ROHHAD syndrome spectrum in 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 etiology 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, hyperprolactinemia, hypothyroidism and altered onset of puberty and dysautonomia including severe bradycardia, pain and temperature altered perception or excessive sweating. Abnormal pupillary responses and strabismus are also common as well as behavioral disorders. These patients experience early-onset obstructive sleep apnea (OSA) followed by central hypoventilation, leading to the need of 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 is no reports among older adults at the time of diagnosis. We describe the case of a mature patient with features consistent with the diagnostic criteria of ROHHAD syndrome for the first time.

A 57-year-old female was hospitalized complaining of hyperphagia with rapid and significant weight gain (30 kg in 3 months, initial BMI at evaluation of 29.7 kg/m²), 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 healthy weight in childhood and young adulthood (BMI of 21.9 kg/m² at 35 years old). She did not have previous behavior, 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 MRI revealing unspecific T1 hypothalamic hyperintensities and spinal MRI and thoracoabdominal CT-scan, both without relevant abnormalities and specifically with no signs of malignancy. Electroencephalography found non-specific diffuse slowing activity with sporadic and brief bitemporal irritative activity only activated during sleep. Routine laboratory tests including tumor markers and immunoglobulins showed no abnormalities. Laboratory testing for autoimmune disease demonstrated positive ANA-HEp-2 (1:640), Anti-dsDNA and hypocomplementemia. Serologies were negative apart from positive IgM and IgG for Varicella-Zoster (VZV). Specific tests assessing onconeural, anti-neuronal surface, anti-muscle and ganglioside antibodies and porphyrins studies were also negative with cerebrospinal fluid (CSF) pattern also non-specific with no oligoclonal bands and negative cultures, serologies and PCR for VZV.

During outpatient follow-up at one month after discharge hyperphagia and increasing obesity persisted together with episodic daytime sleepiness. Initial sleep evaluation was consistent with severe OSA and no evidence of hypoventilation though CO₂ monitoring was not performed (AHI: 54/h, T90/total sleep time under 90%: 11.4%) with lack of central events, leading to CPAP initiation and with adequate adherence. Titration Polysomnography performed with CPAP five months later in the context of severe sleepiness (Epworth score of 24) showed a central apnea index of 2.1/h, T90: 16.3%, sleep latency of 1 minute and prolonged REM latency. Narcolepsy was discarded after normal Multiple Sleep Latency Study, HLA genotyping and absence of clinical response to Modafinil.

Six months after the first admission to hospital the patient was hospitalized 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
hypotension (pH 7.32, PaO$_2$ 34 mmHg, PaCO$_2$ 62.3 HCO$_3$-$ 30$ meq/L). 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, hyperprolactinemia, and hypogonadotropic hypogonadism (initial laboratory results are shown in Table 1). Treatment with Hydrocortisone (40 mg/day) and Levothyroxine (1 mcg/kg/day) was initiated. Intravenous immunoglobulin infusion (4 gr/kg/day) administered twice at different stages produced negligible response. At this point Electromyogram showed mild proximal myopathy, sniff nasal inspiratory pressure test was normal (83 cmH$_2$O) and control ultra-high-field brain MRI remained unchanged. Psychiatric evaluation found neurocognitive impairment with 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 remaining stable in her endocrinological condition with sustained ventilatory support and mild to moderate daytime hypercapnia in clinic visits (PaCO$_2$ 46-57 mmHg and HCO$_3$-$ 26-30.8$ meq/L). Total-full-face mask and oronasal mask was used alternatively with fixed periods of daytime ventilation to achieve normocapnia or permissive mild hypercapnia not to interfere with activities at home, while mouth-piece 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 PHOX2B gene and other antibodies to cell surface neural antigens (serum/CSF) with negative results including NMDA, AMPA, GABA(A)/(B), mGluR1/R5 receptors, LGI1, Caspr2, DPPX, Neurexin-3α and IgLON5. Control abdominal CT and Chromogranin A showed non-specific findings. After normal phrenic nerve conduction study, diaphragmatic pacing was not
implemented due to anatomic limitations. Patient’s behavior precluded tracheostomy and home invasive mechanical ventilation. Sudden death occurred at home following 32 months of symptoms onset and 23 of NIV.

Fishman et al. reported in 1965 the case of a 3½-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 [3]. 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 behavior. In 2007, Ize-Ludlow et al. [5] coined the term ROHHAD also establishing the diagnostic criteria. This syndrome could be distinguished from Congenital Central Hypoventilation Syndrome (CCHS) when mutations in the paired-like homeobox 2B gene (PHOX2B) were not found [1]. The acronym was completed in 2008 for ROHHAD(NET) to include the risk of neuroendocrine tumors [6]. In an extensive review of 43 cases, Harvengt et al. found a NET incidence of 56% and 70% of these tumors were diagnosed within two years after initial weight gain [2]. Based on this fact, follow-up CT scans and neuroendocrine tumor 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 5 first 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 Ize-Ludlow study [5] including 15 patients, hypoventilation had a median age of onset of 6.2 years. Reported mortality rates are high, reaching 60% within the first years after diagnosis [5].

Similarly with pediatric patients, we found a debut with OSA and transition to predominant central alveolar hypoventilation with a challenging assessment for pulmonologists and difficulty to sustain 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 etiology for ROHHAD syndrome and both an epigenetic disorder or an autoimmune process are advocated as etiological hypotheses. Genetic susceptibility though, lack consistent results [7,8]. PHOX2B mutations are absent similarly with other candidate genes like ASCL I, BDNF or HCRT [9], while partial response in some manifestations of hypothalamic dysfunction 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 gray matter and hypothalamus [13]. Recently, Mandel-Brehm et al. [14] have confirmed presence of autoantibodies to Zinc finger and SCAN domain-containing protein 1 (ZSCAN1) in 7 of 9 pediatric patients with tumor-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 could not also be established. We believe that laboratory findings were
in relation 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 Mandel-Brehm study, 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 last 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 had an ominous prognosis too in the context of severe hypoventilation. Investigators searching 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.
Table 1 Hormone levels at baseline

<table>
<thead>
<tr>
<th>Determination</th>
<th>Values</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH</td>
<td>1.5</td>
<td>(17.7 - 58.5 mIU/mL)</td>
</tr>
<tr>
<td>FSH</td>
<td>9.5</td>
<td>(25.8 – 134 mIU/mL)</td>
</tr>
<tr>
<td>Estradiol</td>
<td>5</td>
<td>(&lt; 55 pg/mL)</td>
</tr>
<tr>
<td>Prolactin</td>
<td>87.7</td>
<td>(4.79 – 23.30 ng/mL)</td>
</tr>
<tr>
<td>ACTH</td>
<td>&lt; 5</td>
<td>&lt; 46 pg/mL</td>
</tr>
<tr>
<td>Basal Cortisol</td>
<td>18.4</td>
<td>(5 – 26.5 mcg/dL)</td>
</tr>
<tr>
<td>IGF-1</td>
<td>56.65</td>
<td>(44 - 240 ng/mL)</td>
</tr>
<tr>
<td>TSH</td>
<td>0.20</td>
<td>(0.27 – 4.20 mcU/mL)</td>
</tr>
<tr>
<td>Free T4</td>
<td>1.44</td>
<td>(0.93 – 1.70 ng/dL)</td>
</tr>
<tr>
<td>Free T3</td>
<td>1.60</td>
<td>(1.80- 4.30 pg/mL)</td>
</tr>
</tbody>
</table>

Legend: LH: Luteinizing hormone; FSH: Follicle stimulating hormone; ACTH: Adrenocorticotropic hormone; IGF-1: Insulin-like growth factor 1; TSH: Thyroid-stimulating hormone; T4: Thyroxine; T3: Triiodothyronine.

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Conflict of interest

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