Narcolepsy, metabolic syndrome and obstructive sleep apnea syndrome as the causes of hypersomnia in children. Report of three cases

Wasilewska J, Jarocka-Cyrta E, Kaczmarski M*

III Department of Pediatrics, Medical University of Białystok, Poland

Abstract

Hypersomnia is a significant problem in about 5% of the general population. We discussed clinical aspects in 3 patients with hypersomnia diagnosed in our sleep laboratory. All of the patients, both obese and non-obese, presented abnormal oral glucose tolerance test (OGTT) and plasma insulin level. (1) A 17-year-old girl (BMI=20.3) with a two-year history of daytime sleep attacks (e.g. on the bus, in a classroom, while reading or eating), followed by refreshed feeling. The first symptoms appeared 2 years after spine injury (L2-L3). Total sleep time was >98 perc. The diagnosis of narcolepsy was confirmed by sleep-onset REM periods in 3 of 4 daytime naps (positive Multiple Sleep Latency Tests) and HLA-DQB1 (alleles *0201,*0602). (2) A 16-year-old girl (BMI=32.4) with a history of increased sleepiness (Epworth Sleepiness Scale score=13), not refreshing naps, along with BMI increase, since the age of 13. The metabolic syndrome was diagnosed based on the presence of obesity, hypercholesterolemia (CH=240 mg/dl, HDL-CH=49 mg/dl) and insulin resistance (HOMA index =6.75, hyperinsulinemia – 367 μU/mL at 30'after OGTT). (3) A 6-year-old boy (BMI=16.0) with a 10-month history of daytime sleep attacks and postprandial sleepiness; nocturnal enuresis, high simple carbohydrate diet, low plasma insulin level after OGTT. Diagnosis of food-related hypersomnia and obstructive sleep apnea was confirmed when the boy recovered after his nutrition habits had been changed, which resulted in decreased respiratory disturbance index (RDI) from 17.7/h in October 2005 to 2.9/h in October 2006. Within that time his parents did not observe any episodes of daytime sleepiness, irritability or nocturnal enuresis.

* CORRESPONDING AUTHOR:
III Department of Pediatrics, Medical University of Białystok,
15-274 Białystok, ul. J. Waszyngtona 17, Poland
Fax: +48 85 7423841
e-mail: jolanta@amb.edu.pl (Jolanta Wasilewska)

Received 22.03.2007 Accepted 10.04.2007

Key words: hypersomnia, narcolepsy, metabolic syndrome, sleep apnea, polysomnography.

Introduction

Pediatric sleep disorders are common, affecting approximately 25% to 40% of children and adolescents [1]. Excessive daytime sleepiness (EDS) is a significant problem in about 5% of the general population, being common but often unrecognized [2]. It typically affects adolescents and young adults, frequently as a consequence of adolescent's sleep habits – a tendency to delay the timing of sleep, a decrease in total sleep time, and an increase in daytime sleepiness [3]. Hypersomnia can be a symptom of other diseases or other sleep disorders, such as narcolepsy or sleep apnea, but it may also reflect poor sleep hygiene [4]. The prevalence of narcolepsy has been calculated at about 0.04%, with the peak onset of symptoms occurring in adolescence [2]. The present report describes three patients with daytime sleepiness of a different origin, but all associated with disregulation of glucose homeostasis.

Case Reports

Between October 2005 and April 2006, three patients with hypersomnia were admitted to the III Department of Pediatrics, Medical University of Białystok. A detailed history, sleep questionnaire (*Tab. 1*), physical examination (*Tab. 2*), laboratory tests (*Tab. 3*), oral glucose tolerance test (OGTT) (*Fig. 1*), blood insulin curve after oral glucose intake (*Fig. 2*) and a sleep assessment involving polysomnography in sleep laboratory (*Tab. 4*) were performed in all 3 patients. Family history of sleep disturbances was negative in all the children.

Table 1. **Sleep questionnaire in three patients with different origin of hypersomnia**

History of sleep	Narcolepsy	Metabolic syndrome	Obstructive sleep apnea and food-related hypersomnia
No of naps/day	5-15	3-6	0-5
Type of napping	Paroxysmal sleep attacks, Not related to meal	Daytime Sleepiness, often postprandial	Sleep attacks and postprandial sleepiness
Daytime sleep (h)	5	2	1-2
Nighttime sleep (h)	9	10	11
Nighttime sleep (%)*	90-98	90-98	50-75
Total sleep time (h)	14	12	12.5
Total sleep time (%)*	>98	>98	90-98
Snoring	7/week	7/week	1/week
Nocturnal enuresis	no	no	6 /week
Nightmares	1/week	no	no
Myoclonus at sleep onset	3/week	2/mo	no
Family history of sleep disturbances	negative	negative	negative
Night sleep onset	1-2 min	>5 min	<5 min

* Iglowstein I et al. Pediatrics 2003, 111: 302-7 [19]

Table 2. **Physical examination in three patients with different origin of hypersomnia**

Physical examination	Narcolepsy	Metabolic syndrome	Obstructive sleep apnea and food-related hypersomnia
Age	17 y	16 y 9 mo	6 y 8 mo
Gender	F	F	M
BMI (kg/cm^2)	20.3	32.4	16.0
BMI percentile for age and sex*	42	97	64
Cole's Index	101.54%	161.73%	105.76%
WHR (waist-to-hip ratio)	0.92	0.87	0.87
Neck circumference (cm)	35	39	29
Blood pressure mmHg	98/54	108/65	106/65
ORL examination	normal	normal	normal

* BMI according to Child and Teen Calculator (www. apps.nccd.cdc.gov)

Table 3. **Laboratory tests in three patients with different origin of hypersomnia**

Laboratory tests and diabetes symptoms	Narcolepsy	Metabolic syndrome	Obstructive sleep apnea and food-related hypersomnia
Diabetes polytriad:			
Polyuria	no	no	no
Polydypsia	yes	yes	yes
Polyphagia	no	yes	no
Lipemia	no	yes	no
Fasting glucose (mg/dl)	88	86	88
Fasting insulin (uIU/ml)	9.3	31.8 (52.1)	3.3
Fasting Insulin-to-Fasting Glucose ratio	0.11	0.37	0.04
HOMA-IR#	2.02	6.75	0.73
Glucosuria	negative	negative	negative
Cholesterol (mg/dl)	136	240	209
HDL-cholesterol (mg/dl)	48	49	57
Triglyceride (mg/dl)	91	130	106
Uric acid (mg/dl)	3.11	6.1	3.6
HLA	DQB1*0201,*0602	Not studied	Not studied

#HOMA index – homeostasis model assessment index

Figure 1. **Oral Glucose Tolerance Test in three patients with hypersomnia**

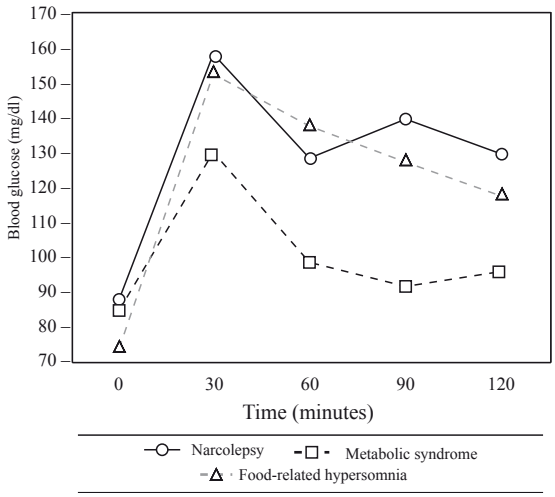

Figure 2. **Blood insulin in three patients with hypersomnia**

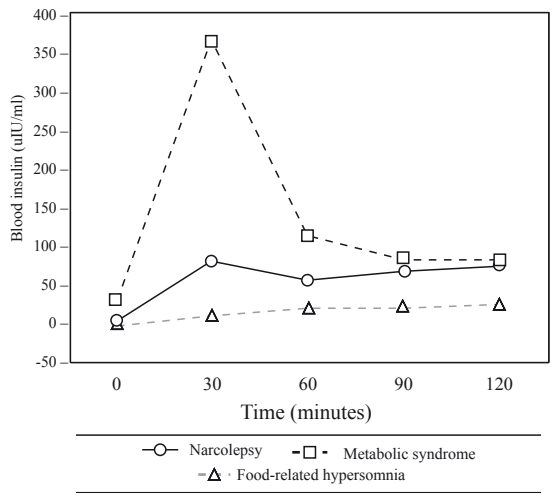

Table 4. **Polysomnnographic findings in three patients with different origin of hypersomnia**

Polysomnographic data	Narcolepsy	Metabolic syndrome	Obstructive sleep apnea and food-related hypersomnia	
Date	Oct. 2005	April 2006	Oct. 2005	Oct. 2006
RDI / hour	4.7	7.1	17.7	2.9
Central apnea index /h	2.2	3.7	2.9	1.0
Central apnea total time (min)	3.08	7.21	5.56	4.81
Central apnea % of sleep	0.3	0.7	0.6	0.5
Obstructive apnea index /h	1.3	1.1	6.2	1.3
Hypopnea index /h	1.0	1.4	9.8	0.6
Oximetry – average (%)	97	95	96	96
FRT(%)*	1.6	8.9	not studied	not studied
Body temperature at 17 p.m. (°C)	36.4	36.2	36.4	36.3

*Fractional Reflux Time – marker of acid gastroesophageal reflux =% time pH<4.0 in pH-metry

Case 1

History A 17-year-old girl with a history of spine injury (L2-L3), with negative radiological findings at the age of 13, was taken to hospital due to her two-year history of daytime sleep attacks lasting from a few seconds to half an hour (e.g. on the bus, in a classroom, while reading or eating) followed by refreshed feeling, ESS score =15. Nocturnal sleep with primary snoring was disturbed by nightmares. Total sleep time was elevated above 98 percentile. She had been previously hospitalized in the Department of Neurology where the first suspicion of narcolepsy was made and other neurological diseases were excluded. Her diet contained circa 1,500-3,000 ml of industrial fruit juice per day. Her main psychopathological problem was low self-esteem and anxiety.

Physical examination The physical examination was non-contributory, BMI=20.3 kg/m^2.

Diagnostic tests The oral glucose tolerance test revealed high levels of blood glucose at 120 min of OGTT and normal serum level of insulin after glucose intake (*Fig. 1, Fig. 2*). Total body and lumbar spine Body Mass Density (using DEXA-Lunar) were normal: 1.117 g/cm^2 (50-75 percentile) and 1.258 g/cm^2 (>75 percentile).

Polysomnographic findings The diagnosis of narcolepsy (without cataplexy) was confirmed by polysomnographic findings and sleep-onset rapid eye movement (REM) periods in daytime naps [5]. The Multiple Sleep Latency Test (MSLT) was performed after overnight polysomnography, consisting of four opportunities to nap at two-hour intervals; the mean sleep latency was 3.5 minutes and she had three sleep-onset REM episodes in this test**.** She was HLA class II positive for DQB1 (alleles *0201,*0602).

Case 2

History A 16-year-old girl with a two-year history of increased daytime sleepiness, not refreshing naps, along with a rise in BMI (since she was 13), was admitted to hospital due to suspected narcolepsy. The findings revealed: Epworth Sleepiness Scale (ESS) score =13. Her diet contained circa 1 000 ml of cow's milk, circa 1 000 ml of fruit juice per day and sweets several times a day. Hyperphagia was also observed by nurses

in the course of hospitalization. Her major daily life problem was low self-esteem, difficulty with mood regulation, memory impairment, learning difficulties and familial dysfunction.

Physical examination In physical examination, she presented with a typical obesity profile (BMI=32.4 kg/m^2) (*Tab. 2*).

Diagnostic tests The diagnosis of metabolic syndrome was based on the nutrition state (presence of obesity) and metabolic findings: total cholesterol =240 mg/dl, HDL-cholesterol =49 mg/dl, euglycemic hyperinsulinemia (367 µU/mL at 30' after glucose intake) (*Fig. 2*) and insulin resistance (HOMA-index =6.75).

Polysomnographic findings Elevated RDI (7.1/h) mainly due to the elevated central apnea index (3.7/h) and acid gastroesophageal reflux (FRT =8.9%).

Case 3

History A 6-year-old eutrophic boy was hospitalized for the evaluation of daytime sleep attacks (once or twice a week, e.g. during playing or sitting on stairs) and postprandial sleepiness of 10-month duration. Total sleep time was 90-98 percentile; nocturnal enuresis (6/week) without nephrological abnormalities. History of gastroesophageal reflux and allergic rhinitis (serum IgE anti-weed antibodies – 5 class RAST) manifested by mild clinical symptoms in late summer. His diet contained circa 500 ml of cow's milk, circa 500-1 000 ml of sweet fruit juice per day and sweets several times a day. He had low appetite for non-sweet foods. He's behavior was characterized by irritability and hyperactivity.

Physical examination Unremarkable except for "fetor ex ore". ORL examination by an ORL specialist was normal.

Diagnostic tests Borderline serum total cholesterol= =209 mg/dl, normal serum HDL-cholesterol =59 mg/dl, borderline glucose level at 120 min of OGTT, low plasma insulin concentration after glucose intake, glycated hemoglobin in normal range (A1C-5.6%). Cow's milk allergy was excluded based on lack of serum specific IgE antibodies; negative results of skin "prick by prick" tests and negative results of atopy patch tests with cow's milk.

Polysomnographic findings Polysomnographic results presented parameters of obstructive sleep apnea-hypopnea syndrome: RDI before treatment 17.7/h.

The diagnosis of food-related hypersomnia was confirmed when the boy recovered after his nutritional habits had been changed (low simple carbohydrate diet) and antireflux therapy, resulting in reduced respiratory disturbance index from 17.7/h in October 2005 to 2.9/h in October 2006. Within that time, his parents did not observe any episodes of daytime sleepiness, psychological problems or nocturnal enuresis.

Discussion

In this paper, we present three patients in whom three different diseases are accompanied by the same clinical symptom – daytime somnolence and by biochemical abnormalities. These metabolic findings may be temporary or may be prodromal for type I or II diabetes. Hypersomnia is the major symptom of narcolepsy, one of the hypersomnias of central origin in individuals with genetic predisposition [6]. Narcolepsy may be underestimated in children since the classic tetrad of symptoms (sleep attacks, cataplexy, sleep paralysis, hypnagogic hallucinations) is uncommon in this age group, and therefore the final diagnosis is often delayed [7-9]. In our 17-year-old female patient, the time between the onset of symptoms and diagnosis of narcolepsy was 2 years. We consider spine injury a potential challenge factor revealing genetic predisposition to narcolepsy in this patient. The metabolic syndrome is a common pathophysiological condition with implications in the development of many chronic diseases [10]. Genetic predisposition or early-life adverse events may contribute to insulin resistance. Daytime somnolence in metabolic syndrome may be a sequel of sleep disturbances and gastrological problems (e.g. GERD). Also obesity plays an important role in the association between severity of sleep-disordered breathing and increased morning fasting insulin levels in adults and children [11-14]. In childhood, daytime sleepiness is not recognized as abnormal [4]. In our 6-year-old patient, parents' anxiety was caused by sleep attacks only and not by daytime somnolence. Total regression of hypersomnia, psychological problems, nocturnal enuresis and disappearance of obstructive sleep-disordered breathing after diet intervention and antireflux therapy in this patient emphasize the role of improper nutrition habits in sleep disorders [15]. The aim of this paper is to draw attention to a likely association between obesity-dependent and obesity-independent daytime somnolence and metabolic disturbances in children. Parameters of carbohydrate metabolism should be assessed and monitored in patients with hypersomnia of a different origin. Children with hypersomnia need multidirectional differential diagnosis (e.g. towards neurological, endocrinological, pulmonological and gastroenterological disorders) and multispecialist medical and psychological care [16]. These children need psychological support irrespective of hypersomnia origin due to many behavioral symptoms: low self-esteem, difficulty with mood regulation, learning difficulties or hyperactivity [17,18].

Acknowledgements

This study was supported by The State Committee for Scientific Research Project 3PO5E08125.

References

1. Meltzer LJ, Mindell JA. Sleep and sleep disorders in children and adolescents. Psychiatr Clin North Am, 2006; 29: 1059-76.
2. Guilleminault C, Brooks S. Excessive daytime sleepiness. A challenge for the practising neurologist. Brain, 2001; 124: 1482-91.
3. Carskadon MA. Patterns of sleep and sleepiness in adolescents. Pediatrician, 1990; 17: 5-12.
4. Vgontzas AN, Kales A. Sleep and its disorders. Annu Rev Med, 1999; 50: 387-400.
5. Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. Sleep, 1986; 9: 519-24.
6. Planelles D, Puig N, Beneto A, Gomez E, Rubio P, Mirabet V, Bonanad S, Blasco I, Montoro JA. HLA-DQA, -DQB and -DRB allele contribution to narcolepsy susceptibility. Eur J Immunogenet, 1997; 24: 409-21.

7. Kotagal S, Hartse KM, Walsh JK. Characteristics of narcolepsy in preteenaged children. Pediatrics, 1990; 85: 205-9.

8. Zachariev Z, Djurkova A. Clinico-polysomnographic diagnostics of narcolepsy-cataplexy. Folia Med, 1999; 41: 5-12.

9. Ohayon MM, Ferini-Strambi L, Plazzi G, Smirne S, Castronovo V. How age influences the expression of narcolepsy. J Psychosom Res, 2005; 59: 399-405.

10. Wolk R, Somers VK. Sleep and the metabolic syndrome. Exp Physiol, 2007; 92: 67-78.

11. Kaditis AG, Alexopoulos EI, Damani E, Karadonta I, Kostadima E, Tsolakidou A, Gourgoulianis K, Syrogiannopoulos GA. Obstructive sleep-disordered breathing and fasting insulin levels in nonobese children. Pediatr Pulmonol, 2005; 40: 515-23.

12. Gruber A, Horwood F, Sithole J, Ali NJ, Idris I. Obstructive sleep apnoea is independently associated with the metabolic syndrome but not insulin resistance state. Cardiovasc Diabetol, 2006; 5: 22.

13. Wiernsperger N, Nivoit P, Bouskela E. Obstructive sleep apnea and insulin resistance: a role for microcirculation? Clinics, 2006; 61: 253-66.

14. Nowak M, Kornhuber J, Meyrer R. Daytime impairment and neurodegeneration in OSAS. Sleep, 2006; 29: 1521-30.

15. Wasilewska J, Kaczmarski M. Sleep-related breathing disorders in small children with nocturnal acid gastro-oesophageal reflux. Rocz Akad Med Bialymst, 2004; 49: 98-102.

16. Zeman A, Britton T, Douglas N, Hansen A, Hicks J, Howard R, Meredith A, Smith I, Stores G, Wilson S, Zaiwalla Z. Narcolepsy and excessive daytime sleepiness. BMJ, 2004; 329: 724-28.

17. Ward T, Mason TB, 2nd. Sleep disorders in children. Nurs Clin North Am, 2002; 37: 693-706.

18. Stores G, Montgomery P, Wiggs L. The psychosocial problems of children with narcolepsy and those with excessive daytime sleepiness of uncertain origin. Pediatrics, 2006; 118: 1116-23.

19. Iglowstein I, Jenni OG, Molinari L, Largo RH. Sleep duration from infancy to adolescence: reference values and generational trends. Pediatrics, 2003; 111: 302-7.