Endocrine Manifestations of the Rapid-Onset Obesity with Hypoventilation, Hypothalamic, Autonomic Dysregulation, and Neural Tumor Syndrome in Childhood

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Context: Rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation, and neural tumor (ROHHADNET) is a newly described syndrome that can cause cardiorespiratory arrests and death. It mimics several endocrine disorders or genetic obesity syndromes during early childhood and is associated with various forms of hypothalamic-pituitary endocrine dysfunctions that have not yet been fully investigated.

Objective: The current report aspires to facilitate the earlier recognition and appropriate treatment of the ROHHADNET syndrome when children present with various endocrine manifestations, such as early obesity, growth failure, pseudo-Cushing's syndrome, glucocorticoid insufficiency, congenital hypopituitarism, or adrenal tumors. A more widespread knowledge of the syndrome will help characterize its molecular origin.

Design: Endocrine studies were performed in six patients admitted for seemingly common early-onset obesity associated with growth failure in five of them. The six patients later showed distinctive features of the ROHHADNET syndrome.

Results: Abnormalities of the pituitary adrenal axis ranged from a true Cushing-like profile (one of six), to glucocorticoid deficiency with normal ACTH (two of six). Complete GH deficiency with low IGF-I was observed in four of six, hypogonadotropic hypogonadism in four of six, hyperprolactinemia in six of six, and various degrees of TSH/T_4 abnormalities in five of five patients. All had increased natremia without diabetes insipidus. Five children had unilateral macroscopic adrenal ganglioneuroma. Two patients died at 8.5 and 12 yr of age.

Conclusions: Various hypothalamic-pituitary endocrine dysfunctions are associated with ROHHADNET, carrying a risk of misdiagnosis until other elements of the syndrome make it more easily recognizable. Given its severity, ROHHADNET syndrome should be considered in all cases of isolated, rapid, and early obesity. **(*J Clin Endocrinol Metab* 93: 3971–3980, 2008)**

Central hypoventilation syndrome is a heterogeneous group of seemingly overlapping diseases. Paired-like homeobox 2B (PHOX2B) was identified as the disease-causing gene in patients with congenital central hypoventilation syndrome (CCHS) (1–6). CCHS was initially known to occur in newborns exclusively (1–3), but PHOX2B mutations were later identified in children and adults with CCHS (4–6). However, other patients with central hypoventilation do not have PHOX2B mutations, among whom a subgroup with late-onset central hypoventilation syndrome and hypothalamic dysfunction (HD) was first

0021-972X/08/$15.00/0

Printed in U.S.A.

doi: 10.1210/jc.2008-0238 Received February 1, 2008. Accepted July 8, 2008.

First Published Online July 15, 2008

Abbreviations: BMI, Body mass index; CCHS, congenital central hypoventilation syndrome; CT, computed tomography; GN, ganglioneuroma; HD, hypothalamic dysfunction; HDDST, high-dosage dexamethasone suppression test; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; PHOX2B, paired-like homeobox 2B; POMC, proopiomelanocortin; ROHHAD, rapid-onset obesity with hypoventilation, hypothalamic dysfunction, and autonomic dysregulation; ROHHADNET, rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation, and neural tumor; SDS, SD score; UFC, urinary free cortisol.

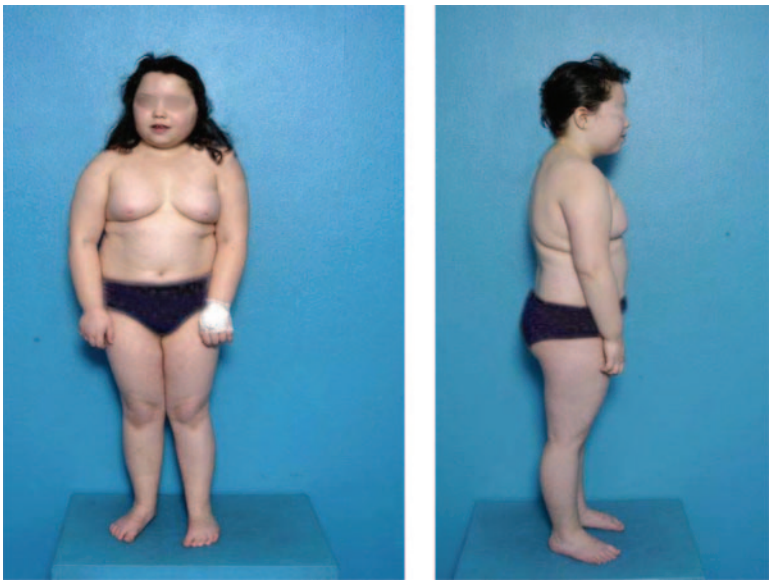

FIG. 1. Physical characteristics of patient 4.

described in 1965 (7). Because obesity is a constant and distinctive feature within this subgroup, a syndrome was recently named rapid-onset obesity with hypoventilation, HD, and autonomic dysregulation (ROHHAD) by Ize-Ludlow *et al.* (8). The variable presentation of ROHHAD includes the following main symptoms: hyperphagia and obesity, alveolar hypoventilation or altered respiratory control, thermal or other hypothalamic dysregulations, neurobehavioral disorders, and tumors of neural crest origin (9–17). Clinically overlapping cases exist because CCHS phenotype can also include autonomic nervous system dysregulation (18), or tumors of neural crest origin (19).

ROHHAD takes place within the 30 pleiotropic syndromes with obesity as a central clinical feature that could affect young children in association with mental retardation, dysmorphic features, and organ-specific developmental abnormalities (20). For a comprehensive list of syndromes in which obesity is a recognized part of the phenotype, see Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim/). Notably, in the vast majority of cases described to date, the causative mutation disrupts the function of hypothalamic integrative centers and results in increased food intake. An extensive search in the cases reported in the pediatric literature revealed no clear-cut manifestations of HD or hypoventilation, or tumors of the sympathetic nervous system in any of these syndromes that could lead them to be misdiagnosed with the fully symptomatic ROHHADNET syndrome. However, yet incomplete forms of ROHHADNET could be confused with several of these syndromes.

On the other hand, two problems specific to the diagnosis of obesity in young children could obscure the recognition of the ROHHADNET syndrome. One is the frequent association of common infantile obesity with secretory dysfunctions of GH (21, 22) and TSH (22), as well as with sleep apnea (23). The other is the association of rapid obesity with growth failure, a distinctive feature of ROHHADNET that is also characteristic of pediatric Cushing's disease (24, 25). Abnormalities of the corticotropic axis, Rathke's cleft cyst, or adrenal tumors that have been reported in ROHHADNET (19) may add to the diagnostic difficulties *vs.* Cushing's syndrome (24, 25). Even in recent reviews, adrenal ganglioneuromas (GNs) are not quoted among adrenal tumors or hyperplasia in childhood (26). Because of the frequent occurrence of these potentially undiagnosed or misdiagnosed neural tumors (GN more frequently than neuroblastoma), we propose to rename the syndrome ROHHADNET for rapid obesity, hypoventilation, hypothalamic, and autonomic dysfunctions, neural tumors. We anticipate that, if the diagnosis of ROHHADNET is not considered by a pediatrician or endocrinologist faced with rapid-onset obesity in a young child, then catastrophic consequences may occur, as noted in many of the cases reported in the literature (8) or the current study.

The current report describes six cases of children referred for rapid-onset obesity and growth failure to the same pediatric endocrinology department between 1988 and 2007 with the clinical suspicion of Cushing's syndrome, in whom the diagnosis of ROHHADNET syndrome was made at referral or years later, even before the syndrome was named, based on the characteristic manifestations found associated with obesity.

Patients and Methods

Patients

Six young children were admitted in 1988, 1991, 1998, 2000, 2003, and 2006, respectively, for the exploration of a rapidly evolving obesity (Fig. 1) associated with a concomitant decrease of growth rate in five of six (Fig. 2 and Table 1). The onset of obesity was dated as the point in time when the weight curve changed its slope to indicate a rapid weight accretion. Parents gave their consent to the studies, and children did the same when they were old enough to be asked. All patients had associated manifestations that are described in Table 1. Endocrine studies displayed numerous abnormalities that are described in Tables 2–5.

For comparison, we used our five youngest patients with Cushing's disease whose main characteristics are presented in Table 5. We also used for comparison young obese patients from the large Saint Vincent de Paul Cohort of Childhood Obesity study described by Le Stunff *et al.* (27), who were recruited for endocrine, metabolic, and genetic studies (27–31) according to the bioethics rules for medical research at the national and institutional levels. This cohort includes 421 children who became obese before the age of 5 yr. Depending on the age at which we wanted to perform comparisons, we selected children from this early-onset obesity subgroup (Tables 2–4).

Methods

All endocrine function tests were performed according to standard operating procedures based on current knowledge and literature. Twenty-four-hour urinary free cortisol (UFC), plasma ACTH, and cortisol were measured using methods described by Assie *et al.* (32). Blood sampling was performed through an indwelling pediatric catheter to minimize stress over the whole period of study. IGF-I and GH concentrations, and other pituitary hormones, were measured using the methods reported in Refs. 28, 29, 32, and 33. Our methods for performing oral glucose tolerance tests (OGTTs) with glucose and insulin

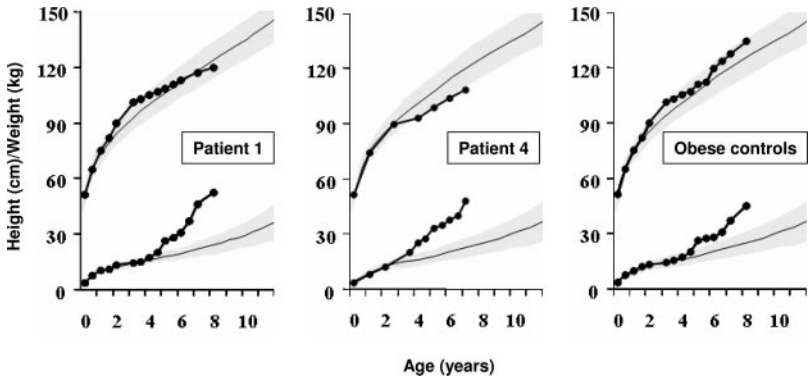

FIG. 2. Height and weight curves in patients 1 and 4 compared with the mean values observed in 48 children (28 females/20 males) who developed common early-onset obesity and for which precise growth data were available.

measurements are described by Dos Santos *et al.* (30). Plasma leptin concentration was measured as reported (31). Measurements of catecholamine and catecholamine metabolites were performed as reported (34).

Results

Early-onset obesity in early childhood

A remarkable feature of these patients is the apparent normality of their first 2–4 yr of life, before the first signs of the ROHHADNET syndrome start to appear (Table 1). In the six patients, the initial manifestation was rapid-onset obesity, which began between 1.5 and 4.3 yr of age (2.8 ± 0.8). Almost simultaneously, height velocity started to decrease at a mean rate of −0.8 ± 0.3 SD score (SDS) per year (Fig. 2). Soon after obesity onset, mean body mass index (BMI) reached 15.6 ± 7.6 and 17.2 ± 8 SDS at 5 and 6 yr of age, respectively, as a result of a continuous and dramatic increase of weight. By 6 yr of age, all children had massive obesity of facio-troncular predominance, often with marked adipomastia (Fig. 1). They had a chubby face, slight buffalo neck, no erythrosis on cheeks, no striae, and a normal skin. Only one parent reported ventilatory symptoms at this age. Clinical examination was negative in six of six children. Primary (erroneous) diagnoses in the referring pediatric centers were common hyperphagic obesity (patients 2, 3, and 5), Prader-Willi syndrome (patient 6), GH deficiency (patient 1), and Cushing's disease (patient 4).

The pituitary adrenal axis (Table 2)

In three of six patients, midnight cortisol value was above 4.4 μg/dl, the cutoff threshold proposed by Batista *et al.* (25) for the diagnosis of pediatric Cushing's disease. However, 24-h UFC was abnormal only in patient 4, reaching values that are only encountered in patients with Cushing's disease (Table 2, and Refs. 24 and 25). Normal diurnal cortisol variation was defined as normal or near normal by a 0800-h value being 2-fold or more the 1900-h value. Two patients lacked such diurnal variation (Table 2), suggesting altered circadian periodicity of corticotropin-releasing factor secretion at the hypothalamic level. Very low

TABLE 1. Main characteristics of the ROHHADNET syndrome in the six studied patients

	Patients					
	1	2	3	4	5	6
Rapid obesity						
Age at onset (yr)	4.3	3	3.1	2.7	2	1.5
BMI at 6 yr (kg/m^2)	22.3	40.4	29	34.7	23.5	43.8
SDS	7.2	25	14	19.7	8.5	28.8
Hypoventilation						
Age at diagnosis (yr)	8.5	4.4	4.3	5.5	8.5	8
Alveolar hypoventilation	Yes	Yes	Yes	Yes	Yes	Yes
Obstructive sleep apnea	No	Yes	No	Yes	No	No
Hypothalamic-pituitary disorders						
Age at diagnosis (yr)	8.5	8.1	4.5	5.5	8.5	9.7
Hypernatremia[a]	156	161	150	151	145	149
Pituitary dysfunctions	Yes	Yes	Yes	Yes	Yes	Yes
Autonomic dysregulation						
Age at diagnosis (yr)	8.5	14	4.5	8	8.9	14
Thermal instability	Yes	Yes	Yes	Yes	Yes	Yes
Ophthalmological	Yes			Yes		
Neurobehavioral disorders						
Age at diagnosis (yr)	5	6				
Mental retardation	Yes	Yes	No	No	No	No
Psychosis	Yes	No	No	No	No	No
GN						
Age at diagnosis (yr)	8.4	7	4.5	6.8	8.6	16
Location	Mediastinal	Right adrenal	Left adrenal	Left adrenal	Left adrenal[b]	Right adrenal
Size (cm diameter)	2	0.5	2.5	3	3	4

[a] Although hypernatremia is defined by a value superior to 160 mEq/liter, we call here hypernatremia values that were consistently greater than +2 SD for age (145 mEq/liter).

[b] See Fig. 3.

TABLE 2. Evaluation of the pituitary-adrenal axis in the six current patients with ROHHADNET compared with 43 age-matched nonobese healthy controls. Patient 4 had an erroneous diagnosis of Cushing's disease.

	Patients						Reference values
	1	2	3	4	5	6	
UFC (μg/m^2·d)[a]	34 ± 2	19 ± 1	13 ± 5	146 ± 10	29 ± 1	6.6 ± 1	17 ± 4
Plasma cortisol (μg/dl)							
0800 h	19/13	27/21	2/1.1	29/44	1.2/1.4	16/13	16.8 ± 1.2
2400 h	5.6/6.4	6/7.1	1.5/1.2	5.3/5.6	1.2/1.8	2.9/6.6	1.7 ± 0.7
0800 h plasma ACTH (pg/ml)	24	39/43	59/52	65/59	27/19	24	24 ± 4
HDDST (% cortisol suppression)[b]	50	67	73	60	90	78	82 ± 4
Diurnal cortisol variation[c]	Yes	Yes	No	Yes	No	Yes	Yes

[a] Mean ± SD of three to six measurements.

[b] Percent suppression = 100 − (after dexamethasone/before dexamethasone × 100).

[c] Defined as normal or near normal 24-h profile measurements over 1–3 d, defined as 0800 h value being 2-fold or more of the 1900 h value.

plasma cortisol levels (<5 μg/dl) were observed in two patients at repeated testing, associated with low-normal UFC and normal ACTH levels, which we tentatively interpreted as a partial glucocorticoid deficiency resulting from a hypothalamic-pituitary regulatory dysfunction. Diurnal plasma cortisol variation was normal in four of six patients. High-dosage dexamethasone suppression tests (HDDSTs) showed adequate suppression of cortisol secretion in all patients (24). We also performed a low-dose 1-mg dexamethasone test in three of six children, although this test has not been studied well in children, as discussed in a recent survey of pediatric Cushing's disease (25). Plasma cortisol at 0800 h the following morning was 1.3 and 1.5 μg/dl, respectively, in patients 1 and 2 [values that are below the cutoff level of 1.8 μg/dl validated in adult patients (35)], and 5.9 μg/dl in patient 4. Pituitary magnetic resonance imaging (MRI) performed at various ages was normal in all patients except in patient 4, in whom a hypodense image was misinterpreted as a corticotropic microadenoma because of the clinical and biological signs mimicking Cushing's disease. After pituitary surgery, the image was reanalyzed as a Rathke's cleft cyst, which had already been reported in a ROHHADNET patient (19). Computed tomography (CT) scan of the adrenal glands revealed adrenal tumors in five of six patients [see the *GN: imaging and pathological features (Table 1)* section].

GN: imaging and pathological features (Table 1)

GNs were diagnosed at a median of 8.6 ± 3.6 yr (range 4.5–16) after the onset of obesity. The locations were the posterior

TABLE 3. Evaluation of the hypothalamic-pituitary function in the six patients compared with corresponding values in age-matched normal children and children with common obesity studied in the same clinic

	Patients						Obese children (n = 41)[c]	Normal children (n = 43)[c]
	1[a]	2[a]	3	4[a,b]	5	6[a]		
Age at test (yr)	8	7.4	8.2	5	8.5	10.4	8.4 ± 0.5	8.2 ± 0.5
GH peak after AI or GB (ng/ml)	3 (GB)	5.3 (AI)	0.6 (AI)	22 (AI)	11 (AI)	6.4 (AI)	8.3 ± 1.1(AI)	16.2 ± 3 (AI) 15.1 ± 3 (GB)
IGF-I (ng/ml)	25	49	90	41	227	115	451 ± 23	350 ± 250
SDS	−2.8	−2.5	−2.1	−2	−1	−2	0.9 ± 0.5	
FT4 (pg/ml)	8.5	9.8	17.1	16	16	12.4	13.8 ± 0.8	14.9 ± 0.7
TSH (μU/ml)	10.7	2.8	3.6	9.1	3.8	6.2	1.9 ± 0.9	1.5 ± 0.8
PRL (ng/ml)	19	39	14	22	31	34	5.3 ± 1.1	5.4 ± 1.2
TRH test								
TSH peak (μU/ml)	55	12.6	46	12	17	18	15 ± 3	14 ± 2
TSH 120 min	47	9.4	41	4	15	16	5 ± 3	6 ± 1
							Obese children (n = 48)[c]	**Normal children (n = 41)[c]**
GnRH test								
Age (yr)	13.4	14.2		14.6		13.8	14.1 ± 0.3	14.3 ± 0.3
LH basal (mU/ml)	<0.5	0.8	<0.5	<0.5	1.5	0.8	2.8 ± 0.3	2.9 ± 0.2
LH peak (mU/ml)	1.4	2.2	1.2	1.5	2.7	2.1	10.9 ± 0.3	11.4 ± 0.3
FSH basal (mU/ml)	1.2	1.1	<0.5	<0.5	4.2	1.4	4.2 ± 0.3	4.2 ± 0.3
FSH peak (mU/ml)	1.5	2.8	10.6	2.1	11	4.3	17.7 ± 0.6	18.1 ± 0.7

AI, Arginine-insulin; FT4, free T_4; GB, glucagon-betaxolol; PRL, prolactin.

[a] These patients did not show pubertal development in later evolution.

[b] Before pituitary surgery.

[c] Children who are age matched for comparison with patients having the ROHHADNET syndrome.

TABLE 4. Metabolic characteristics of the six studied children with ROHHADNET syndrome compared with three children with Cushing's disease and with 87 age-matched obese children

	Patients						Cushing's disease (n = 3)	Obese children (n = 87)
	1	2	3	4	5	6		
Age at test (yr)	8	7.4	8.2	5	8.5	10.4	9 ± 0.5	8.4 ± 0.5
OGTT								
Glucose (mmol/liter)								
Basal	4.7	3.4	4.2	4.5	4.3	4.1	4.4 ± 0.2	4.3 ± 0.06
Peak	7.7	4.7	6.5	6.3	6.2	7	6.9 ± 0.8	6.6 ± 0.1
120 min	5.4	4.1	5.3	4.8	4.8	4.6	5.8 ± 0.6	5.6 ± 0.1-
Insulin (μU/ml)								
Basal	48	2	24	9	11	17	9 ± 2	10.4 ± 0.5
Peak	262	4	132	64	69	149	61 ± 24	82 ± 17
120 min	51	3	37	11	14	25	40 ± 9	51.3 ± 3.8
Leptin (ng/ml)	55	56	43	39	38	42	31 ± 5	38 ± 7

mediastinum (one of six) and adrenal gland (five of six) (Fig. 3). GNs averaged 2.5 ± 1.1 cm in diameter at imaging, and three of six (patients 3, 4, 6) underwent surgical resection. Briefly, GNs were composed of ganglion cells (some of which may be immature) and mature Schwann cells (mature stroma) as reported (36). Cellular atypia, mitotic activity, and necrosis or neuroblasts were not observed. There was no evidence of inflammatory lesions in the resected tumors.

At CT, calcifications were not observed, whereas they are relatively frequent in large series of GNs (37–40). The GNs were low attenuation and homogeneous on unenhanced CT scans and demonstrate slight to moderate enhancement, which was heterogeneous or homogeneous (37–41). At MRI two GNs had low-signal intensity on T1-weighted images and heterogeneous high-signal intensity on T2-weighted images. None of the three studied GNs accumulated metaiodobenzylguanidine. Homovanillic acid, vanillymandelic acid, metanephrine, normetanephrine, epinephrine and norepinephrine, dopamine were measured two to three times in plasma or urine in all five patients, and none ever showed any abnormal value (values not shown). In the largest series of GNs to date (49 cases), 37% of patients had elevated vanillymandelic acid or homovanillic acid levels (42, 43). Concentrations of all circulating adrenal steroids (δ-4-androstenedione, dehydroepiandrosterone DHA, dehydroepiandrosterone sulfate DHAS, and testosterone) were normal in the five current patients with adrenal GN (data not shown).

TABLE 5. Comparison of the main criteria allowing the diagnosis of Cushing's disease in young children with early obesity having ROHHADNET syndrome, Cushing's disease, or common obesity

	ROHHADNET (n = 6)	Cushing's disease (n = 5)	Common obesity (n = 87)
Age at diagnosis (yr)	8.8 ± 1.3	8.4 ± 0.9	8.4 ± 0.5
Wt SDS	11 ± 8	3.9 ± 1.1	4.9 ± 1.1
Ht SDS	−1.2 ± 0.8	−1.1 ± 0.5	+1.9 ± 0.7
BMI SDS	17.5 ± 8	5.3 ± 1.7	4.4 ± 1
UFC (mg/m^2·d)			
Mean ± SD	41 ± 48	372 ± 122	30.3 ± 2.4
Range	6.6–146	268–573	21–42
Midnight plasma cortisol (μg/dl)	4.7 ± 2.4	20 ± 7.8	3.4 ± 1
0800-h plasma ACTH (pg/ml)	38 ± 16	39 ± 8	21 ± 5
HDDST (% cortisol suppression)	70 ± 13	58 ± 45	82 ± 11[a]
Diurnal cortisol variation (+ or −)[b]	4+/2−	1+/4−	87+

Ht, Height; Wt, weight.

[a] Tested in 34 of 87 obese children.

[b] See Table 2.

Combined multiple hypothalamic-pituitary dysfunctions (Table 3)

Table 3 depicts the various abnormalities observed in the patients. Four had true GH deficiency with growth failure, low GH response to stimulation tests, and low-circulating IGF-I, four had various degrees of hyperprolactinemia, two had low T_4 with elevated TSH in one case (patient 1), two had isolated slightly elevated TSH levels with normal T_4, and four had TSH responses to TRH that indicate HD (43). Hypogonadotropic hypogonadism was suspected in patients 1, 2, 4, and 6 on the basis of undetectable gonadotropin responses to an LHRH test in late childhood (Table 4), then confirmed by the fact that none of these

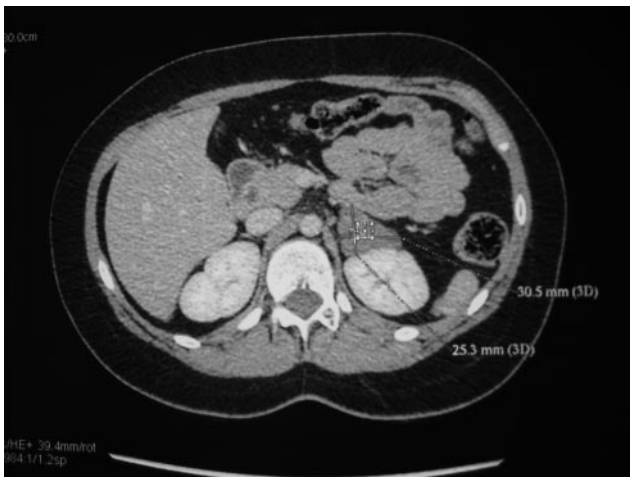

FIG. 3. CT scan of the left adrenal GN in patient 5.

TABLE 6. Main phenotypes of ROHHAD in the 15 pediatric cases collected by Ize-Ludlow *et al.* (8) and in the six current patients with ROHHADNET observed in a single pediatric endocrinology service

	Ize-Ludlow cases	Current cases
No. of reported patients with ROHHAD	15	6
Hypothalamic endocrine manifestations		
Early and rapid onset obesity	15/15	6/6
Deceleration of growth rate	4/15	4/6
Failed GH stimulation test[a]	9/15	4/6
Adrenal insufficiency	4/15[b]	2/6
Cushing's syndrome	0/15	1/6
Hypernatremia[c]	7/15	6/6
Diabetes insipidus	5/15[d]	0/6
Hyperprolactinemia	7/15	4/6
Hypogonadotropic hypogonadism	5/15	4/6
Precocious puberty	2/15	0/6
Respiratory manifestations	15/15	6/6
Cardiorespiratory arrest	9/15	3/6
Autonomic dysregulation	9/15	2/6
Tumors of neural crest origin	5/15	6/6
Adrenal GN	1/15	5/6
Neurobehavioral disorders	8/15	2/6

Differences across the two series are likely to be due to the different circumstances of recruitment due to our pediatric subspecialty.

[a] Cutoff level for GH peak less than 10 ng/ml.

[b] ACTH not reported.

[c] See footnote "[a]" in Table 1.

[d] Without a confirmatory water deprivation test.

four patients had any spontaneous pubertal when they were reexamined at 13.4, 14.2, 14.6, and 13.8 yr of age, respectively: no breast had appeared in the female patients, nor did testicular enlargement occur in boys. After the LHRH stimulation test, LH peak remained inferior to 3 UI/ml in these four patients. Other patients, although they have not been studied at adolescence, appeared to have stimulatable levels of gonadotrophins in childhood, which did not allow, however, to predict normal puberty.

Other HDs

Increased natremia was present in six of six patients (Table 1), and was not due to diabetes insipidus as shown by the lack of polyuria (24 h urine volume not greater than 0.89 liter), posterior hypophyseal bright spot on MRI, and by the fact that serum osmolality remained unchanged, and urine osmolality ranged from 680–851 mosmol/kg after an overnight fast and water deprivation. However, one cannot exclude subtle vasopressin deficiency. Three patients experienced cardiorespiratory arrests. For two patients there was evidence of abnormal respiratory control before the arrest, manifested as hemoglobin desaturation during sleep and obstructive sleep apnea. These manifestations were present from 6–25 months before the cardiopulmonary arrest. Obstructive sleep apnea was symptomatic in another patient. All six patients studied in various respiratory physiology laboratories demonstrated alveolar hypoventilation, with variable severity of resultant hypercarbia and hypoxemia during wakefulness. During the same evaluation, obstructive sleep apnea was also documented for one patient. Patients 3 and 4 required 24 h/d artificial ventilation. These two patients had a lethal cardiorespiratory arrest at 8.5 and 12 yr of age despite ventilatory support and could not be resuscitated. Hypothalamus, brainstem, and whole brain were found strictly normal at autopsy of the patients who died. There was no evidence of inflammatory lesions in these tissues.

Autonomic dysregulation

Symptoms of autonomic dysregulation were identified for all six patients. The most common was thermal dysregulation, manifest as episodes of hyperthermia or hypothermia in four patients. Two other patients had pupillary dysfunction (primarily altered responses to light) and one strabismus; one patient had both. Gastrointestinal dysmotility was reported for one patient who had constipation and chronic diarrhea.

Metabolic studies (Table 4)

None of the patients displayed abnormal glycemic levels in the fasting state or during the OGTT. Fasting insulin concentration and secretory response of insulin to the OGTT were clearly higher in patient 1 than in most children with common obesity who rarely have insulin peak values exceeding 150 μU/ml during the early phase of the OGTT. In contrast, insulin levels were very low in patient 1 and did not show elevation during the OGTT. These two abnormal cases suggest that hypothalamic regulation of insulin secretion could also be altered in these patients. Plasma leptin concentrations in ROHHADNET patients were comparable with those observed in obese children of comparable BMI (le stunff leptin) (Table 4).

Developmental and neurobehavioral disorders (Table 1)

Two patients had developmental delay before the onset of hypoventilation and were later diagnosed as having mild mental retardation. One patient was reported to have generalized tonic-clonic seizures possibly associated with episodes of hypoxemia. One patient had developmental regression, and was also diagnosed as having pervasive developmental and obsessive-compulsive disorder, with episodes of psychosis. One patient was found to have brain MRI abnormalities after experiencing cardiorespiratory arrest (ischemic injury in the frontal and parietal lobes).

Discussion

In early infancy, the ROHHADNET syndrome can easily be confused with severe but common hyperphagic obesity. This is because common obesity can be associated with variable degrees of pituitary dysfunction, such as GH unresponsiveness to stimulation tests (20) or increased TSH levels (21), as well as with sleep apnea (22) that may resemble features of the ROHHADNET syndrome. However, unlike ROHHADNET, common obesity is associated with increased height velocity (44, 45) and elevation of circulating IGF-I (46). In contrast, height velocity and IGF-I were found to be abnormally low in four of six of the current children with the ROHHADNET syndrome, as seen in true GH deficiency. In addition, none of the characteristic features of ROHHADNET such as alveolar hypoventilation or autonomic

dysregulation, or tumors of the sympathetic nervous system are encountered in common childhood obesity. Nevertheless, as observed in the present cases, the difficulty may still be to distinguish early ROHHADNET cases that do not yet have their full pleiotropic expression from cases of common obesity of early onset (8).

It may even be more difficult to recognize ROHHADNET among other early-obesity syndromes with associated disorders. The more frequent is the Prader-Willi syndrome in which hyperphagia and obesity associate with hypotonia, mental retardation, short stature, GH deficiency, hypogonadotropic hypogonadism, sleep apnea, features that can all be found in the ROHHADNET syndrome. Bardet-Biedl syndrome is a rare, autosomal recessive disease characterized by obesity, mental retardation, dysmorphic extremities, retinal dystrophy or pigmentary retinopathy, hypogonadism, and structural or functional abnormalities of the kidney. Leptin-deficient humans are characterized by severe early-onset obesity and intense hyperphagia (47, 48). They have very low leptin levels, in contrast with the current ROHHADNET cases. Some of them failed to undergo pubertal development with biochemical evidence of hypogonadotropic hypogonadism. Ozata *et al.* (49) reported abnormalities of sympathetic nerve function in leptin-deficient humans consistent with defects in the efferent sympathetic limb of thermogenesis. We participated in the description of the mutation in the leptin receptor in three obese sisters from a consanguineous Kabilian family (50), who were born with normal birth weight, exhibited rapid weight gain in the first few months of life, with severe hyperphagia and aggressive behavior when denied food. They had early growth failure and true GH deficiency with unresponsiveness to stimulation tests and low IGF-I levels, hypogonadotropic hypogonadism with a complete lack of puberty, mildly elevated TSH with low T_4, and UFC ranging from 60–107 μg/24 h, *i.e.* within the Cushing's range (25). These endocrine features are reminiscent of those observed in the current ROHHADNET patients. The three girls had emotional lability, and one had episodes of psychosis and committed suicide. We identified these patients easily among many common obesity cases because of their remarkably elevated circulating leptin levels (670, 600, and 526 ng/ml). Leptin was measured in the same laboratory in the current cases of ROHHADNET and found to be within a range proportional to the degree of obesity (31). Two unrelated obese German children with homozygous or compound heterozygous mutations in proopiomelanocortin (POMC) (51) were hyperphagic and developed early-onset obesity as a result of impaired melanocortin signaling in the hypothalamus. They presented in neonatal life with adrenal crisis due to ACTH deficiency (POMC is a precursor of ACTH in the pituitary), and had pale skin and red hair due to the lack of MSH function at melanocortin 1 receptors in the skin (51). Notably, two of the current cases of ROHHADNET had cortisol deficiency, which led to a negative search of POMC mutations. A child with severe, early-onset obesity was found to be a compound heterozygote for the complete loss of function mutations in prohormone convertase 1 (52). Although failure to cleave POMC is a likely mechanism for the obesity in these patients, prohormone convertase 1 cleaves a number of other neuropeptides in the hypothalamus, such as glucagon-like-peptide 1, which may influence feeding behavior and other hypothalamic functions. Phenotypical studies of patients with melanocortin 4 receptor mutations reveal that this syndrome is characterized by an increase in lean body mass and bone mineral density, increased linear growth throughout childhood (unlike the current observations), hyperphagia, and severe hyperinsulinemia (53). Finally, a loss-of-function mutation in neurotrophic tyrosine kinase receptor type 2 was identified in a patient with severe obesity and hyperphagia who also had impaired nociception (54). In summary, most of the aforementioned syndromes have distinctive clinical or biological manifestations that would help distinguish them relatively easily from the full ROHHADNET syndrome. The clinical phenotype closest to ROHHADNET, including the endocrine manifestations, is leptin receptor deficiency, but leptin levels permit distinguishing the two syndromes.

Similarly, once ROHHADNET is suspected, there is little diagnostic overlap with Cushing's disease, a rare disease in infants (23, 24). However, in few cases ROHHADNET patients may present with facio-troncular obesity of early onset, concomitant growth failure, elevated UFC, or midnight cortisol level, and normal to elevated ACTH levels, the characteristic features of Cushing's disease (24) that could mislead the diagnosis if ventilatory disorders or HD is not yet present or still minimal in the early ROHHADNET syndrome, as reported by Ize-Ludlow *et al.* (8) or observed in patient 4. This patient mistakenly underwent pituitary surgery because he had a clinical and hormonal profile typical of Cushing's disease and a MRI hypodense lesion in the pituitary. Analysis of cases in a recent series of children with Cushing's disease, as well as our own experience, indicates that the risk of misdiagnosis is limited by the fact that: 1) Cushing's disease (24) usually manifests later in childhood or adolescence and is very rarely symptomatic before the age of 5 yr, 2) UFC and midnight cortisol values are much higher in pediatric Cushing's disease than in ROHHADNET (Table 3 and Ref. 24).

Unilateral adrenal GNs were found in five patients, which could also lead to diagnostic difficulties (55). None of these tumors was found to secrete catecholamines or catecholamine metabolites. None of the children had significant protracted episodes or a fortiori intractable diarrhea that could reveal a vasoactive intestinal polypeptide-secreting GN (56). Several studies support a relationship between neuroblastoma (not "pure" GN) and a paraneoplastic syndrome of HD that could be triggered by an autoimmune process generated by the tumor (15, 57, 58). The fact that two of the current tumors underwent resection without inducing any change in the clinical or hormonal manifestations suggests that paraneoplastic secretion of unmeasured neuropeptides by the tumors could not have contributed to the endocrine or hypothalamic manifestations of ROHHADNET. Neither were the current GN tumors exposed to misdiagnosis with adrenocortical tumors, known to affect very young children (26), because these tumors usually secrete large amounts of adrenal steroids and are revealed by obvious androgenic manifestations, including accelerated growth, without obesity (25, 26, 59). Pure glucocorticoid secreting adrenocortical tumors revealed by a Cushing's syndrome with suppressed ACTH have not been reported, to our knowledge, at this age. Because of the consistent finding of GN in our patients and previously reported

cases, we propose to include GN in the acronym (ROHHADNET), even if GNs are not always present, to warn clinicians about this potential complication. There is also the potential risk of unnecessary anesthesia and adrenal surgery if ROHHADNET has not been recognized. When MRI scans of one adrenal gland reveal a small tumor, the diagnosis of primary pigmented nodular adrenocortical disease should also be excluded if the young patient has Cushing's syndrome of atypical evolution (60). None of our patients showed cyclical hypercortisolemia that permitted distinguishing ROHHADNET *a priori* from certain forms of Cushing's syndrome with (24) or without primary pigmented nodular adrenocortical disease (60).

A remarkable feature of our patients is the apparent normality of their first 2–4 yr of life, followed by sudden rapid weight gain and concomitant growth failure according to a remarkably consistent pattern, then by autonomic dysregulation and later hypoventilation. There is a wide variation in the reported age at onset of autonomic or HD, as well as in the interval between the onset of obesity and hypoventilation, so that it remains possible that some children with ROHHADNET could receive false endocrine diagnoses such as ACTH-dependent Cushing's syndrome, adrenal tumors, complete isolated GH deficiency, or congenital combined multiple pituitary hormone deficiency or diabetes insipidus. These diagnoses may lead to erroneous treatments, some of which could be detrimental to ROHHADNET patients. For example, GH has often been given to ROHADD patients who have documented GH deficiency (19) (and here). However, there is a risk that GH aggravates airway obstruction in patients with Prader-Willi syndrome and sleep apnea syndrome (61, 62), possibly also in ROHHADNET patients with ventilatory problems.

The forms of ROHHADNET that we report here are biased by a recruitment based on our pediatric endocrinology specialty. When compared with the 15 U.S. patients reported by Ize-Ludlow *et al.* (8) (Table 6), it appears that endocrine manifestations are certainly frequent, but not constant, in ROHHADNET patients.

If not identified (63) or not treated properly, the alveolar hypoventilation of ROHHADNET can be fatal, as evidenced by the high incidence of cardiorespiratory arrest in our patients or the literature (8, 62). The clinical management of ROHHADNET patients requires detailed physiological assessment, including: evaluation of the hypothalamic-pituitary axis with hormonal replacement only when needed; respiratory physiological assessment during wakefulness and sleep; and MRI or CT screening of the chest and abdomen for neural crest tumors (GNs or ganglioneuroblastomas). Brain imaging should always be performed to exclude the possibility of hypothalamic-pituitary abnormalities (64) attributable to intracranial lesions. Treatment of GNs consists of complete surgical resection when possible, which ensures that a confident diagnosis of GN can be made. Local recurrence has been reported, so periodical radiological surveillance is performed after resection (42).

Better characterization and the availability of a larger patient collection would be necessary for advancing knowledge regarding the cause of this syndrome. We are conscious that the clinical manifestations of ROHHADNET in patients referred to a pediatric endocrinology department may be biased *vs.* the pleiotropic features of the syndrome, but we want to stress that the delay between early obesity-endocrine and later respiratory manifestations of the syndrome can expose patients to diagnostic errors and fatal evolution. Children with early obesity should be investigated for alveolar hypoventilation if there is even the smallest suspicion of the ROHHADNET syndrome.

Acknowledgments

We thank J. C. Job, B. Luluyer, C. Teinturier, G. P. de Filippo, and M. François, who were involved in the clinical care of the studied patients. Many hormonal measurements were performed in Dr. N. Lahlou's laboratory.

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Disclosure Statement: The authors have nothing to declare.

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