Hypocretin-1 Deficiency in a Girl With ROHHAD Syndrome

abstract
Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) is a rare and complex pediatric syndrome, essentially caused by dysfunction of 3 vital systems regulating endocrine, respiratory, and autonomic nervous system functioning. The clinical spectrum of ROHHAD is broad, but sleep/wake disorders have received relatively little attention so far, although the central hypothalamic dysfunction would make the occurrence of sleep symptoms likely. In this case report, we expand the phenotype of ROHHAD with a number of striking sleep symptoms that together can be classified as a secondary form of narcolepsy. We present a 7-year-old girl with ROHHAD who displayed the classic features of narcolepsy with cataplexy: excessive daytime sleepiness with daytime naps, visual hallucinations, and partial cataplexy reflected in intermittent loss of facial muscle tone. Nocturnal polysomnography revealed sleep fragmentation and a sleep-onset REM period characteristic for narcolepsy. The diagnosis was confirmed by showing an absence of hypocretin-1 in the cerebrospinal fluid. We discuss potential pathophysiological implications as well as symptomatic treatment options. Pediatrics 2013;132:e788–e792

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KEY WORDS
narcolepsy, cataplexy, orexin, hypocretin

ABBREVIATIONS
PSG—polysomnography
REM—rapid eye movement
ROHHAD—rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation

Dr Dhondt conceptualized and designed the study in this patient and drafted the initial manuscript; Dr Verloo revised the manuscript; Drs Verhelst and Van Coster reviewed and revised the manuscript; Dr Overeem supervised the designed study in this patient, codrafted the initial manuscript, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) is a rare pediatric syndrome first described in 1965.1 Children with ROHHAD present after 1.5 years of age with hyperphagia resulting in rapid weight gain. Afterward other hypothalamic abnormalities appear, including inappropriate antidiuretic hormone secretion, hyperprolactinemia, central hypothyroidism, growth hormone deficiency, and precocious or delayed puberty.2–5 Autonomic nervous system symptoms include constipation, hyper- or hypothermia, and bradycardia. Obstructive sleep apnea may develop, as well as hypoventilation, both gradually or abruptly after rapid weight gain. Seizures and developmental/behavioral disorders are common. Approximately 40% of children with ROHHAD develop ganglioneuromas or ganglioneuroblastomas at varying times in the disease course.3,5 As 50% to 60% of children with ROHHAD ultimately suffer from cardiac arrest, the prognosis for these children has improved significantly due to early recognition and diagnosis.7

An extensive literature exists on the spectrum of manifestations in ROHHAD.3–5,7 However, sleep/wake disorders have received relatively little attention, although the central hypothalamic dysfunction would make the occurrence of sleep symptoms likely. Here, we describe a child with ROHHAD syndrome who progressively developed symptoms of narcolepsy, a primary sleep disorder caused by a defect in hypothalamic hypocretin (orexin) neurotransmission.

CASE REPORT

A 3-year-old girl was seen in a local hospital because of a stagnation of neurodevelopment, aggressive outbursts, and hyperphagia. One year later, first signs of puberty occurred as seen by pubic hair and breast development. She experienced sleep attacks during the daytime. After she had presented with a drop attack, convulsions, and decreased consciousness, she was admitted to the hospital. She was hypothermic (32°C), hypoxic (SaO2 83%), and increasingly hypercapnic (PCO2 58.7 mm Hg). Chest radiograph showed neurogenic pulmonary edema. Repeated echography of the heart showed no abnormalities. Pulmonary hypertension was not detected. She was intubated and positive end-expiratory pressure was applied. During sleep, hypercapnia and hypoxia became even more pronounced without arousal reactions, indicating a central origin of the ventilatory disturbance. Except for obesity (percentile 97 + 3.5 SD), no other anatomic obstructive elements were found.

Endocrinologic investigations confirmed a central precocious puberty with normal luteinizing hormone releasing hormone. Absence of a cortisol peak after the cortisol stress test and normal adrenocorticotropin level also pointed in the direction of secondary adrenal cortical insufficiency. Episodes of bradycardia (61/min), hypotension (44/29 mm Hg), neurogenic pulmonary edema, and decreased pain perception all fitted with a central autonomic dysregulation. As a central hypoventilation was suspected, an overnight polysomnography (PSG) was performed but had to be interrupted because of severe hypercapnia (Paco2 59.6 mm Hg) and hypoxia (SpO2 73%) occurring soon after sleep onset. MRI of the brain focused on the hypothalamus and pituitary gland was normal. A ganglioneuroma or ganglioneuroblastoma could not be detected despite extensive investigation. Blood counts and liver and kidney function were normal. Dopamine or norepinephrine production and catecholamine metabolites in a 24-hour urine collection were normal. CT scan of the abdomen and thorax and echography of the heart, kidneys, and adrenal glands were normal. Metaiodobenzylguanidine scan was not performed. Chromosomal analysis revealed 48, XX and no deletions in chromosome 15. Prader Willi syndrome was further excluded by small nuclear ribonucleoprotein polypeptide N (SNRP) gene methylation analysis. Micro-array (60K resolution) revealed no abnormalities. At the age of 7 years, her weight increased dramatically (+11 kg in 6 months). She was obsessed by food, seeking it constantly.

Given the combination of hypothalamic, autonomic, and respiratory symptoms, the diagnosis of ROHHAD was finally made when she was 7 years old. She was treated with decapeptyl and hydrocortisone. Noninvasive ventilation during sleep was attempted at home, but was not tolerated. A physiotherapist noticed intermittent speech difficulties and a curious protrusion of the tongue, although this did not receive further attention. At the age of 7.5 years, the girl was admitted to our hospital because of a postpericardiotomy syndrome after pacemaker implantation. Hospitalization was prolonged because of cardiac arrest preceded by an apneic event accompanied by manifest desaturations. Shortly after successful resuscitation, an apneic event followed by cardiac arrest occurred again. She was intubated again. Echocardiography showed normal systolic ventricular function. After slow reduction of positive end-expiratory pressure she was extubated. Nocturnal noninvasive ventilation remained impossible because of the girl’s behavior.

During daytime, her behavior was extremely fluctuating. Daytime sleep episodes alternated with panic attacks and anxiety accompanied by visual hallucinatory experiences while awake and normal respiratory control. She had intermittent slurred speech with facial weakness and mild protrusion of the tongue, triggered by emotional excitation.
Because of prominent daytime sleepiness, visual hallucinations, and episodic loss of facial muscle tone, the possibility of a secondary form of narcolepsy with cataplexy was raised and further investigated. A PSG was performed and a Multiple Sleep Latency Test was planned, although the latter was impossible to perform because of noncompliance. PSG showed a short sleep latency of 8 minutes with a sleep-onset REM period. For further details, see Fig 1.

Nocturnal sleep findings characterized by short sleep latency, sleep-onset REM period, and sleep fragmentation fitted well with the diagnosis of narcolepsy. As the Multiple Sleep Latency Test could not be performed, a final diagnosis was not established yet. To confirm the diagnosis, a lumbar puncture was performed for measurement of cerebrospinal hypocretin-1 levels. Hypocretin-1 was found to be completely absent (normal, >110 pg/mL), firmly establishing a diagnosis of narcolepsy. HLA-typing was not performed. Shortly thereafter, a new cardiorespiratory arrest occurred and the girl died. Autopsy was refused by the parents.

**DISCUSSION**

In this report we expand the phenotype of ROHHAD with a number of striking sleep symptoms that together can be classified as a secondary form of narcolepsy with cataplexy. Moreover, we

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**FIGURE 1**
Nocturnal polysomnographic registration. From top to bottom, the hypnogram, periodic limb movements (PLM), respiratory events, and oxygen saturation are shown. The hypnogram shows a highly fragmented sleep pattern with increased wake time, and a sleep efficiency of 78%. The arousal-awakening index was increased (21.5/hour of sleep) regardless of saturation levels. In addition, there is a very short latency to REM sleep (sleep-onset REM), all fitting with narcolepsy. There is an increase in PLM, with a PLM index of 33.5 per hour of sleep. Hypoventilation was seen (SpO2 between 88% and 92%; Pco2 mean 54.2 mmHg, maximum 58.1 mmHg) for 3 hours during the night. Apnea-hypopnea index was normal at 3.6/hour sleep, although during these events, marked decreases in oxygen saturation occurred. A, awake; CA, central apnea; HYP, hypopnea; M, movements; OA, obstructive apnea; 1, NREM stage 1; 2, NREM stage 2; 3/4, NREM stage 3.
show that secondary narcolepsy in ROHHAD is directly caused by hypothalamic dysfunction, as hypocretin-1 levels were absent.

Narcolepsy has a peak incidence around 14 to 15 years of age, and usually is a sporadic disorder. Secondary narcolepsy has been described in various neurologic disorders affecting hypothalamic function. Although, in retrospect, the symptoms of narcolepsy in our patient were present soon after disease onset, but were not recognized for a long time. Narcolepsy was not mentioned in earlier published reports on ROHHAD. This may be due to difficulties diagnosing narcolepsy in children. Excessive daytime sleepiness can be misinterpreted as “normal naps,” especially in young children, whereas toddlers often become hyperactive when sleepy. Furthermore, cataplectic attacks may present differently in children than in adults, often with striking facial involvement, including intermittent tongue protrusion, sagging of the jaw, and ptosis, leading to a so-called “facies cataplectica.” In our patient, this had been noticed by a physiotherapist but was interpreted as speech difficulties and “slurred speech,” and not recognized as cataplexy.

Sporadic narcolepsy is caused by loss of hypothalamic hypocretin producing neurons. Besides the relevance of hypocretin neurotransmission in sleep regulation, its function in autonomic and metabolic regulation is currently a subject of interest. Neuroanatomic and physiologic data indicate an important role of hypocretin in the regulation of the autonomic system. Neurophysiological tests demonstrated signs of autonomic dysregulation, including increased heart rate variability and blunted pupillary oscillations under constant illumination. The hypocretins play an important role in central cardiovascular regulation, enhancing sympathetic outflow and plasma catecholamine release. Fronczek suggested a reduced sympathetic tone in narcoleptic patients. In ROHHAD, autonomic manifestations were present in all studied patients and appear quite early, at disease onset. In part, these symptoms may relate to hypocretin dysfunction.

Metabolic changes also appear in the early stage of both narcolepsy and ROHHAD. Rapid-onset obesity is one of the first manifestations in children with ROHHAD. In patients with narcolepsy, weight gain is common, usually occurring around disease onset. Dysregulation of insulin secretion was mentioned by Bougnères as a possible cause of obesity in ROHHAD. In narcoleptic patients, Plazzi suggested that overweight could be a clinical manifestation of the underlying autonomic dysfunction. Shen showed that high-dose hypocretin administrated to rats results in lipolysis, whereas lack of hypocretin signaling inhibits lipolysis and leads to fat storage. In both narcolepsy and ROHHAD, lipogenesis may thus be surpassing lipolysis. Absence of other hypothalamic and hormonal dysfunctions in narcolepsy remains an important differential sign. An autoimmune-mediated process has been speculated as a possible cause of ROHHAD, illustrated by the positive effect of immunosuppressive treatment with high-dose cyclophosphamide. Ganglioneuromas and ganglioneuroblastomas are often present and frequently associated with autoimmune-mediated paraneoplastic syndromes, although autoantibodies have never been identified in ROHHAD. Lymphocytic infiltration of the thalamus and hypothalamus was shown in some patients. De Pontual reported 1 patient with IgA deficiency. In narcolepsy, an autoimmune cause is suspected too, fitting with the selective loss of hypocretin-producing neurons and the strong HLA association: 95% of narcolepsy patients carry the DQB1*0602 allele. This particular allele was not found by Pontual et al in patients with ROHHAD. However, the hypothesis of autoimmune-mediated destruction of hypocretin neurons in ROHHAD remains tantalizing, as hypocretin peptides are expressed in ganglioneuroblastomas, providing a potential immune target.

This is the first time a patient with ROHHAD syndrome is described with a secondary form of narcolepsy/cataplexy associated with a hypocretin deficiency. This extension of the ROHHAD phenotype may have therapeutic opportunities, although the possible role of stimulants or anticitaplectic therapy remains to be established. Further research should focus on the presence and clinical presentation of narcolepsy/cataplexy features in children with ROHHAD. Such studies may not only increase our understanding of ROHHAD, but of sporadic narcolepsy as well.

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