ROHHAD syndrome spectrum in an adult: a possible new variant

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To the Editor:

Rapid-onset obesity with hypothalamic dysregulation, hypoventilation and autonomic dysregulation (ROHHAD syndrome) is a rare condition of unknown aetiology appearing in early childhood, with typical onset at 1.5–7 years old. So far, only 120 cases have been reported. ROHHAD initiates in previously healthy children with hyperphagia, leading to a rapid-onset obesity (10–15 kg in 6–12 months). In the following years, patients develop different disorders in hypothalamic function, the most frequent being electrolyte imbalance, hyperprolactinaemia, hypothyroidism and altered onset of puberty, and dysautonomia including severe bradycardia, pain and altered temperature perception or excessive sweating. Abnormal pupillary responses and strabismus are also common, as well as behavioural disorders. These patients experience early-onset obstructive sleep apnoea (OSA) followed by central hypoventilation, leading to a need for home mechanical ventilation, and carrying the most relevant impact on prognosis, with frequent cardiorespiratory arrest events [1, 2]. No survival has been reported from the third decade of life and to date, there have been no reports among older adults at the time of diagnosis. We describe, for the first time, the case of a mature patient with features consistent with the diagnostic criteria of ROHHAD syndrome.

A 57-year-old female was hospitalised complaining of hyperphagia with rapid and significant weight gain (30 kg in 3 months, initial body mass index (BMI) at evaluation of 29.7 $kg \cdot m^{-2}$), hypersomnia, asthenia, syncope or presyncope events in relation to fatigue, gait instability, and strabismus with horizontal diplopia and exophoria. Relevant medical history included chronic autoimmune hepatitis, recent menopause and inactive multinodular gout. She had four pregnancies and worked as a professional caregiver. The patient had a healthy weight in childhood and young adulthood (BMI of 21.9 $kg \cdot m^{-2}$ at 35 years old). She did not have previous behaviour, psychiatric or psychological disorders, and she did not take medications that could cause hyperphagia. At examination, the patient showed mild motor impairment in shoulder girdle muscles.

At this point, complementary test included brain magnetic resonance imaging (MRI) revealing unspecific T1 hypothalamic hyperintensities, and spinal MRI and thoracoabdominal computed tomography (CT), both without relevant abnormalities and, specifically, with no signs of malignancy. Electroencephalography found nonspecific diffuse slowing activity with sporadic and brief bitemporal irritative activity only activated during sleep. Routine laboratory tests including tumour markers and immunoglobulins showed no abnormalities. Laboratory testing for autoimmune disease demonstrated positive antinuclear antibody HEp-2 (1:640), anti-double stranded DNA and hypocomplementaemia. Serologies were negative apart from positive immunoglobulin M and G for varicella–zoster virus (VZV). Specific tests assessing onconeural, antineuronal surface, antimuscle and ganglioside antibodies, and porphyrin studies were also negative; with cerebrospinal fluid (CSF) pattern also nonspecific with no oligoclonal bands, and negative cultures, serologies and PCR for VZV.

During outpatient follow-up 1 month after discharge, hyperphagia and increasing obesity persisted together with episodic daytime sleepiness. Initial sleep evaluation was consistent with severe OSA and there was no evidence of hypoventilation, although carbon dioxide monitoring was not performed. The apnoea–hypopnoea index was 54 per h and total sleep time with oxygen saturation <90% (t_{90}) was 11.4% with a lack of central events, leading to continuous positive airway pressure (CPAP) initiation with adequate adherence. Titration polysomnography performed with CPAP 5 months later in the context of severe sleepiness (Epworth score of 24) showed a central apnoea index of 2.1 per h, t_{90} 16.3%, sleep latency of

Shareable abstract (@ERSpublications)
This case report describes for the first time the evolution of a mature patient with all the diagnostic criteria for ROHHAD syndrome. It shows a rare case of central alveolar hypoventilation with hypothalamic impairment, dysautonomia and rapid weight gain. https://bit.ly/49AN3Vv

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1 min and prolonged rapid eye movement latency. Narcolepsy was discarded after a normal Multiple Sleep Latency Study, human leukocyte antigen genotyping and absence of clinical response to modafinil.

6 months after the first admission to hospital, the patient was hospitalised again following a syncope. After acute severe hypoventilation and no response to noninvasive ventilation (NIV), she was intubated. Initial arterial blood gases at admission revealed acute on chronic hypoventilation (pH 7.32, arterial oxygen tension 34 mmHg, arterial carbon dioxide tension (P_{aCO_2}) 62.3 mmHg and bicarbonate (HCO_3^-) 30 mEq·L^{-1}). At discharge after 12 weeks and following difficult weaning, the patient required prolonged NIV (pressure-controlled ventilation with assured volume mode) with 50% of daily hours support, persisting recurrent episodes of daytime sleepiness lasting minutes with extreme oxygen desaturation, no respiratory effort and episodic bradycardia. Endocrinological assessment found central hypothyroidism, central adrenal insufficiency, hyperprolactinaemia and hypogonadotropic hypogonadism (initial laboratory results are shown in table 1). Treatment with hydrocortisone (40 mg·day^{-1}) and levothyroxine (1 µg·kg^{-1}·day^{-1}) was initiated. Intravenous immunoglobulin infusion (4 g·kg^{-1}·day^{-1}) administered twice at different stages produced negligible response. At this point, an electromyogram showed mild proximal myopathy, sniff nasal inspiratory pressure test was normal (83 cmH_2O) and control ultra-high field brain MRI remained unchanged. Psychiatric evaluation found neurocognitive impairment with a lack of impulse control. Comprehensive cardiac examination was also performed including analysis of cardiac rhythm, which only found progressive basal bradycardia with no other alterations.

Subsequent outpatient follow-up revealed progressive urinary incontinence but she remained stable in her endocrinological condition with sustained ventilatory support and mild-to-moderate daytime hypercapnia on clinic visits (P_{aCO_2} 46–57 mmHg and HCO_3^- 26–30.8 mEq·L^{-1}). A full-face mask and oronasal mask were used alternatively with fixed periods of daytime ventilation to achieve normocapnia or permissive mild hypercapnia not to interfere with activities at home, while mouthpiece ventilation was excluded based on lack of cooperation and unpredictability of the episodes described with sudden sleepiness and oxygen desaturation. Total weight gain was 47 kg (BMI 45.4 kg·m^{-2}). Molecular studies were completed with the search for mutations in the paired-like homeobox 2B gene (*PHOX2B*) and other antibodies to cell surface neural antigens (serum/CSF) with negative results including *N*-methyl-D-aspartate receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, γ-aminobutyric acid receptors A and B, metabotropic glutamate receptors 1 and 5, LGI1, CASPR2, DPPX, neurexin-3α and IgLON5. Control abdominal CT and chromogranin A showed nonspecific findings. After a normal phrenic nerve conduction study, diaphragmatic pacing was not implemented due to anatomic limitations. The patient's behaviour precluded tracheostomy and home invasive mechanical ventilation. Sudden death occurred at home 32 months after symptom onset and following 23 months of NIV.

Fishman *et al*. [3] reported in 1965 the case of a 3.5-year-old male patient with the typical phenotype of the syndrome developing late-onset central hypoventilation (LO-CHS) and describing hypothalamic dysfunction for the first time. In 2000, Katz *et al*. [4] established a distinctive condition between LO-CHS and late-onset central hypoventilation syndrome with hypothalamic dysfunction, reviewing 11 cases showing features of hypothalamic failure, hyperphagia, thermal dysregulation, hypersomnolence, endocrinopathies and unstable behaviour. In 2007, Ize-Ludlow *et al*. [5] coined the term ROHHAD and established the diagnostic criteria. This syndrome could be distinguished from congenital central

TABLE 1 Hypothalamic hypophysiotropic hormone levels at baseline

Determination	Value	Normal range
LH, mIU·mL^{-1}	1.5	17.7–58.5
FSH, mIU·mL^{-1}	9.5	25.8–134
Oestradiol, pg·mL^{-1}	5	<55
Prolactin, ng·mL^{-1}	87.7	4.79–23.30
ACTH, pg·mL^{-1}	<5	<46
Basal cortisol, µg·mL^{-1}	18.4	5–26.5
IGF-1, ng·mL^{-1}	56.65	44–240
TSH, µU·mL^{-1}	0.20	0.27–4.20
Free T4, ng·dL^{-1}	1.44	0.93–1.70
Free T3, pg·mL^{-1}	1.60	1.80–4.30

LH: luteinising hormone; FSH: follicle-stimulating hormone; ACTH: adrenocorticotropic hormone; IGF-1: insulin-like growth factor 1; TSH: thyroid-stimulating hormone; T4: thyroxine; T3: triiodothyronine.

hypoventilation syndrome (CCHS) when mutations in *PHOX2B* were not found [1]. The acronym was completed in 2008 as ROHHAD(NET) to include the risk of neuroendocrine tumours [6]. In an extensive review of 43 cases, Harvengt *et al*. [2] found a neuroendocrine tumour incidence of 56% and 70% of these tumours were diagnosed within 2 years after the initial weight gain. Based on this, follow-up CT scans and neuroendocrine tumour markers were performed, without findings. In the same series, OSA was detected at a median age of 4 years and central hypoventilation occurred at 5.3 years, and was diagnosed for 83% of the patients in the first 5 years after the beginning of obesity. Tracheostomy or NIV were indicated in 24 cases (median age of 4.8 *versus* 6.3 years). In the study by Ize-Ludlow *et al.* [5] including 15 patients, hypoventilation had a median age of onset of 6.2 years. Reported mortality rates were high, reaching 60% within the first years after diagnosis [5].

Similarly to paediatric patients, we found a debut with OSA and transition to predominant central alveolar hypoventilation, with a challenging assessment for pulmonologists, and difficulty sustaining prolonged NIV in a patient with no indication of tracheostomy, not interfering with limited activities during daytime including walking. Initial BMI and the rest of clinical features, together with a rapid progression of the disease, were not concordant with an obesity hypoventilation syndrome. We also believe that physiological transition in the context of late menopause, including changes in weight and ventilatory drive, could not contribute significantly to the globality of manifestations of the disease. As in other central alveolar hypoventilation syndromes, in this case, we could estimate a highly variable and unpredictable ventilatory demand together with potential limitations to trigger the ventilator; thus, specific ventilation strategies were used.

There is no clear aetiology for ROHHAD syndrome but both an epigenetic disorder or an autoimmune process have been advocated as aetiological hypotheses. Genetic susceptibility, though, lacks consistent results [7, 8]. *PHOX2B* mutations are absent, as is the case for other candidate genes, like *ASCL1*, *BDNF* and *HCRT* [9]. Partial response in some manifestations of hypothalamic disfunction has been achieved with immunoglobulins [10] and investigators have described an intrathecal synthesis of oligoclonal bands after CSF analysis [11], immune-cell infiltrates in the brain [12], and MRI signs of focal inflammation in the periaqueductal grey matter and hypothalamus [13]. Recently, Mandel-Brehm *et al*. [14] confirmed the presence of autoantibodies to ZSCAN1 (zinc finger and SCAN domain-containing protein 1) in seven out of nine paediatric patients with tumour-associated ROHHAD. In our case, a complete panel for immune-mediated encephalitis was negative and immunoglobulins produced imperceptible results.

A *de novo* mutation or the possibility of an autosomal-dominant inherited disease not expressed in the previous generation could explain this sporadic presentation. A variation of autoimmune hypothalamitis with central hypoventilation could also be linked to the case, with a typical age and gender. However, isolated autoimmune hypothalamitis is rare and the presence of a suprasellar mass is a major diagnostic criterion. A viral prodrome both linked to autoimmune disease and dysautonomia also could not be stablished. We believe that laboratory findings relate to autoimmune hepatitis and that VZV could not act alone triggering this process after CSF and MRI analysis. Interestingly novel antihypothalamic antibodies and other diagnostic markers, as in the study by Mandel-Brehm *et al*. [14], might be applied to the spectrum of ROHHAD in adults.

ROHHAD manifestations overlap with other disorders including, CCHS and Prader–Willi syndrome, with phenotypic features allowing us to discard the latter disease [15]. Whole-exome sequencing was not performed. Another limitation was the lack of specific tests to complete dysautonomia evaluation due to the condition of the patient, although several features of impairment at different stages were found.

After completing an exhaustive search in the literature, we could not find a case at a mature age with this delayed debut of manifestations typically described in ROHHAD. Our patient met the diagnostic criteria consistent with those established for children and also had an ominous prognosis in the context of severe hypoventilation. A search for similar cases among adults, and for novel candidate genes and autoimmune biomarkers, is to be encouraged for the potential definition of a new variant.

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