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REVIEW

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 al[1] 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]

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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.[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.

Genetic Theory

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

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

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, aniridia, genitourinary anomalies, mental retardation	2
HCRT	Hypocretins	Sleep-wake cycle regulation, energy balance, regulation of food intake	Narcolepsy	14
HCRTR1	Hypocretin receptor type 1	Sleep-wake cycle regulation, energy balance, regulation of food intake	Narcolepsy	14
HCRTR2	Hypocretin receptor type 1	Sleep-wake cycle regulation, energy balance, regulation of food intake	Narcolepsy, cluster headache	14
HTR_{1A}	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 1	Craniofacial and nervous system development, neuronal differentiation, regulator of the circadian cycle	Smith–Magenis syndrome, alacrimia, achalasia, mental retardation	17

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.[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.[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_{1A}), orthopedia (*OTP*), pituitary adenylate cyclase activating polypeptide (*PACAP*) were analyzed but they were not significantly correlated with ROHHAD syndrome.[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.[13–15] Mutations in *NECDIN* gene with role in respiratory rhythmogenesis and hypothalamic insufficiency and in *ASCLI* gene, required for the generation of ventral neuroendocrine neurons which acts as potential modifier gene of *PHOX2B* were not correlated with ROHHAD syndrome.[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.[17]

Epigenetic Theory

Epigenetic hypothesis is supported by report of discordant presentation of ROHHAD syndrome in monozygotic twins.[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.[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.[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.[23,24] Association with celiac disease, may suggest further evidence for immune-mediated etiology.[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.[15,26,27] 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.[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.[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.[2,4,5] 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

(hypernatremia and hyponatremia) may be present and is linked with impaired water balancing such as polydipsia or diabetes insipidus.[4,5,30,31,34] 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.[4,5,32–34]

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.[4,5,26–28,34]

Neurologic Abnormalities

Neurologic abnormalities consist of seizure, blurring of consciousness, sleep disturbance, hypersomnolence, 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.[4,5,34,35]

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.[36,37]

Hypothyroidism, one of the most common associated endocrine disorders can influence the central ventilatory control based on decrease of oxygen consumption.[2,4,5]

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.[3–5] 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.[4] Most of the children recorded a short period of time (approximatively two years) between the onset of obesity and the diagnosis of neural crest origin tumor.[5]

Dysmorphic Features

Dysmorphic features as depressed nasal bridge, macrocephaly, anteverted nares and hypertelorism were also described in ROHHAD patients.[32]

Metabolic Disorders

Insulin resistance, impaired glucose intolerance, diabetes mellitus, hypertriglyceridemia and progressive fatty liver disease were reported in several cases.[2,5,38]

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.[4,5,33] Recurrent upper respiratory tract infections are reported in these children.[39]

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, pneumology, 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, gonadotropic function, corticotropic 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 I^{123} scintigraphy
Metabolic disorders		Glucose, cholesterol, triglycerides, insulin

Note: Data from these studies.[4,5,32,35,38]

Abbreviations: EEG, electroencephalography; IGF-1, insulin-like growth factor 1; MIGB I^{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 therapeutical 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	Yes	No	No
	Growth hormone deficiency	Sometimes	Sometimes	No
	Hypothyroidism	Sometimes	Sometimes	No
	Hyperprolactinemia	Yes	No	No
	Adrenal dysfunction	Sometimes	Sometimes	No
	Precocious puberty	Sometimes	Sometimes	No
	Hypogonadism	Sometimes	Sometimes	No
Autonomic dysregulation	Bradycardia	Sometimes	No	Sometimes
	Gastrointestinal dysmotility	Yes	No	Yes
	Thermal dysregulation	Yes	Yes	Yes
	Cold extremities	Yes	No	
	Increased sweating	Yes	No	Yes
	Ophthalmologic abnormalities	Yes	Yes	Yes
	Altered pain perception	Yes	Yes	Yes
Behavioral disorders		Sometimes	Yes	Sometimes
Neurologic abnormalities	Seizures	Sometimes	Sometimes	Sometimes
	Sleep abnormalities	No	Yes	Sometimes
Neural crest tumors		Yes	No	Yes
Decreased fetal movement		No	Yes	No
Neonatal hypotonia		No	Yes	No
Delayed motor skills		No	Yes	Yes
Delayed cognitive development		Sometimes	Yes	Yes
Dysmorphic facial features		Sometimes	Yes	Sometimes
Small hands and feet		No	Yes	No
Scoliosis		Sometimes	Yes	No
Genetic testing		No candidate genes	Parent-specific DNA methylation	*PHOX2B* gene mutation

Note: Data from these studies.[6,40–42]

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 etiopathogenetic 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 Antidiarrhea drugs
	Neuropsychological	Antiepileptics Antipsychotics
	Thermal dysregulation	Regulation of ambient temperature
Neural crest tumors		Surgical removal Multimodal treatment
Metabolic disorders		Antidiabetic drugs Hypolipemiant drugs

Note: Data from these studies.[4,5]

Disclosure

The authors report no conflicts of interest in this work.

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