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Rapid-Onset Obesity With Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation Presenting in Childhood

Diego Ize-Ludlow, MD, Juliette A. Gray, BSc, Mark A. Sperling, MD, Elizabeth M. Berry-Kravis, MD, PhD, Jeff M. Milunsky, MD, I. Sadaf Farooqi, MD, PhD, Casey M. Rand, BSc, Debra E. Weese-Mayer, MD

ABSTRACT

OBJECTIVE. The goal was to characterize the phenotype and potential candidate genes responsible for the syndrome of late-onset central hypoventilation with hypothalamic dysfunction.

METHODS. Individuals with late-onset central hypoventilation with hypothalamic dysfunction who were referred to Rush University Medical Center for clinical or genetic assessment in the past 3 years were identified, and medical charts were reviewed to determine shared characteristics of the affected subjects. Blood was collected for genetic testing of candidate genes (PHOX2B, TRKB, and BDNF) and for high-resolution conventional G-banding, subtelomeric fluorescent in situ hybridization, and comparative genomic hybridization analysis. A subset of these children were studied in the Pediatric Respiratory Physiology Laboratory at Rush University Medical Center.

RESULTS. Twenty-three children with what we are now naming rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation were identified. Comprehensive medical charts and blood for genetic testing were available for 15 children; respiratory physiology studies were performed at Rush University Medical Center on 9 children. The most characteristic manifestations were the presentation of rapid-onset obesity in the first 10 years of life (median age at onset: 3 years), followed by hypothalamic dysfunction and then onset of symptoms of autonomic dysregulation (median age at onset: 3.6 years) with later onset of alveolar hypoventilation (median age at onset: 6.2 years). Testing of candidate genes (PHOX2B, TRKB, and BDNF) revealed no mutations or rare variants. High-resolution chromosome analysis, comparative genomic hybridization, and subtelomeric fluorescent in situ hybridization results were negative for the 2 patients selected for those analyses.

CONCLUSIONS. We provide a comprehensive description of the clinical spectrum of rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and auto-
nomic dysregulation in terms of timing and scope of symptoms, study of candidate genes, and screening for chromosomal deletions and duplications. Negative PHOX2B sequencing results demonstrate that this entity is distinct from congenital central hypoventilation syndrome.

The classic cases of that presents exclusively after infancy, is distinct from nervous system dysregulation, with tumors of neural period. Similarly, the CCHS phenotype includes autonomic nervous system. As CCHS gains visibility, some of these ancestral functions as they relate to the autonomic nervous system. As CCHS gains visibility, other, seemingly overlapping diseases can be distinguished. Late-onset central hypoventilation syndrome (LO-CHS) with hypothalamic dysfunction (HD) is a less well known but potentially related condition of autonomic dysregulation. LO-CHS/HD was first described in 1965. LO-CHS/HD has a variable presentation including the following constellation of symptoms: hyperphagia and obesity, alveolar hypoventilation, altered respiratory control, thermal dysregulation, water imbalance, pain hyposensitivity, behavioral disorders, strabismus, pupillary anomalies, hyperprolactinemia, altered onset of puberty, and tumors of neural crest origin. In 2000, Katz et al. reported on 1 child and provided a comprehensive review of 10 previously published cases of children with LO-CHS. One more case was reported subsequently. Katz et al. suggested that LO-CHS/HD, an entity that presents exclusively after infancy, is distinct from CCHS. The classic cases of PHOX2B mutation-confirmed CCHS present in the newborn period with alveolar hypoventilation in the absence of primary lung, cardiac, or neuromuscular abnormalities or an identifiable brain-stem lesion that can account for the hypoventilation. However, a growing number of individuals with PHOX2B mutation-confirmed CCHS are being identified with presentation in childhood and adulthood, in contrast to the typical presentation in the newborn period. Similarly, the CCHS phenotype includes autonomic nervous system dysregulation, with tumors of neural crest origin and endocrine abnormalities, including growth hormone deficiency and hypothyroidism (unpublished data), in a subset of children.

There seems to be overlap in the clinical presentation of LO-CHS/HD and CCHS, but introduction of PHOX2B as the disease-defining gene for CCHS allows for genetic distinction of LO-CHS/HD and CCHS and the opportunity to distinguish the 2 disease entities more clearly.

Two other candidate genes that might account for the phenotype of LO-CHS/HD encode the neurotrophin brain-derived neurotrophic factor (BDNF) and its receptor, TRKB, both of which are involved in neuronal development and maintenance and synaptic plasticity. Furthermore, evaluation of numerical and structural chromosome rearrangements with high-resolution, metaphase, comparative genomic hybridization (CGH) for patients with neurocognitive delays, with or without congenital anomalies/ unusual phenotypes, has proved useful for uncovering the etiology and demonstrating interstitial chromosome deletions and duplications as small as 3 megabases.

Taken together, the phenotype of LO-CHS/HD suggests a cohesive entity that might have a genetic basis. In an effort to describe more fully the phenotype of LO-CHS/HD, we sought (1) to identify all children with symptoms consistent with this diagnosis who were referred for physiologic study or genetic testing in order to provide clear diagnostic criteria, (2) to rename the disease, to improve and to expedite patient identification and treatment, (3) to provide recommendations for testing, to confirm the diagnosis and to optimize long-term follow-up monitoring, and (4) to conduct candidate gene analysis.

METHODS

Case Identification

Individuals with clinical features consistent with LO-CHS/HD who were referred to Rush University Medical Center (RUMC) for clinical or genetic assessment between 2002 and 2006 were identified for inclusion in this institutional review board-approved study. Medical charts for each proband were reviewed by 2 authors (Drs Ize-Ludlow and Weese-Mayer), to determine the shared characteristics of LO-CHS/HD. Additional testing or records were requested on a case-by-case basis, to ensure uniform clinical assessments. Some of the children were studied in the Pediatric Respiratory Physiology Laboratory at RUMC.

Criteria for Preliminary Diagnosis

Our criteria for LO-CHS/HD included onset of alveolar hypoventilation after the age of 2 years and evidence of HD, as defined by ≥1 of the following findings: rapid-onset obesity, hyperprolactinemia, central hypothyroidism, disordered water balance, failed growth hormone stimulation test, corticotropin deficiency, or delayed or precocious puberty.

Medical Chart Review

All available clinical events, physical examination results, ancillary studies, laboratory data, diagnoses, and treatments were added to a deidentified database. The database was examined for patterns in presentation.
Height, weight, and BMI percentiles were calculated by using Epi Info 3.3.2 (Centers for Disease Control and Prevention, Atlanta, GA).

DNA Analyses

Sample Preparation and Testing Procedures
DNA from blood samples was prepared according to standard procedures and screened for the polyalanine expansion mutation in PHOX2B that is characteristic of CCHS. If this standard clinical test revealed the normal genotype coding for 20 alanine repeats on each allele, then institutional review board-approved, informed consent was obtained for sequencing of the entire coding sequence and intron-exon boundaries of PHOX2B, as well as other candidate genes. Genotyping of the PHOX2B polyalanine repeat, sequencing of the PHOX2B gene, and screening for mutations in BDNF and NTRK2 (the gene encoding TRKB) were performed as described by Weese-Mayer et al., Garcia-Barcelo et al., and Gray et al., respectively. In a subset of cases, high-resolution chromosome analysis, high-resolution metaphase CGH, and subtelomeric fluorescent in situ hybridization (FISH) analysis were performed.

High-Resolution Chromosome Analysis
Harvesting and G-banding were performed according to standard procedures. Twenty metaphases were analyzed at a resolution exceeding 600 bands.

High-Resolution Metaphase CGH
Slides with normal lymphocyte metaphase chromosomes for CGH analysis were stored at −20°C before hybridization. CGH was performed as described by Kirchhoff et al. The CGH hybridization slides were analyzed by using CytoVisionSystem 2.72 high-resolution CGH analysis software (Applied Imaging, Santa Clara, CA). Ten to 15 metaphases were captured by using a Zeiss fluorescence microscope with an integrating charge-coupled device camera (Photometrics, Tucson, AZ). The green (patient DNA) to red (reference DNA) fluorescence ratio along the length of the chromosomes was calculated. The standard reference interval was based on an average of normal cases, as described by Kirchhoff et al. The intervals were scaled automatically to fit the test case. The mean ratio profile of each case, with 99.5% confidence intervals, was compared with the average ratio profile of the normal cases, with similar confidence intervals.

Subtelomeric FISH Analysis
FISH with a subtelomeric DNA probe panel specific for the subtelomeric ends of each chromosome arm was performed according to the manufacturer’s instructions (Abbott Molecular, Des Plaines, IL). Computer-assisted analyses were performed by using a Zeiss Axioskop 2 fluorescence microscope with an integrating charge-coupled device camera (Photometrics).

RESULTS

Case Identification
We identified 23 referred children with clinical features consistent with LO-CHS/HD. Comprehensive medical charts were available for 15 of those children (6 male subjects and 9 female subjects), of whom 9 were studied in the Pediatric Respiratory Physiology Laboratory at RUMC. Referrals were primarily from pediatric pulmonologists, because of hypoventilation without recognition of the associated abnormalities.

Phenotype Data for LO-CHS/HD

Prevalent Manifestations
Review of the 15 cases with comprehensive medical charts revealed many characteristic features that occurred in all patients, as well as rare features that occurred in only a few patients. The age at onset and the frequency of each symptom are provided in Tables 1 and 2, respectively. The most prevalent manifestations were overweight (BMI of >95th percentile) with rapid-onset obesity and alveolar hypoventilation, followed in frequency by ophthalmologic manifestations, gastrointestinal dysmotility, and thermal dysregulation. The temporal relationships of these phenotypic features to one another are presented in Figs 1 and 2. The earliest manifestations were hypothalamic (median age at onset: 3 years), followed by autonomic (median age at onset: 3.58 years), behavioral (median age at onset: 4.8 years), and then respiratory (median age at onset: 6.17 years). All data in the sections that follow pertain to the 15 patients for whom comprehensive data were available. In the respiratory section, however, findings for the 15 patients are reviewed and then physiologic studies for the 9 children who were evaluated comprehensively at RUMC are reported.

HD
Evidence of HD was found for all 15 patients for whom complete medical charts were available. For 12 patients (80%), the initial symptom was rapid-onset obesity, which began in early life (see Fig 3 for BMI curves for patients with available growth data); for the remaining 3 patients, the initial symptom was hypernatremia (n = 2; 13%) or polydipsia (n = 1; 6%). The second most common hypothalamic feature was altered water balance for 13 patients (86%), presenting most commonly as hypernatremia (n = 7; 46%) and leading to 6 of those 7 patients being classified as having diabetes insipidus but without a confirmatory water deprivation test. Although the 6 patients who were classified as having diabetes insipidus experienced some improvement with the use of desmopressin, water intake designed to meet minimal
daily requirements resolved the hypernatremia for all 7 affected patients. Four patients (26%) suffered episodes of hyponatremia (2 classified as transient syndrome of inappropriate antidiuretic hormone secretion, temporally associated with the use of carbamazepine in 1 patient).

Nine patients (60%) had growth hormone stimulation tests performed; all of them were reported to have a maximal growth hormone response of <10 ng/mL, which is generally considered as evidence for growth hormone deficiency. Although 4 patients displayed deceleration of their growth rate, only 3 of those 4 patients had short stature, defined as height below the 5th percentile. Nevertheless, 6 of the 9 patients were treated with growth hormone, without evidence of improvement in body composition (BMI). With a strict diet and exercise program one of the patients showed significant improvement in BMI, with no evident improvement in clinical features. Other prominent features of HD were hyperprolactinemia (n = 7; 46%), hypothyroidism (n = 5; 33%), adrenal insufficiency (n = 4; 26%), and alterations in pubertal development (n = 4; 26%).

### Respiratory Manifestations

Of the 15 patients with available comprehensive medical charts, 9 (60%) experienced cardiorespiratory arrest. For 4 of those 9 patients, there was evidence of abnormal respiratory control before the arrest, manifested as hemoglobin desaturation during sleep for 2, cyanotic episodes during wakefulness for 1, and obstructive sleep apnea for 1. These manifestations were present from 2 months to a few days before the cardiopulmonary arrest. Obstructive sleep apnea was present for 8 of the 15 patients, and it preceded central hypoventilation for 2. All 15 patients demonstrated alveolar hypoventilation; during the same initial evaluation, obstructive sleep apnea was also documented for 5 patients (33%). Seven (47%) of the 15 patients required 24-hour/day artificial ventilation, with the remainder needing support during sleep only. The support was provided with a tracheostomy and mechanical ventilation in 7 cases (47%) and with bilevel positive airway pressure mask ventilation in 8 cases (53%). Patients who required 24-hour/day ventilation had an earlier onset of respiratory manifestations, with a median onset at 3.8 years for the 24-hour/day ventilation group, compared with 7.8 years for the nighttime-only ventilation group (P = .03, Mann-Whitney test). No clinical differences in HD or autonomic dysregulation were found between patients who required continuous versus nighttime-only ventilatory support.

All 9 patients studied in the Respiratory Physiology Laboratory at RUMC were evaluated awake and asleep, in a temperature-controlled room. While awake, all 9 patients demonstrated relative tachypnea during spontaneous breathing, regardless of the measured hemoglo-
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SIADH indicates syndrome of inappropriate antidiuretic hormone secretion; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor-binding protein; ADHD, attention-deficit/hyperactivity disorder.
bin saturation and end tidal carbon dioxide level (mean ± SD respiratory rate: 34 ± 13 breaths per minute). All 9 patients demonstrated alveolar hypoventilation, with variable severity of resultant hypercarbia (mean ± SD end tidal carbon dioxide level: 56 ± 7 mm Hg) and hypoxemia (mean ± SD hemoglobin saturation: 89 ± 6%) during wakefulness. All 9 children demonstrated alveolar hypoventilation during spontaneous breathing in non-rapid eye movement sleep, but none demonstrated an increase in rate or depth of breathing in response to the resulting endogenous challenges of hypercarbia (mean ± SD end tidal carbon dioxide level: 62 ± 13 mm Hg) and hypoxemia (mean ± SD hemoglobin saturation: 75 ± 17%). In rapid eye movement sleep with artificial ventilatory support, none of the children added “extra breaths” to their mechanical ventilator/bilevel positive airway pressure respiratory rate. One of the 9 children demonstrated obstructive sleep apnea in spontaneous breathing trials during sleep. Two of the 9 patients were reported as being “great swimmers,” with parental reports of cyanosis during swimming.

Among the 9 children studied at RUMC, 5 breathed spontaneously while awake, but 2 of those 5 children required supplemental oxygen because of apparent hypoventilation. Four of the 9 children had a tracheostomy and mechanical ventilation 24 hours/day, typically in the pressure-plateau mode to optimize oxygenation (hemoglobin saturation: ≥95%) and ventilation (end tidal carbon dioxide level: 35–45 mm Hg). Five of the 9 children used bilevel positive airway pressure mask ventilation in the spontaneous timed mode for all sleep time; mask ventilation was unsatisfactory for the 2 children with more-severe awake hypoventilation and oxygen requirements, and a tracheostomy was recommended.

Autonomic Dysregulation
Symptoms of autonomic dysregulation were identified for all 15 patients for whom comprehensive medical charts were available. The most common manifestations were ophthalmologic, occurring among a total of 13 patients (86%). Eight patients had pupillary dysfunction (primarily altered responses to light) and 7 strabismus; 4 patients had both. Poor upward gaze and opsoclonus were reported for 2 patients each; alacrima, increased blinking, oculomotor apraxia, and ptosis were each reported for 1 patient.

Gastrointestinal dysmotility was reported for 10 patients (66%). Constipation and chronic diarrhea were the most common forms of dysmotility (present for 5 and 4 patients, respectively). Two of the patients with chronic diarrhea developed rectal prolapse; 2 of the patients with constipation were also reported to have gastroesophageal reflux. Thermal dysregulation, manifest as episodes of hyperthermia or hypothermia, were reported for 11 patients (73%). Tumors of neural crest origin were described for 5 (33%) of the 15 patients, that is, ganglioneuroblastoma for 3 and ganglioneuroma for 2. These neoplasms were diagnosed at a median of 2.4 years (range: 0–9 years) after the onset of HD and hypoventilation. Three of those tumors were found in the chest, and 2 were found in the abdomen.

Developmental Disorders
Of the 15 patients with comprehensive records, 3 (20%) were reported to have developmental delays, documented before the onset of hypoventilation for 1 patient. One of the patients with developmental delay was later diagnosed as having mild mental retardation. Three other patients (20%) presented developmental regression, 1 before and 2 after the onset of hypoventilation. One of the patients with developmental regression was also diagnosed as having pervasive developmental disorder, attention-deficit/hyperactivity disorder, and Asperger’s syndrome.

Behavioral Disorders
Eight (53%) of the 15 patients were reported to have behavioral disorders. Two patients were diagnosed as having depression, 1 of whom was diagnosed as also having Tourette’s syndrome, obsessive-compulsive disorder, and episodes of psychosis.

Other Findings
To date, 1 of the 15 patients has died (the patient was found disconnected from ventilatory support, cyanotic with a weak pulse, and could not be resuscitated). Two patients were found to have abnormalities on brain MRI.
scans before suffering cardiorespiratory arrest (a self- resolved Rathke’s cleft cyst and hypointensities in the pons and midbrain). Five patients (33%) were found to have brain MRI abnormalities after experiencing cardiorespiratory arrest (basal ganglia hypointensities for 2 patients and hypointensities in the pons and midbrain, ischemic injury in the frontal, parietal, and occipital lobes, and a partial empty sella for 1 patient each). Five patients (33%) were reported to have generalized tonic-clonic seizures at the time of initial diagnosis or associated with subsequent episodes of hypoxemia. One of the patients has significant seizure activity and no longer communicates verbally.

Other common characteristics are described on Table 1. Abnormalities not included in the aforementioned categories were found in isolated patients and are provided in Tables 1 and 2.

Genetic Testing

Tested Group
Genetic testing was performed for 15 of the 23 identified children for the clinical PHOX2B assay and sequencing of the PHOX2B gene was performed on 11 children for the TRKB and BDNF genes. Two samples were studied through high-resolution chromosome analysis, CGH, and subtelomeric FISH.

PHOX2B
None of the tested children with the LO-CHS/HD phenotype had a CCHS-related mutation in the PHOX2B gene.

TRKB and BDNF
No novel or rare variants were identified in the coding regions of either NTRK2 or BDNF for these patients. Two of the 11 subjects were heterozygous for the previously reported, common BDNF polymorphism Val66Met (rs6265), which reflects the expected frequency in the population.30–33

High-Resolution Chromosome Analysis, CGH, and Subtelomeric FISH
High-resolution chromosome analysis, CGH, and subtelomeric FISH results were negative for the 2 patients selected for these analyses.

Other Testing
Five (33%) of these patients had previous negative testing for Prader-Willi syndrome (DNA methylation), and 1
tested negative for the DiGeorge syndrome-associated chromosome 22q11.2 microdeletion. Karyotyping was performed for 4 patients, and results were normal for all of them.

**DISCUSSION**

On the basis of the findings from our systematic analysis of comprehensive medical charts, previously reported cases, and our clear genetic distinction between this syndrome of LO-CHS/HD and CCHS, we propose the term rapid-onset obesity with HD, hypoventilation, and autonomic dysregulation (ROHHAD) for this entity. A remarkable feature of these patients is the apparent normality of their first 2 to 4 years of life, with sudden onset of HD, typically with the onset of rapid weight gain and obesity early in life, followed by autonomic dysregulation and later hypoventilation. There is wide variation in the reported age at onset of autonomic dysfunction, as well as in the interval between the onset of HD and hypoventilation. If it is not identified or is treated inadequately, then the alveolar hypoventilation can be fatal, as evidenced by the high incidence of cardiorespiratory arrest in this group, or induce potential morbidity. The clinical management of these patients requires detailed physiologic assessment, including comprehensive evaluation in the baseline state and with perturbation; evaluation of the hypothalamic-pituitary axis with hormonal replacement when needed; respiratory physiologic assessment during wakefulness and sleep; and MRI or computed tomographic screening of the chest and abdomen for neural crest tumors (ganglioneuromas or ganglioneuroblastomas). Because of the unclear nature of the water balance abnormalities, we recommend performing formal water deprivation tests, with measurements of arginine-vasopressin levels. Brain imaging should be performed to exclude the possibility of hypothalamic-pituitary abnormalities attributable to intracranial lesions. The clinical evaluation should be performed with the understanding that some of the features noted might not be explained by more-common disorders, as illustrated by the fact that many of these patients were classified as having diabetes insipidus, whereas a more appropriate diagnosis might have been hypodipsic hyponatremia and perhaps partial diabetes insipidus. Another example is treatment of these patients with growth hormone on the basis of a failed growth hormone stimulation test. Although abnormalities in the growth hormone axis might exist, these were not clinically evident from the growth patterns; moreover, severe obesity can result in lack of growth hormone responses during stimulation tests.

The available data have allowed us to detail more thoroughly the characteristics of this syndrome, including the earliest presenting symptoms and typical time course, and to document the previously unreported high incidence of cardiorespiratory arrests in this syndrome. Better characterization and the availability of a larger database would be invaluable for advancing knowledge regarding the cause of this syndrome and improving the identification and treatment of these children and might provide key insights into the normal physiologic processes of some of the most basic, vital, neurologic functions. Such characterization could likely guide future candidate gene analysis. Although some features of the CCHS phenotype are seen in patients with ROHHAD, the latter demonstrate an even wider spectrum of involved systems, suggesting a defect in a more-proximal or different genetic pathway involved in autonomic nervous system differentiation or development. The absence of PHOX2B mutations in patients with ROHHAD establishes this syndrome as a separate entity.

On the basis of the phenotype seen in animal studies, BDNF/TRKB signaling seemed to be a reasonable candidate pathway that could contribute to several of the features seen in patients with ROHHAD. Firstly, BDNF-deficient mice have deficits in control of breathing. Indeed, BDNF is known to be important in the develop-

![Figure 3](image-url)
ment and maintenance of neuronal populations involved in respiratory control. Neurotrophin signaling has also been implicated in the development and function of sensory neurons involved in pain sensation. Homozygous null mutations in Ntrk2, the gene encoding TrkB, are lethal in rodents. However, in the first week of life, surviving Ntrk2<sup>−/−</sup> mice do not respond to sharp pinpricks in the vibrissae region. Furthermore, TRKB syndrome should guide us to the genetic basis for this disease. Detailed phenotyping and new insights into pathways relevant to the autonomic and endocrine functions of the nervous system should be considered. With comprehensive studies during wakefulness and sleep in a pediatric respiratory physiology laboratory as soon as the diagnosis of ROHHAD is suspected. Once the diagnosis is confirmed, it is essential to monitor the child with serial studies at 3- to 6-month intervals, to ensure optimal oxygenation and ventilation as indicated during wakefulness and sleep, aiming for hemoglobin saturation values of ≥95% and end tidal carbon dioxide values of 35 to 45 mm Hg. With early ventilatory support, highly trained home nursing with continuous pulse oximetry, end tidal carbon dioxide measurements during sleep, and spot checks during wakefulness, and close follow-up monitoring, the ventilatory care for children with ROHHAD can be optimized. Vigilant screening for tumors of neural crest origin should also be a part of ongoing care for children with ROHHAD, with chest and abdominal imaging every 12 to 18 months. If no tumor is identified in 10 years, then it would be reasonable to decrease the frequency of imaging to every 2 years. By providing a detailed clinical description, a name that reflects the main features of this syndrome, and guidelines for management, we aspire to facilitate the earlier recognition, appropriate treatment, and characterization of the molecular origin of this syndrome.

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