



## ROHHAD in a 9-year-old boy — clinical case

### Zespół ROHHAD u 9-letniego chłopca — opis przypadku

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#### Abstract

ROHHAD syndrome (Rapid-onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation) is characterised by rapid-onset obesity in young children, hypoventilation, and hypothalamic and autonomic dysfunction. The exact aetiology of the disease remains unknown, and the number of reported cases seems to be underestimated.

We present the case of a nine-year-old male patient suspected of ROHHAD due to weight gain since early childhood, decreased height velocity, hypoventilation, hypodipsia, excessive perspiration, and pyrexial episodes. The presented symptoms, and laboratory and imaging findings met the criteria of ROHHAD syndrome.

ROHHAD should be considered in differential diagnosis for obesity in children. Early identification of the disease prevents potential complications specific for the syndrome, in particular a life-threatening cardio-pulmonary arrest. Patients with ROHHAD require regular follow-up by a multidisciplinary team. (*Endokrynol Pol* 2016; 67 (2): 226–231)

**Key words:** ROHHAD syndrome; obesity; central hypoventilation; hypothalamus dysfunction

#### Streszczenie

ROHHAD (*Rapid-onset Obesity with Hypothalamic Dysfunction, Hypoventilation and Autonomic Dysregulation*) to rzadki zespół charakteryzujący się pojawiającą się we wczesnym dzieciństwie szybko narastającą otyłością, hipowentylacją oraz zaburzeniami funkcji podwzgórza i układu autonomicznego. Przyczyny zespołu pozostają nieznane, a diagnostyka i postawienie ostatecznego rozpoznania następuje z wieloma trudnościami. Przypuszcza się, że liczba przypadków zespołu jest znacznie niedoszacowana.

W pracy zaprezentowano pierwszy w Polsce przypadek 9-letniego pacjenta z otyłością, zwolnieniem szybkości wzrastania, zaburzeniami oddychania, hipodipsją, nadmierną potliwością i epizodami gorączek. Całość obrazu klinicznego, wyniki badań laboratoryjnych i obrazowych spełniają kryteria rozpoznania zespołu ROHHAD u prezentowanego pacjenta.

Zespół ROHHAD powinien być brany pod uwagę w diagnostyce różnicowej otyłości u dzieci. Wczesne postawienie rozpoznania może pomóc uniknąć powikłań wpisanych w obraz zespołu i zabezpieczyć pacjenta przed najgroźniejszym z nich — czyli nagłym zatrzymaniem krążenia i oddechu. Pacjenci z zespołem ROHHAD wymagają wielospecjalistycznej opieki i systematycznych badań kontrolnych. (*Endokrynol Pol* 2016; 67 (2): 226–231)

**Słowa kluczowe:** zespół ROHHAD; otyłość; centralna hipowentylacja; dysfunkcja podwzgórza

#### Introduction

ROHHAD syndrome (Rapid-onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation) is characterised by rapid-onset obesity in young children, hypoventilation, and hypothalamic and autonomic dysfunction [1–6]. The aetiology of the disease remains unknown. Genetic, epigenetic, autoimmune, and paraneoplastic factors are taken into account as possible causes of ROHHAD [1–9]. There have only been 76 reported cases of ROHHAD [2]. This number seems to be underestimated. The diagnostic criteria for ROHHAD include central hypoventilation appearing after the first year of life and one or more symptoms such as: rapid-onset obesity, hyperprolactinaemia,

water balance disturbance, secondary hypothyroidism, growth hormone deficiency, secondary adrenal insufficiency, or delayed puberty [1].

Other symptoms consistent with ROHHAD involving the hypothalamic dysfunction include hyperphagia, precocious/delayed puberty, nycturia, hypodipsia, diabetes insipidus, hypernatraemia/hyponatraemia, Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), and hypersomnolence. Respiratory manifestations embrace sleep apnoea, cyanotic episodes (after swimming), reduced CO<sub>2</sub> ventilatory response, alveolar hypoventilation, recurrent pneumonia, and respiratory failure sometimes resulting in cardiac arrest. Autonomic dysregulation appears in the form of thermal disturbances, increased sweating, dilated



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pupils with abnormal reaction to light, strabismus, gastrointestinal tract dysmotility, bradycardia, cold hands and feet, decreased sensitivity to pain, and tumours of neural crest origin. Behavioural disorders comprise emotional lability, depression, psychotic symptoms, cataplexic episodes, panic and anxiety attacks, Tourette's syndrome, seizures, and delay or regression of psychomotor development. Type 2 diabetes mellitus, impaired glucose tolerance, and hypercholesterolaemia may also be noted in children with ROHHAD [1–5].

## Case report

A nine-year-old male patient presented with obesity, short stature, thermoregulatory disturbances, and sleep apnoea. The patient was born as the first child of nonconsanguineous parents, after normal vaginal delivery, with adequate birth weight and length. His Apgar score was nine, and neonatal and infancy period were uneventful. Since the age of four years, he demonstrated weight gain, decreased height velocity, and sleep apnoea at the same time. At the age of five years, the patient underwent adenotomy due to sleep apnoeas. At the age of six years, he developed new symptoms such as hypodipsia, abdominal discomfort, and nocturnal pyrexial episodes up to 39 degrees Celsius, followed by profuse sweating. Fever episodes without evidence of infection were accompanied by lower body temperature (min. 34 degrees Celsius) during the day and pseudo-Reynaud's phenomenon on his limbs. At the age of seven years, the patient was admitted to hospital due to short stature and excessive weight gain. Physical examination showed height below 3 pc, obesity (> 97 pc according to height, BMI > 97 pc) as well as prepubertal male sex development. Laboratory tests (Table I) revealed moderately increased activity of AST (61–84 U/L, N < 47 U/L), elevated platelet count, and HbA1c of 6.21% (N: 4.8–5.9%). Endocrine investigations showed normal adrenal and thyroid axes, failed growth hormone stimulation tests (max. 0.3 ng/mL), IGF-1 198 ng/mL, low fasting insulin 1.59  $\mu$ U/mL (N 2.6–24.9), as well as normal insulin and glucose in the oral glucose tolerance test (OGTT). Imaging studies showed normal brain and pituitary scans, and delayed bone maturation by about three years (according to Greulich and Pyle atlas). The patient was started on growth hormone therapy. Since then, acceleration in growth velocity was observed nevertheless with no effect on the body weight or other symptoms (Fig. 1 and 2).

During the next elective hospital admission hypodipsia, nycturia, and abdominal discomfort were observed. On physical examination obesity, scoliosis, profuse sweating, livedo reticularis, and pseudo-Reynaud's phenomenon on limbs were present. The

patient's hands and feet were cold and clammy. The cardio-respiratory system was normal, except for transient hypertension. On palpation, there was no hepatosplenomegaly or lymphadenopathy. Emotional lability with normal intellectual development and no abnormalities in neurological evaluation were observed. Additional laboratory examinations revealed hypernatraemia (148–161 mmol/L), hypercholesterolaemia (232 mg/dL), moderate hyperprolactinaemia of 73 ng/mL (N: 1.8–15.9), four-fold elevated plasma rennin activity, normal aldosterone, slightly elevated adrenaline, and VMA in urine. Chromogranin A (ChA) and neuron-specific enolase (NSE) were near the upper normal limit. Abdominal ultrasound and CT scans of the abdomen and thorax appeared normal. Repeated brain MRI revealed no lesions. MIBG scintigraphy and  $^{99m}$ Tc-tectretotide-scintigraphy were performed and excluded a tumour of neural crest origin. Echocardiography showed no structural and functional abnormalities. In 72-hour ECG, the heart rate was 56/min — 183/min (mean frequency — 110/min), atrio-ventricular dissociation periods were observed, with no pauses > 3 s.

Tuberculosis, Borrelia, HCV, HBV, Toxoplasma gondii, and active CMV were ruled out. Tissue-specific autoantibodies were negative, the ANA test was slightly positive (1:80), nailfold capillaroscopy showed regular capillary loops.

Retested catecholamine and metabolites in 24-hour urine collection were normal. Sleep apnoea was confirmed by episodes of haemoglobin desaturation at night (min. SatO<sub>2</sub> 78%, HR > 100/min.), transcutaneous oxygen and carbon dioxide analysis during the sleep — PaO<sub>2</sub> was decreased to 60 mmHg and PaCO<sub>2</sub> was within normal limits. Polysomnogram results indicated mild (AHI 5.5), mixed-type sleep apnoea with an obstructive component of about 30%. Nasofibroscopy did not reveal any abnormalities, and tonsillar hypertrophy Grade 2 was diagnosed. The patient was scheduled for a home ventilation program on non-invasive mask ventilation using positive pressure ventilation during the night and he underwent tonsillectomy. At one-month follow-up, polysomnography confirmed improvement in air passage after the operation, nevertheless AHI increased to 6.3. Genetic studies did not confirm mutation in gene PHOX2B resulting in congenital central hypoventilation syndrome nor abnormal methylation pattern in 15q 11-13 region specific for Prader-Willi syndrome.

At six-month follow-up visit, the parents reported significantly reduced frequency of fever episodes and sweating, hands and feet became less reddened, and the patient stopped gaining weight. Emotional lability, hypodipsia, and nycturia were still present. Further cardiologic evaluation (72-hour ECG) revealed episodes of bradycardia (minimum 45/min.) with QTc increased

Table I. Symptoms and laboratory findings

Tabela I. Objawy i wyniki badań laboratoryjnych

Symptoms and laboratory findings	Historical data	At 6 months of observation	At 14 months of observation
Rapid onset obesity	BMI +3.0SD	BMI +1.95SD	BMI +1.35SD
Short stature	-2.4 SD	-1.0 SD (at 18 months of GH therapy - 0.42 U/kg/week)	-0.7 SD (at 26 months of GH therapy - 0.49 -0.53 U/kg/week)
Failed GH stimulation tests			
Insulin	Max. 0.09 ng/mL		
Clonidine	Max. 0.31 ng/mL		
Overnight	Max. 0.3 ng/mL		
Hypodipsia	(+)	(+)	(+)
Nycturia	(+)	(+)	(+)
Hyperthermia/hypothermia degrees of Celsius	34-39	34.2-37.8 (39 degrees of Celsius 1 ×/month)	35.5-36.5 (38.5 degrees of Celsius 2 × 7-9-days periods)
Profuse sweating	(+++)	(+/++)	(+/++) (++++ during fever periods)
Altered colour of hands and feet	(+++)	(+/++)	(+/++) (++) during fever periods)
Emotional lability	(+)	(+)	(+)
Gastrointestinal dysmotility	Abdominal discomfort	(-)	(-)
Sleep apnoea	AHI — 5.5 Obstructive sleep apnoea 30%	AHI — 6.3 Obstructive sleep apnoea (-)	
Bradycardia	(-) min. 56/min.	(+) min.45/min.	(+) min.45/min.
Hypernatremia	148-161 mmol/L (N: 135-145mmol/L)	144-145 mmol/L	141 mmol/L
Osmolality of blood	306-325 mOsm/kg H2O (N: 270-295)	294 mOsm/kg H2O	282 mOsm/kg H2O
Osmolality of urine	720-1035 mOsm/ kg H2O (N: 50-1400)		161 mOsm/kg H2O
Hyperprolactinaemia	73.6 ng/mL (N: 1.8-15.9)	20.1 ng/mL	24.8 ng/mL
Hypercholesterolaemia	Total ch. 232 mg/dL (N: 105-223)	207 mg/dL	194 mg/dL HDL 98 mg/dL LDL 80 mg/dL
AST	78 U/L (N < 53)	59 U/L	51 U/L
ARO	36.6 ng/mL/h (N: 1.5-5.7)	5.01 ng/mL/h	5.87 ng/mL/h
VMA	8.7-8.3 mg/d (N: 2.0-3.2)	2.7-3.0 mg/d (2.0-3.2)	3.1-3.2 mg/d (2.3-5.2)
Adrenalin (A)	15.4-11.3 µg/d (N: 2.4-9)	8.7-10.7 µg/d (2.4-9.0)	6.4-9.3µg/d (1.3-14.5)

to 0.49. Imaging investigations remained negative for tumour of neural crest origin.

During the diagnostic process, the patient underwent a wide range of specialist examinations by our nephrology, oncology, rheumatology, neurology, cardiology, pulmonology, genetics, laryngology, and pulmonology teams.

## Discussion

The presented symptoms, and laboratory and imaging findings allowed us to diagnose our patient with ROHHAD. Improved general condition and reduced/diminished intensity of the observed symptoms coincided with the starting of non-invasive ventilation

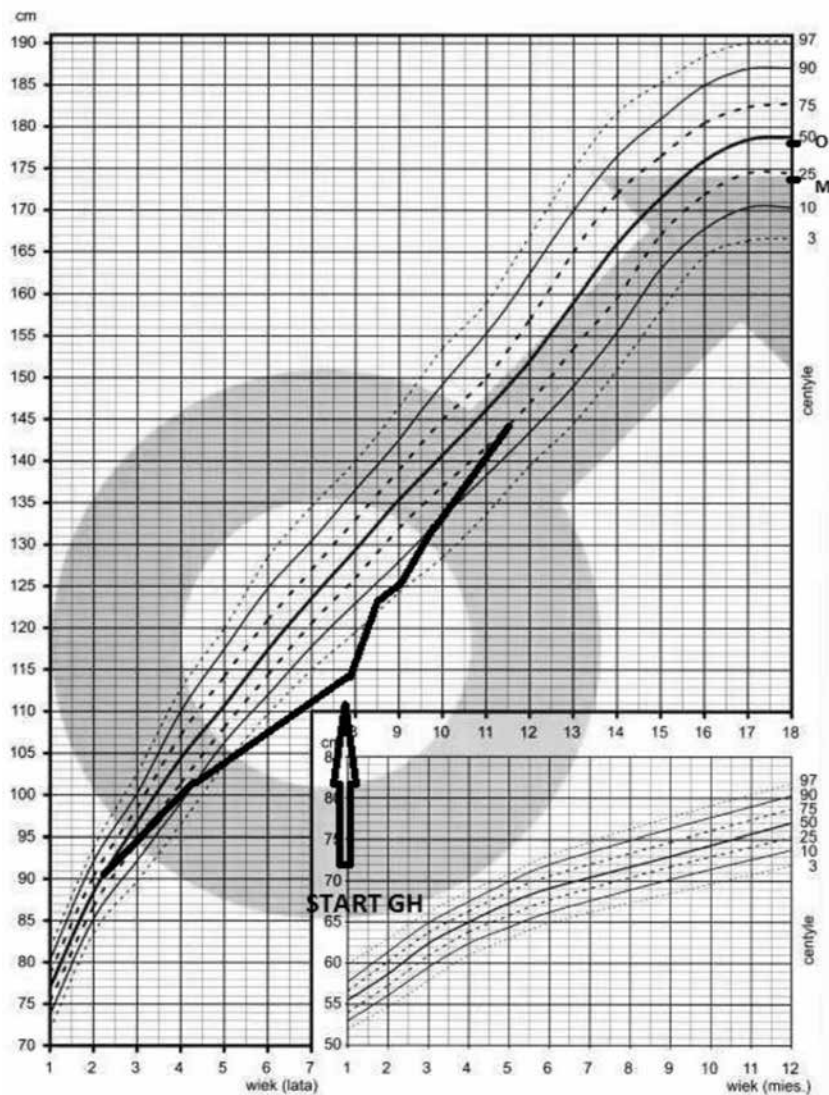


Figure 1. Growth chart

Rycina 1. Siatka centylowa wysokości ciała

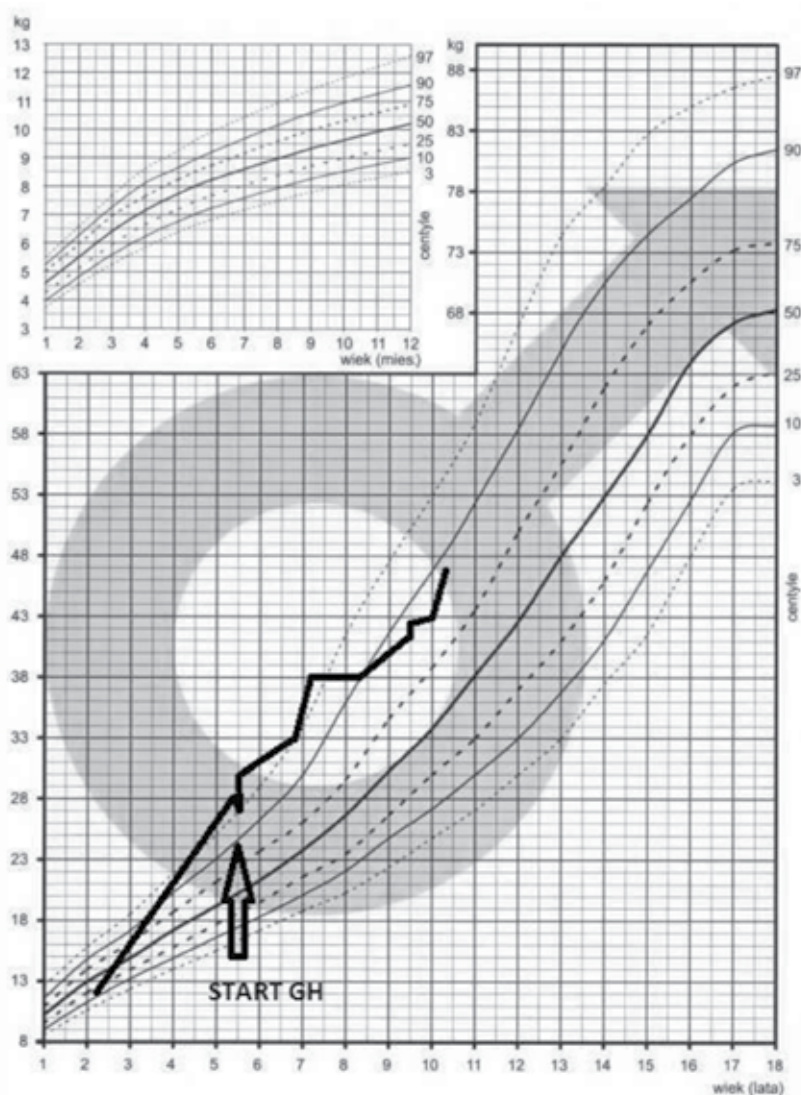
support and improved airway passage. This kind of treatment surely prevents complications of sleep apnoea and cardio-pulmonary arrest. Nevertheless, the aetiology and pathomechanism of the disease are still to be determined.

ROHHAD should be considered in differential diagnosis for obesity in children. Identification of the disease is extremely difficult. Other conditions accompanied by obesity should be checked, such as Prader Willi Syndrome (PWS), Bardet-Biedel Syndrome (BBS), Cushing Syndrome, mutation in MC4R gene, mutation in POMC gene, leptin receptor gene, and Congenital Central Hypoventilation Syndrome (CCHS). Cardiac, pulmonary, rheumatologic, neuromuscular, and metabolic abnormalities must be ruled out as well.

Prader-Willi Syndrome [10] (frequency 1/10,000 to 1/30,000 live births) is in 75% cases caused by chromosome 15q11-q13 deletion on the paternal chromosome. Sym-

ptoms common for ROHHAD and PWS are: rapid-onset obesity in early childhood, hyperphagia, short stature, secondary adrenal insufficiency, thermal disturbances, hypogonadotrophic hypogonadism, and mixed central-obstructive type of hypoventilation. Characteristic features also include: feeding difficulties during infancy, hypotonia, scoliosis, and learning and attention difficulties.

Bardet-Biedel Syndrome [11] (frequency in Europe 1/160,000 live births) is a heterogenic disease caused by mutations in one of 16 known genes leading to defects in the cellular ciliary structure. Obesity appears at the age of 2–4 years. Other specific symptoms are: retinitis pigmentosa, polydactyly, syndactyly, hypogonadotrophic hypogonadism, developmental delay, cognitive deficit, genitourinary malformations, cardiovascular abnormalities, dental abnormalities, Hirschprung's disease, polydipsia, polyuria, nephrogenic diabetes insipidus, and diabetes mellitus.



**Figure 2.** Body weight (for growth) chart

**Rycina 2.** Siatka centylowa masy ciała

Congenital Central Hypoventilation Syndrome [12] (Ondine's Curse Syndrome) is caused by mutation in *PHOX2B* gene encoding transcription factor involved in autonomic nervous system development. The disease is recognised in newborns presenting severe hypoventilation requiring mechanical ventilation, with the absence of ventilatory response to hypercapnia and hypoxia. There exists a group of patients with late manifestation of CCHS out of the newborn period. Other autonomic nervous system-related symptoms are: bradycardia to cardiac asystoles, respiratory rate variability, thermal dysregulation, abnormal pupillary reactivity, sweating, swallowing difficulties, oesophageal dysmotility, Hirschprung's disease, and tumours of neural crest origin.

Hypoventilation, autonomic dysregulation, and tumours of neural crest origin are common symptoms for ROHHAD and CCHS.

## Conclusions

ROHHAD should be considered in differential diagnosis of obesity in children, particularly when obesity is followed by hypothalamic, autonomic dysregulation, or respiratory hypoventilation symptoms. Identification of the disease may be difficult. Final diagnosis and immediate adequate treatment is crucial for patients threatened with cardio-pulmonary arrest, cognitive performance deterioration, and tumours of neural crest origin. Patients with ROHHAD require regular follow-up by a multidisciplinary team.

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