS
HLA DQB1*06:02, %	92.3	97	NS
CSF hypocretin 1, pg/mL	25.11 ± 26.48	22.63 ± 32.34	NS
Obesity familial predisposition,%	21.2	28.1	NS
Dyslipidemia familial predisposition,%	27.3	31.3	NS
Type 2 diabetes familial predisposition,%	27.3	34.4	NS
Hypertension familial predisposition,%	51.5	68.8	NS
Body mass index, Kg/m²	26.11 ± 5.15	19.58 ± 2.69	0
Age at weight gain, y	8.57 ± 2.55	9.12 ± 2.43	NS
Metabolic syndrome, %	28.6	6.9	0.027
Precocious Puberty, %	20.5	12.1	NS
Onset before PP cut-off, %	56.4	57.6	NS
Diagnosis before PP cut-off, %	23.1	33.3	NS
Systolic blood pressure, mm Hg	114.14 ± 10.76	103.04 ± 12.89	0.001
Diastolic blood pressure, mm Hg	69.21 ± 10.60	63.29 ± 9.31	0.046
HDL cholesterol, mg/dL	50.50 ± 13.48	59.70 ± 14.29	0.012
LDL cholesterol, mg/dL	103.75 ± 33.99	97.30 ± 22.47	NS
Glucose AUC, mg/dL	14228.71 ± 2334.52	13713.46 ± 1708.79	NS
Insuline AUC, µU/mL	11903.6 ± 9313.82	7154.89 ± 3469.77	0.015
Fasting plasma glucose, mg/dL	78.81 ± 8.02	77.64 ± 5.92	NS
Fasting plasma insuline, µU/mL	15.89 ± 13.27	10.39 ± 4.18	NS
Inhalers allergy, %	15.4	27.3	NS
Food allergy, %	10.3	12.1	NS
Atopic dermatitis,%	8.3	6.7	NS
ASO ≥ 200 IU/ml, %	60.5	76	NS
Positive throat colture for GAS, %	25.9	22.2	NS

Values are indicated as mean ± standard deviation or number/number. ASO, anti-streptolysin O; AUC, area under the curve; CSF, cerebrospinal fluid; GAS, Group A Streptococcus; HLA, human leukocyte; antigen; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NT1, Type 1 Narcolepsy; n, number; PP, precocious puberty; y, year.

Table 3

	Group 1 (n=35)			Group 2 (n=21)		
	T0	T1	Wilcoxon Test	T0	T1	Wilcoxon Test
	M ± SD	M ± SD	P-Value	M ± SD	M ± SD	P-Value
Age at observation, y	11.27 ± 2.96	12.18 ± 2.98	0	10.1 ± 2.39	11.01 ± 2.38	0.000161
Height, cm	148.83 ± 16.6	152.5 ± 15.38	0.000013	142.81 ± 14.5	149.51 ± 13.26	0.000087
Weight, kg	55.06 ± 22.23	52.67 ± 19.52	0.168587	46.55 ± 16.34	51.5 ± 15.03	0.000718
BMI	23.99 ± 5.84	21.99 ± 5.53	0.000415	22.24 ± 4.45	22.59 ± 3.47	0.305198
Height z-score	0.68 ± 0.93	0.39 ± 1.04	0.053268	0.59 ± 0.96	0.79 ± 1.16	0.476136
Weight z-score	1.29 ± 1.05	0.63 ± 1.16	0.000007	1.03 ± 0.77	1.08 ± 0.84	0.590064
BMI z-score	1.19 ± 1	0.5 ± 1.23	0.000007	1.02 ± 0.9	1.03 ± 0.76	0.986134

BMI, body mass index; M, mean; SD standard deviation; T0, time at diagnosis, T1, time corresponding to

Table 4

	Model 1			*Model 2*		
	SO	Modafinil	SO+Modafinil	SO	Modafinil	SO+Modafinil
Coefficient	-1.32	-0.33	-0.56	-1.28	-0.29	-0.54
Standard Error	0.3	0.29	0.28	0.3	0.29	0.28
P-Value	0	0.267	0.05	0	0.322	0.061
95% CI: lower	-1.91	-0.91	-1.12	-1.89	-0.89	-1.1
95% CI: upper	-0.72	0.25	0	-0.69	0.29	0.02

CI, confidence interval; SO, Sodium Oxybate

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 1.70±2.13 y, and 56.5% 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 reassessment 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, sleepiness, 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 1)**.

Conclusions:

♣ Childhood NT1 has been associated with endocrine disorders like obesity and precocious puberty. These comorbidities may challenge the diagnosis, require 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*

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Nothing to disclose

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