ROHHAD (Rapid-onset Obesity with Hypoventilation, Hypothalamic Dysfunction, Autonomic Dysregulation) Syndrome—What Every Pediatrician Should Know About the Etiopathogenesis, Diagnosis and Treatment: A Review

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Abstract: Rapid-onset obesity with hypoventilation, hypothalamic dysfunction, autonomic dysregulation (ROHHAD) syndrome is a rare disease with unknown and debated etiology, characterized by precipitous obesity in young children, hypoventilation and autonomic dysregulation with various endocrine abnormalities. Neuroendocrine tumors can be associated in more than half of the cases. This rare condition has a severe outcome because of high morbidity and mortality. We provide a comprehensive description of the etiopathogenetic theories of the disease, clinical presentation, diagnostic workup and treatment possibilities.

Keywords: obesity, hypoventilation, hypothalamic dysfunction, autonomic dysregulation

Introduction

Rapid onset obesity with hypoventilation, hypothalamic dysfunction and autonomic dysregulation (ROHHAD) syndrome is a rare disease first described by Fishman et al1 and renamed ROHHAD by Ize-Ludlow et al in 2007.2 The acronym ROHHAD describes the typical sequence of symptoms. This disease is characterized by early and rapid onset of obesity associated with hypoventilation, autonomic dysregulation and endocrine abnormalities. The association with tumors with neural crest origin has included the termination NET into the acronym (ROHHADNET).3–5

The clinical manifestations of ROHHAD syndrome overlap with those of congenital central hypoventilation syndrome (CCHS) and late-onset central hypoventilation syndrome (LO-CHS). Clear delineation from these entities is provided on genetic basis (mutation of the paired-like homeobox 2B gene PHOX2B which is present in patients with CCHS) and the absence of hypothalamic dysfunction in LO-CHS.6 The diagnosis of ROHHAD syndrome is challenging due to unknown etiology, absence of confirmatory tests and is made based on clinical presentation. The condition is characterized by high morbidity and mortality rates.4,5
Because of global epidemic of childhood obesity, it is very important for every pediatrician to recognize this condition early in order to avoid the complications and ensure a good quality of life for these patients.

Incidence
ROHHAD syndrome is a very rare disorder, about 100 cases being reported to date and it is considered a relatively new disease.\textsuperscript{4,5} Because of the explosion of the exogenous obesity in children worldwide, ROHHAD syndrome must be considered for differential diagnosis in obese children.

Etiopathogenesis
Three main etiopathogenetic hypothesis have been postulated: genetic, epigenetic, and autoimmune.

**Table 1 Candidate Genes in ROHHAD Syndrome**

| Gene       | Protein                                                                 | Function                                                                                          | Associated Diseases                                                                 | References |
|------------|-------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------|
| ASCL1      | Human achaete-scute homolog 1                                           | Regulation of neuroendocrine cell differentiation, development of specific neuronal lineages       | Central hypoventilation syndrome, neuroblastoma                                       | 16,18      |
| BDNF       | Brain-derived neurotrophic factor                                        | Neuronal development, differentiation of selected neuronal populations, synaptic activity, regulation of energy balance, inflammation | Central hypoventilation syndrome, Wilms’ tumor, anirida, genitourinary anomalies, mental retardation | 2          |
| HCRT       | Hypocretins                                                             | Sleep-wake cycle regulation, energy balance, regulation of food intake                           | Narcolepsy                                                                          | 14         |
| HCRTR1     | Hypocretin receptor type I                                              | Sleep-wake cycle regulation, energy balance, regulation of food intake                           | Narcolepsy                                                                          | 14         |
| HCRTR2     | Hypocretin receptor type I                                              | Sleep-wake cycle regulation, energy balance, regulation of food intake                           | Narcolepsy, cluster headache                                                        | 14         |
| HTR1A      | 5-hydroxytryptamine (serotonin) receptor 1A                                                                 | Hypothalamic (appetite control and energy regulation), neural activity, behavior, mood          | Periodic fever, generalized anxiety disorder                                           | 12         |
| NECDIN     | Necdin                                                                  | Nervous system development, including peripheral autonomic neurons                               | Prader–Willi syndrome                                                                | 16,19      |
| NTRK2      | Tropomyosin receptor kinase B (TrkB)                                     | Neuronal development, synaptic plasticity                                                        | Obesity, hyperphagia, developmental delay, epileptic encephalopathy                  | 20,21      |
| OTP        | Orthopedia homeobox                                                     | Hypothalamic neuroendocrine cells differentiation                                                 | Kwashiorkor, marasmus                                                                | 12         |
| PACAP      | Pituitary adenylate cyclase activating polypeptide                        | Brain (respiratory, cardiovascular, visceral, thermoregulatory control, energy homeostasis)     | Sudden infant death syndrome                                                          | 12         |
| PHOX2B     | Paired-like homeobox protein 2B                                          | Respiratory, development of the autonomic nervous system                                         | Congenital central hypoventilation syndrome, neuroblastoma                           | 2,12       |
| RAI1       | Retinoic-acid induced                                                | Craniofacial and nervous system development, neuronal differentiation, regulator of the circadian cycle | Smith–Magenis syndrome, alacrimia, achalasia, mental retardation                     | 17         |

**Genetic Theory**

Genetic basis of ROHHAD syndrome has been extensively investigated and various studies ruled out the mutations in several candidate genes, including \textit{PHOX2B}, the gene causative for congenital central hypoventilation syndrome and genes responsible for development and function of the hypothalamic, neuroendocrine and autonorm systems. Candidate genes studied and their role in the pathogenesis of ROHHAD syndrome are presented in Table 1.

\textit{PHOX2B} encodes a transcription factor that has an important role in the regulation of neural crest migration and development of the autonomic nervous system and is considered the disease-defining gene for CCHS. Similarly with ROHHAD syndrome, the CCHS phenotype includes autonomic nervous system dysregulation and endocrine...
abnormalities, which makes the clinical differentiation very difficult, but consideration of PHOX2B as a disease-defining gene for CCHS allows the genetic distinction between the two entities.\textsuperscript{2,6-9}

Mutations in the gene of BDNF with roles in the neuronal development and the impairment of activation of its receptor TrkB were analyzed in patients with ROHHAD syndrome and obesity and no significant correlation was found.\textsuperscript{2,10,11}

Variations of the genes with role in the development of the hypothalamus and autonomic nervous system such as 5-hydroxytryptamine receptor 1A (HTR\textsubscript{1A}), orthopedia (OTP), pituitary adenylate cyclase activating polypeptide (PACAP) were analyzed but they were not significantly correlated with ROHHAD syndrome.\textsuperscript{12} The absence of hypocretin-1 in the cerebrospinal fluid of a patient with ROHHAD syndrome and narcolepsy was reported, suggesting a causative relation, but other studies demonstrated the absence of mutations in HCRT, HCRTR1 and HCRTR2 genes in patients with ROHHAD.\textsuperscript{13-15} Mutations in NECDIN gene with role in respiratory rhythmogenesis and hypothalamic insufficiency and in ASCL1 gene, required for the generation of ventral neuroendocrine neurons which acts as potential modifier gene of PHOX2B were not correlated with ROHHAD syndrome.\textsuperscript{16}

A nonsense mutation was reported in the retinoic acid-induced 1 (RAI1) gene known to cause Smith–Magenis syndrome (SMS), in a patient with morbid obesity and clinical diagnosis of ROHHAD syndrome, suggesting a potential overlap with SMS.\textsuperscript{17}

Epigenetic Theory

Epigenetic hypothesis is supported by report of discordant presentation of ROHHAD syndrome in monozygotic twins.\textsuperscript{15,22} Patwari et al reported a pair of monozygotic twin girls with concordant growth and development until eight years of age and characteristic features of ROHHAD syndrome appearance in the affected twin after this age.\textsuperscript{22} The authors highlighted the possibility of variation in the epigenomes of identical twins leading to discordance in phenotypes of twins. Barclay et al did not identify coding differences in the same pair of discordant monozygotic twins.\textsuperscript{15}

Immunologic Theory

The immune-mediated pathogenesis has been suggested by several authors who reported patients with clinical presentation consisted to ROHHAD in whose cerebrospinal fluid analysis disclosed an intrathecal synthesis of oligoclonal bands and antihypothalamus and antipituitary antibodies were detected.\textsuperscript{23,24} Association with celiac disease, may suggest further evidence for immune-mediated etiology.\textsuperscript{25} Autoimmune-mediated process has been illustrated by the positive effect of the intensive immunosuppressive treatment (cyclophosphamide, rituximab, immunoglobulin and corticoids) for the neuropsychological function in four patients with ROHHAD syndrome and ganglioneuroblastoma. In these patients the autoimmune process was considered plausible, given that neuroblastoma is associated with autoimmune-mediated paraneoplastic syndromes, as opsoclonus-myoclonus syndrome.\textsuperscript{13,26,27} In another 15-old-year patient with ROHHAD syndrome with focal inflammation in the periaqueductal grey matter and hypothalamus, corticosteroids, immunoglobulins and mycophenolate mofetil long-term administration had a beneficial effect for the neuropsychological function and autonomic disorders.\textsuperscript{28} Autopsy findings in six children with ROHHAD syndrome revealed features of encephalitis characterized by lymphocytic infiltrate mainly perivascular, various distributing in the brain, suggesting also the immune mediated pathogenesis.\textsuperscript{29}

Clinical Presentation

The onset of this disease ranges from 0 to 9 years, but the most common onset is in early childhood, at ages between two and four years, with hyperphagia and rapid weight gain. Children with ROHHAD syndrome usually have normal growth and development and good general health prior to onset of symptoms. Clinical presentation of these patients is variable in severity and timing.\textsuperscript{24,5} The clinical presentation is heterogenous, there are cases with marked endocrine involvement, while others exhibit marked behavioral disturbances.

Rapid Obesity

Rapid obesity in early childhood is often the first recognizable sign of the disease.

Hypothalamic Dysfunction

Hypothalamic dysfunction may manifest as growth hormone deficiency, diabetes insipidus, transient syndrome of inappropriate antidiuretic hormone secretion (SIADH), hypodipsia, central precocious puberty, premature adrenarche, amenorrhea, hypogonadotropic hypogonadism, hyperprolactinemia, hypothyroidism, corticotrophin deficiency, low or normal IGF1 level. Dysnatremia
(hypertension and hypernatremia) may be present and is linked with impaired water balancing such as polydipsia or diabetes insipidus. These manifestations appear from months to years following the rapid-onset obesity.

**Autonomic Dysregulation**

Autonomic dysregulation may present as ophthalmologic abnormality, such as blurred vision, altered pupil response to light, strabismus, ptosis, altered perception of pain, gastrointestinal dysmotility with chronic constipation or diarrhea, bradycardia, neurogenic bladder, excessive sweating, thermal dysregulation (hypothermia, hyperthermia), cold hands and feet, livedo reticularis, pseudo Raynaud’s phenomenon, syncope, urinary incontinence, dysarthria.

**Behavioral Disorders**

Behavioral change is the most common form of cognitive dysfunction and the symptoms include mood changes such as irritability and aggression, hyperactivity, fatigue, social withdrawal, poor school performance, intellectual disability, flat affect, hallucination, major depressive disorder, anxiety, attention deficit disorder, self-injurious behavior, obsessive-compulsive disorder, oppositional-defiant disorder, bipolar disorder, and psychosis.

**Neurologic Abnormalities**

Neurologic abnormalities consist of seizure, blurring of consciousness, sleep disturbance, hypersomnia, narcolepsy, developmental delay, developmental regression, gait disturbance, nystagmus, general weakness. Seizures may be related to episodes of hypoxemia due to inadequate ventilator support. Enlargement of the pituitary gland and generalized brain atrophy were also reported.

**Hypoventilation**

Hypoventilation is the most life-threatening feature of ROHHAD syndrome because it can lead to cardiorespiratory arrest. Most of children with ROHHAD syndrome have obstructive sleep apnea, hypoxemia and hypercapnia at early ages, but in more severe cases hypoventilation can also occur while awake. The spectrum of sleep disorders breathing is completed by central sleep apnea, abnormal ventilatory response to carbon dioxide, nocturnal hypoventilation, and cyanotic episodes. Early recognition of respiratory abnormalities raises the index of suspicion of ROHHAD syndrome.

Hypothyroidism, one of the most common associated endocrine disorders can influence the central ventilatory control based on decrease of oxygen consumption.

**Tumors of Neural Crest Origin**

Approximately 40–56% of the patients with ROHHAD syndrome develop tumors of neural crest origin such as ganglioneuroma and ganglioneuroblastoma. These tumors are localized in the chest, abdomen or along the sympathetic nervous system chain. Hamartomatous masses with neural elements were also reported in one case. Most of the children recorded a short period of time (approximately two years) between the onset of obesity and the diagnosis of neural crest origin tumor.

**Dysmorphic Features**

Dysmorphic features as depressed nasal bridge, macrocephaly, anteverted nares and hypertelorism were also described in ROHHAD patients.

**Metabolic Disorders**

Insulin resistance, impaired glucose intolerance, diabetes mellitus, hypertriglyceridemia and progressive fatty liver disease were reported in several cases.

**Other Clinical Manifestations**

Other clinical manifestations may be fever, rash, enuresis, headache, edema, pulmonary hypertension, cough, renal failure, rectal prolapse secondary to dysregulation of the digestive system, scoliosis. Recurrent upper respiratory tract infections are reported in these children.

**Diagnosis**

The diagnosis of ROHHAD syndrome is based on clinical presentation and clinical course and involves a cooperative consultation by specialists in the fields of pediatrics, pulmonology, endocrinology, oncology, psychiatry, otorhinolaryngology, cardiology, surgery, nutrition, and psychology. There is no genetic testing available to diagnose this disorder.

The diagnosis is made based on the presence of following features: (1) rapid-onset obesity starting in early childhood and alveolar hypoventilation during sleep; (2) signs and symptoms of hypothalamic dysfunction and autonomic disturbances; and (3) exclusion of other condition causing similar features, such as congenital central hypoventilation syndrome. Rapid onset obesity and the most common endocrine disorders such as precocious puberty and hypothyroidism are very often the early recognizable
signs. Sequential comprehensive evaluation is recommended for children with ROHHAD syndrome as the clinical presentation is very variable (Table 2).

**Differential Diagnosis**

Because of phenotypic similarities, the differential diagnosis of patients with ROHHAD syndrome, typically involves consideration of another disorder marked by early childhood obesity (Prader–Willi syndrome) and a rare disorder with breathing abnormalities and variable features of autonomic nervous system dysregulation (congenital central hypoventilation syndrome). Divergent and similar clinical features of the ROHHAD syndrome, Prader–Willi syndrome (PWS) and congenital central hypoventilation syndrome (CCHS) are presented in Table 3.

**Table 2 Evaluation Workup in ROHHAD Syndrome**

| Clinical Manifestations       | Investigations                                                                 |
|-------------------------------|-------------------------------------------------------------------------------|
| Obesity                       | Morphometry, Biological and imaging investigations for differential diagnosis |
| Hypothalamic dysfunction       | Hormonal investigations: antidiuretic hormone secretion, IGF-1, thyroid function, prolactin secretion, gonadotropin function, corticotropin function Imaging investigations (ultrasound, MRI) |
| Hypoventilation               | Overnight polysomnography, Nocturnal blood gases, Pulse oximetry              |
| Autonomic dysregulation Cardiovascular | Echocardiography, 24-h Holter monitoring, 24-h arterial blood pressure monitoring, Tilt test |
| Gastrointestinal              | Transglutaminase autoantibodies, Gastrointestinal motility studies            |
| Neuropsychological            | Neurocognitive testing, EEG                                                   |
| Ophthalmological              | Ophthalmological examination                                                 |
| Neural crest tumors           | Abdominal ultrasound, Chest and abdominal MRI, MIGB 123 scintigraphy         |
| Metabolic disorders           | Glucose, cholesterol, triglycerides, insulin                                   |

**Note:** Data from these studies 4,5,32,33,35,38

**Abbreviations:** EEG, electroencephalography; IGF-1, insulin-like growth factor 1; MIGB 123, metaiodobenzylguanidine iodine 123, MRI, magnetic resonance imaging.

**Treatment**

Multidisciplinary care is crucial for the management of these patients, to optimize the quality of life. Another very active and important member of this team is the family. Early diagnosis and adequate conservative intervention are critical for optimizing the quality of life and neurocognitive outcome.

The treatment of ROHHAD syndrome is based on the clinical features (Table 4).

- The obesity control based on the strict caloric intake is difficult and requires the intervention of a nutritionist.
- Moderate exertion is recommended and pulse oximetry monitoring is required during exercise.
- Hypothalamic dysfunction is variable and the treatment may include a strict fluid intake regimen and specific hormone replacement.
- Hypoventilation may need artificial ventilation during sleep in the first years of evolution with progressive need for continuous ventilatory support. These procedures, available at home, may improve the quality of life and prevent sudden death. 4,5,36,37 Early recognition of sleep disorders breathing and targeted therapeutic interventions will limit morbidity and mortality associated with ROHHAD syndrome. 36,37
- Autonomic dysregulation may need various therapeutic interventions according to specific symptoms.
- Neural crest tumors require surgical removal and multimodal treatment. 4,5

**Complications and Evolution**

Insulin resistance, diabetes mellitus, hypertriglyceridemia, progressive fatty liver disease, metabolic syndrome, bradycardia, cor pulmonale, right ventricular hypertrophy, pulmonary hypertension, heart failure and scoliosis have been described in patients with ROHHAD syndrome. 38,39,43,44

Mortality rate is high at 50–60%, due to hypoventilation, cardiopulmonary failure and cardiopulmonary arrest. 4,5,36

**Conclusions and Key Points**

- ROHHAD syndrome is a relatively new disease with multisystemic involvement, with potentially severe evolution. Rapid-onset obesity associated with
Table 3 Clinic and Genetic Diagnostic Criteria in ROHHAD Syndrome, PWS and CCHS

| Diagnostic Criteria                  | ROHHAD Syndrome | PWS | CCHS |
|-------------------------------------|-----------------|-----|------|
| Clinical features                   |                 |     |      |
| Rapid-onset obesity                 | Yes             | Yes | No   |
| Hypoventilation                     | Yes             | Sometimes | Yes |
| Hypothalamic dysfunction            | Disturbance of maintenance of water balance | No | No |
|                                     | Growth hormone deficiency | Sometimes | No |
|                                     | Hypothyroidism   | Sometimes | No |
|                                     | Hyperprolactinemia | Yes | No  |
|                                     | Adrenal dysfunction | Sometimes | No |
|                                     | Precocious puberty | Sometimes | No |
|                                     | Hypogonadism     | Sometimes | No |
| Autonomic dysregulation             | Bradycardia      | No  | Sometimes |
|                                     | Gastrointestinal dysmotility | Yes | Yes |
|                                     | Thermal dysregulation | Yes | Yes |
|                                     | Cold extremities | Yes | No  |
|                                     | Increased sweating | Yes | No  |
|                                     | Ophthalmologic abnormalities | Yes | Yes |
|                                     | Altered pain perception | Yes | Yes |
| Behavioral disorders                | Sometimes       | Yes | Sometimes |
| Neurologic abnormalities            | Seizures        | Sometimes | Sometimes |
|                                     | Sleep abnormalities | No | Yes  |
| Neural crest tumors                 | Yes             | No  | Yes  |
| Decreased fetal movement            | No              | Yes | No   |
| Neonatal hypostonia                 | No              | Yes | No   |
| Delayed motor skills                | No              | Yes | Yes  |
| Delayed cognitive development       | Yes             | No  | Yes  |
| Dysmorphic facial features          | Yes             | Yes | Sometimes |
| Small hands and feet                | No              | Yes | No   |
| Scoliosis                           | Yes             | Yes | No   |
| Genetic testing                     | No candidate genes | Parent-specific DNA methylation | PHOX2B gene mutation |

Note: Data from these studies.64–42
Abbreviations: CCHS, congenital central hypoventilation syndrome; DNA, deoxyribonucleic acid; PHOX2B, paired-like homeobox protein 2B; PWS, Prader–Willi syndrome.

- Hypothalamic dysfunction and central hypoventilation are the clinical markers of the disease.
- The etiology of ROHHAD syndrome is still obscure, although genetic, epigenetic and immune-modulated etiopathogenic theories were formulated.
- As there are not specific laboratory findings, the diagnosis is only supported by clinical criteria and the exclusion of CCHS based on the absence of PHOX2B gene mutation.
- Therapeutic options addressed to each clinical disturbance are supportive and involve a multidisciplinary team. Careful monitoring of these children is essential to limit morbidity and mortality associated with ROHHAD syndrome.
Table 4 Therapeutic Options in ROHHAD Syndrome

| Clinical Manifestations | Treatment |
|-------------------------|-----------|
| Obesity                 | Diet, Exercise |
| Hypothalamic dysfunction| Specific hormone replacement |
| Hypoventilation         | Artificial ventilation during sleep or continuous ventilatory support |
|                         | • mask ventilation |
|                         | • continuous positive airway pressure |
|                         | • mechanical ventilation |
|                         | • tracheostomy |
| Autonomic dysregulation | Cardiovascular |
|                         | Antihypertensive medication |
|                         | Cardiac pacemaker |
| Gastrointestinal        | Stool softeners |
| Neurropsychological     | Antiepileptics |
|                         | Antipsychotics |
| Thermal dysregulation   | Regulation of ambient temperature |
| Neural crest tumors     | Surgical removal |
|                         | Multimodal treatment |
| Metabolic disorders     | Antidiabetic drugs |
|                         | Hypolipidemic drugs |

Note: Data from these studies.4,5

Disclosure

The authors report no conflicts of interest in this work.

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