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RESEARCH

Emphasizing autonomic dysregulation evaluation contributes to the diagnosis of ROHHAD syndrome

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Abstract

Objective: Rapid-onset obesity with hypoventilation, hypothalamic dysfunction, and autonomic dysregulation (ROHHAD) is rare, and manifestations of autonomic dysregulation are diverse and may be overlooked. We aimed to evaluate the incidence of these manifestations.

Methods: Patients with ROHHAD syndrome reported before and after 2019 were divided into groups 1 and 2. Patients who were diagnosed at three regional hospitals in China were included in group 3. We collected the age of each specific term of the ROHHAD (neurogenic tumor, NET) acronym and the detailed manifestations of each term, and compared them among the three groups.

Results: A total of 16 patients were diagnosed within the 2-year period. Two had neurogenic tumors and cognitive and behavioral abnormalities before developing rapid obesity. At least 93.8% of the patients had ≥ 4 symptoms of autonomic dysregulation. When comparing autonomic dysregulation among groups 1–3, the rates of cardiovascular manifestations were NA vs 12.8% vs 81.2%; gastrointestinal disturbances were 11.4% vs 8.5% vs 62.5%; strabismus was 25.7% vs 12.8% vs 62.5%; sleep disturbance was NA vs 6.4% vs 50.0%; and abnormal pain threshold was NA vs 10.6% vs 25.0% (all $P < 0.05$). The rates of cognitive and behavioral abnormalities were NA vs 29.8% and 87.5% ($P < 0.01$).

Conclusion: Rapid-onset obesity is not always the first sign of ROHHAD syndrome. Higher rates of autonomic dysregulation and cognitive and behavioral abnormalities with multiple manifestations of autonomic dysregulation coexisted in our cohort, indicating that evaluations of autonomic function and the limbic system should be strengthened when assessing this condition.

Keywords: autonomic dysregulation; cognitive and behavior; rapid obesity; ROHHAD syndrome

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Introduction

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) syndrome was first described by Fishman *et al.*, and renamed ROHHAD by Ize-Ludlow *et al.* in 2007 (1, 2). About 40–50% of patients with ROHHAD syndrome have been observed to have neural crest tumor (NET). The acronym for the disease was therefore changed to ROHHAD (NET) in 2008 (3). The major criterion for the disease is rapid weight gain associated with central hypoventilation occurring between 1.5–7 years of age in a previously healthy child (4). Except for four cases without obesity that were reported in one study, all patients with ROHHAD that have been discussed in the literature thus far presented with rapid weight gain and obesity, typically gaining 20–30 pounds of weight within 3–12 months (5, 6). Rapid weight gain is therefore considered the first sign of ROHHAD syndrome, followed by at least one phenotype of hypothalamic dysfunction, such as pituitary hormone abnormalities (hypernatremia, central hypothyroidism, growth hormone deficiency, adrenocortical insufficiency, and puberty-related disorders) and hyperprolactinemia. Patients may exhibit obstructive sleep apnea syndrome (OSAS) during polysomnography in the early stages of the disease. Autonomic dysregulation is present in patients with ROHHAD syndrome, their response to peripheral and central chemoreceptors is weakened, leading to a lack of perception of hypoxemia and hypercapnia. Initially, patients often experience hypoventilation during night-time sleep. In severe cases, hypoventilation may also be present while awake. Hypoventilation is a significant risk factor for cardiorespiratory arrest. Patients must therefore be closely monitored and should receive timely artificial ventilation to assist with breathing. They can also present with autonomic dysregulation such as ophthalmologic abnormalities, cold and swollen hands and feet, thermal dysregulation, excessive sweating, cardiovascular manifestations (arrhythmias or blood pressure dysregulation), or gastrointestinal disturbances (7).

ROHHAD syndrome is a rare disease, for which misdiagnosis or delayed diagnosis is common. Patients often visit different departments because of symptoms such as cardiorespiratory arrest, recurrent seizures, loss of consciousness, tumors, or behavioral abnormalities. However, the manifestations of the disease are complex, and relatively mild forms of autonomic dysregulation are often overlooked. This study summarizes the clinical characteristics and follow-up results of 16 typical patients with ROHHAD syndrome who were diagnosed at Beijing Children's Hospital, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, and Children's Hospital of Soochow University over the past 2 years, and analyzes how the clinical symptoms and timeline of the syndrome were correctly identified during different periods, thus characterizing the evolving understanding of this condition.

Materials and methods

We included patients with ROHHAD syndrome who were diagnosed at different departments in the inpatient case databases of Beijing Children's Hospital, Capital Medical University, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, and Children's Hospital of Soochow University. These patients had performed cranial and pituitary magnetic resonance imaging (MRI) to rule out hypothalamic-pituitary tumors. All cases reported between 2007 and September 2019 were classified as group 1 (7). We searched for a summary of ROHHAD and ROHHAD (NET) cases reported after October 2019 in the PUBMED database as group 2. The literature screening process is detailed in Fig. 1. The diagnostic criteria for ROHHAD syndrome were based on those used in a previous report (8), as well as the clinical signs and symptoms of ROHHAD (NET) syndrome (Supplementary Table 1, see section on supplementary materials given at the end of this article). We collected the patients' ages when each specific term of the ROHHAD (NET) acronym was reported, as well as the detailed manifestations of each, and compared the clinical features among the three groups.

Next-generation sequencing

The process of whole-exome sequencing (Beijing Mygenostics co., LTD, Beijing, China) includes three steps: DNA Library Preparation, targeted genes enrichment and sequencing, and bioinformatics analysis. Approximately 2 mL peripheral blood (EDTA anticoagulant) of the patients and their parents was collected, and genomic DNA was extracted using QIAamp Blood Midi Kit (Qiagen). Paired-end sequencing libraries then were prepared using a DNA sampleprep reagent set 1 (NEBNext). The amplified DNA was captured using GenCap Whole-exome capture kit (MyGenostics GenCap Enrichment technologies). The capture experiment was conducted according to the manufacturer's protocol. The average sequencing depth > 100X, a fraction of the target covered with at least 10X > 95%. After sequencing, the raw data were saved as a FASTQ format, then followed the bioinformatics analysis, the data would be transformed to VCF format, and variants were further annotated by ANNOVAR and associated with multiple databases, such as 1000 genome, ESP6500, dbSNP, EXAC, Inhouse (MyGenostics), and HGMD. All mutations of minor allele frequency < 1% in East Asian people, and pathogenic, likely pathogenic, or uncertain mutations were possibly related to the disease.

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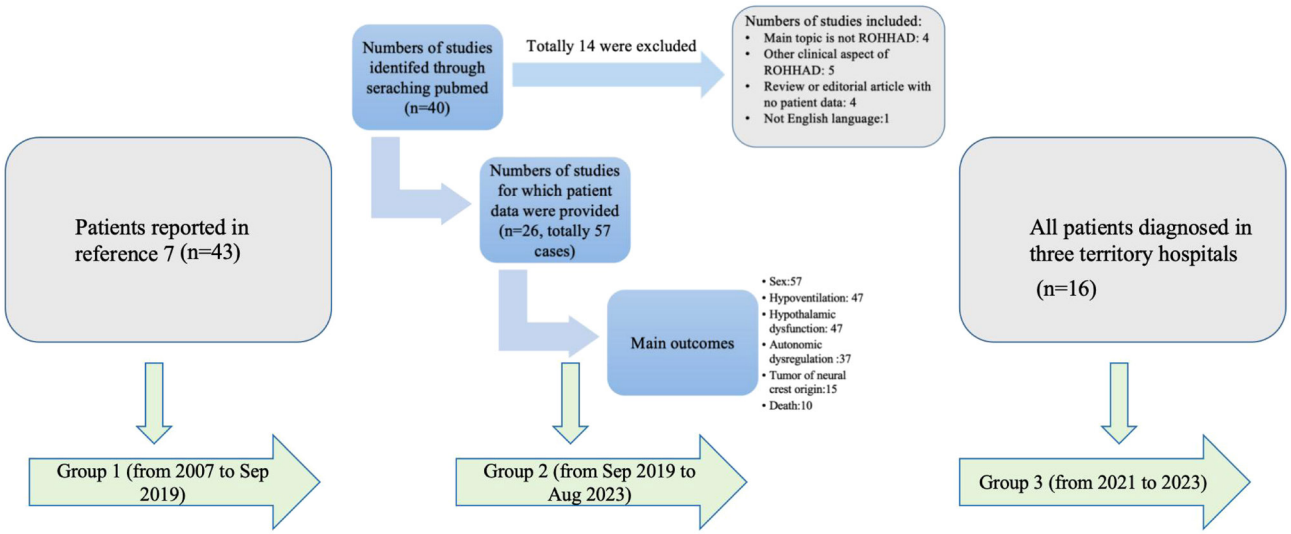

Figure 1

Screening flowchart of three groups.

Statistical analysis

All data were described using median (minimum, maximum), except for BMI (medium ± S.D.), and comparisons between two groups were conducted using four-grid data chi-squared tests. Statistical significance was set at $P < 0.05$. This study was approved by the ethics committee of Beijing Children's Hospital, Capital Medical University. Written informed consent was obtained from the parents or legal guardians of the patients.

Results

Patient characteristics

Sixteen patients (male:female ratio, 8:8) were diagnosed with ROHHAD syndrome over the 2-year study period.

Obesity

All patients exhibited rapid weight gain (weight gain of 3.00–22.50kg within 6–12 months), but not all occurred as the first sign. The median age of rapid-onset obesity occurrence was 3.17 (1.67, 7.92) years. The mean BMI *z*-score was 4.23 ± 1.65. In case 2, neck neuroblastoma was diagnosed at 9 months of age, with rapid-onset obesity at age 6 years. Case 10 was scheduled for strabismus surgery, but the preoperative examination revealed an abnormal blood count – after which further examination revealed a retroperitoneal neurogenic tumor. The patient underwent 12 chemotherapy sessions, 12 radiotherapy sessions, and surgical resection of the tumor within 1 year. During treatment, the patient experienced no adverse reactions such as nausea or vomiting; however, a pronounced appetite increase was observed, resulting in weight gains of 3.00 kg within 1 year, followed by 11.70 kg over the following year (Supplementary Table 1).

Hypoventilation

The median age of onset for central hypoventilation was 5.55 (3.61, 8.25) years and occurred in 93.8% of the patients. All patients, with the exception of case 7, experienced varying degrees of hypoventilation (Fig. 2). Cases 4 and 13 died of respiratory and cardiac arrest within 6 months and 2 years, respectively, following the onset of rapid obesity.

Hypothalamic dysfunction

Hypothalamic dysfunction occurred at 4.46 (1.83, 9.25) years of age, in 93.8% of the cases. Patients with polyuria had a daily urine volume of 2000 mL/m^2 or an increased nocturia frequency that did not meet the diagnostic criteria for diabetes insipidus. Case 3 involved a 12-year-old boy with bilateral cryptorchidism, who exhibited no signs of puberty and was diagnosed with hypogonadotropic hypogonadism. The IGF-1 levels of seven patients (cases 3, 7, 10, 12, 13, 14, and 16) were low, however, the height of cases 10 (median for children of the same age and gender) and 12 (−0.5 S.D. for children of the same age and gender) were normal, and the detailed information of height and growth rate was shown in Supplementary Table 2.

Autonomic dysregulation

All 16 patients exhibited autonomic dysregulation, with a median onset at 3.42 (1.83, 8.00) years.

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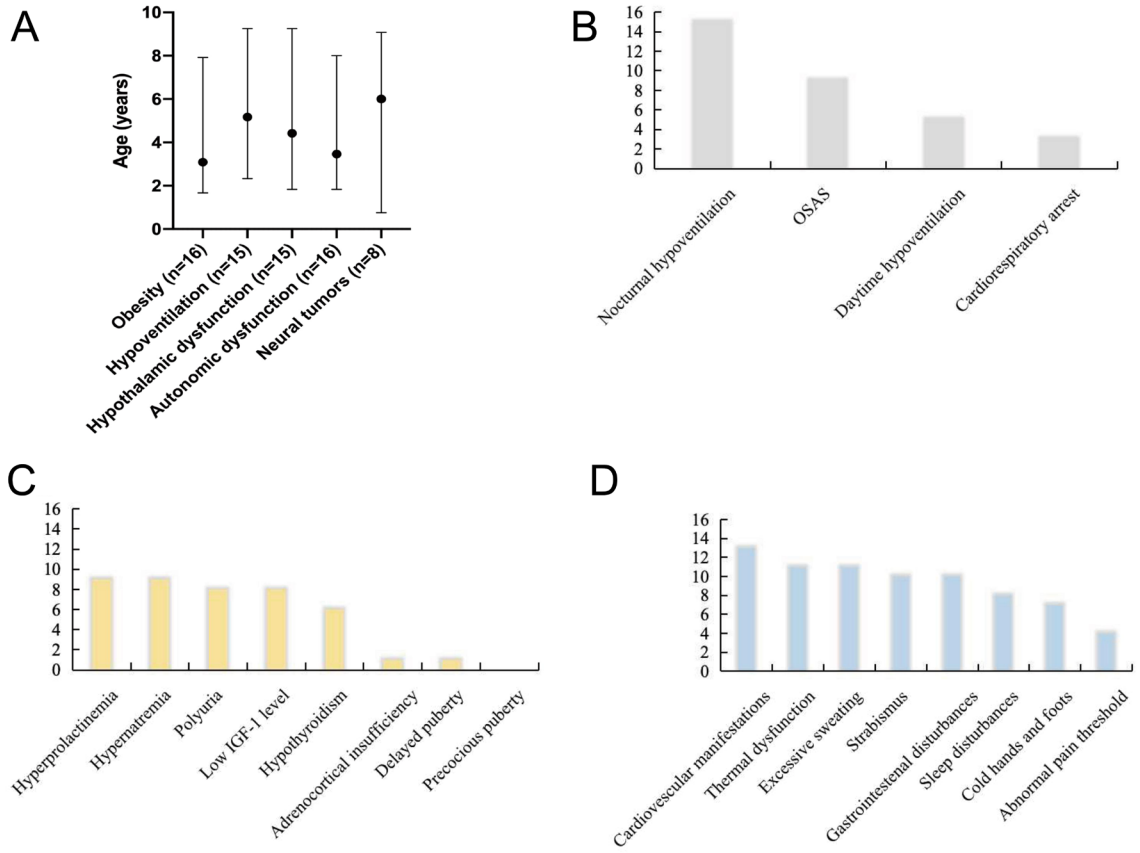

Figure 2

(A) Age distribution for each specific term of the ROHHAD (NET) acronym; (B) Hypoventilation. Case numbers of different types of respiratory events in our cohort; (C) Hypothalamic dysfunction. Case numbers of the main disorders in our cohort. No patients of precocious puberty were reported; (D) Autonomic dysregulation. Case numbers of the different types of autonomic dysregulation.

For example, in case 3, the heart rate fluctuated between 50 and 150 beats per minute. That patient developed constipation at 2.50 years of age and prolonged defecation time (10–30 min) at 4.50 years. Case 10 presented with chronic diarrhea for >3 years, averaging 6–20 episodes per day. This patient demonstrated an exceptionally high pain threshold, showing no reaction during blood draws, vaccinations, or even bone marrow puncture. More than 2 years after undergoing tumor resection surgery, the patient began to complain of severe pain in both paroxysmal lower limbs. After extensive examinations to exclude the possibility of tumor recurrence and autoimmune diseases, the patient was diagnosed with hyperalgesia.

Tumors of neural crest origin

Six patients were found to have neurogenic tumors – including four cases of ganglioneuroblastoma, two of neuroblastoma, and three of unknown type – with a median age of onset of 5.46 (3.71, 7.98) years. The rates of ganglioneuroblastoma in the three groups were 8.3%, 26.3%, and 44.4%, respectively ($P < 0.01$; Table 1).

Genetics

Nine patients and their parents had undergone WES, the other 4 patients had undergone WES but their parents had not. We focused on all the 12 candidate genes including *PHOX2B* in ROHHAD syndrome, only case 2 harbored one heterozygous variant c.125C>T (p. Ala42Val) in the *ABCL1* gene, but it is likely benign according to ACMG. The genetic results for the others were negative (Supplementary Table 3).

Therapy

All patients received supportive treatments. Case 2 was treated with oxytocin. Initially, this decreased her appetite, and her sleep and behavior improved after 2 months of treatment. However, after 4 months, her appetite, sleep, and behavior relapsed and returned to their previous states—although her diarrhea frequency decreased from 5–6 times per day to 1–3 times per day, and continued to improve. Case 10 was treated with oxytocin nasal spray 2 years post-surgery for retroperitoneal neuroblastoma. After 3 months of treatment, the patient's BMI reduced to 1.94 and her

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Table 1 The frequency of tumors and their location of ROHHAD patients by reported time periods.

	Categories	Group 1 (*n* = 43)	Group 2 (*n* = 57)	Group 3 (*n* = 16)	Total percentage (%)
Types of tumor	Total cases (*n*)	24	19	9*	44.8
	Ganglioneuroma# (*n*, %)	18 (75.0)	6 (31.6)	0 (0)	46.2
	Ganglioneuroblastoma# (*n*, %)	2 (8.3)	5 (26.3)	4 (44.4)	21.2
	Neuroblastoma& (*n*, %)	2 (8.3)	1 (5.3)	2 (22.2)	9.6
	Unknown type (*n*, %)	2 (8.3)	7 (36.8)	3 (33.3)	23.1
Location of tumor	Adrenal (*n*)	9	0	5	26.9
	Thoracic (*n*)	5	4	1	19.2
	Retroperitoneal (*n*)	2	0	2	7.7
	Neck (*n*)	1	0	1	3.8
	Unknown location (*n*)	7	15	0	42.3

*Two patients were found to have left adrenal nodules, one patient was mediastinal tumor, but they have no surgery and regularly review imaging changes; #Group 1 vs group 2, group 1 vs group 3, group 2 vs group 3, all $P < 0.01$; &Group 1 vs group 3, group 2 vs group 3, both $P < 0.01$.

appetite decreased. Her frequency of diarrhea decreased from 6–20 times per day to 2–3 times per day, and she did not report any further lower-limb pain. Her mood improved, and she communicated more easily with others. Only case 14 was treated with GH, but 6 days after the first use, he occurred severe hyponatremia and growth hormone treatment was discontinued, half a month after the second use, the patient occurred fever, edema and oliguria, and treatment was discontinued again.

Others

Fourteen patients (87.5%) had emotional, cognitive, and behavioral abnormalities. Parents of three patients consented to have their children complete the Prader–Willi syndrome (PWS) behavior survey, yielding scores of 46, 52, and 73. The main behavioral abnormalities reported included apathy, lack of facial expression, irritability, and childish behavior. The median age of onset for these manifestations was 3.21 (2.25, 7.00) years. Case 2 exhibited behavioral abnormalities at the age of 4 years – 2 years prior to the development of rapid-onset obesity and hypoventilation. Other symptoms included convulsions in seven patients, general fatigue in six, and developmental delay or regression in three.

Comparison with previously reported data

A total of 116 cases (male:female ratio, 60:50; sex unreported in six cases) were included. A total of 33 articles reported on 43 cases between 2007 until the end of September 2019 (group 1), 26 articles reported on 57 cases between October 2019 until the present (group 2) (6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31) and our cohort of 16 patients formed group 3. The age of onset of each symptom across the three groups is detailed in Fig. 3.

The incidence of each symptom is shown in Supplementary Table 4. There was no statistically significant difference between groups 1–3 in terms of rapid-onset obesity, central hypoventilation, and hypothalamic dysfunction. The incidence of abnormal emotion, cognition, and behavior was not reported in group 1, but it was lower in group 2 compared to group 3 (Fig. 4A, B and C). Among the patients in all three groups who had autonomic dysregulation, cardiovascular manifestations, sleep disturbance, and abnormal pain threshold were not mentioned in group 1, and the incidence of these symptoms in group 2 was significantly lower than that in group 3. The rates of excessive sweating, gastrointestinal disturbances, strabismus, and cold hands and feet in groups 1 and 2 were all lower than those in group 3 (Fig. 4D).

The incidence of various neurogenic tumors is shown in Table 1. Ganglioneuroblastoma had the highest incidence in our cohort, which was significantly higher than that in groups 1 and 2.

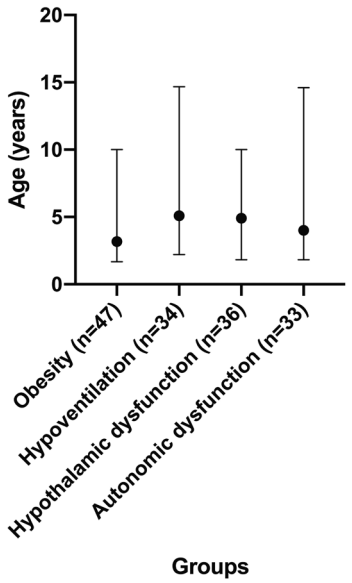

Figure 3

Age distribution at which different symptoms appeared in all patients.

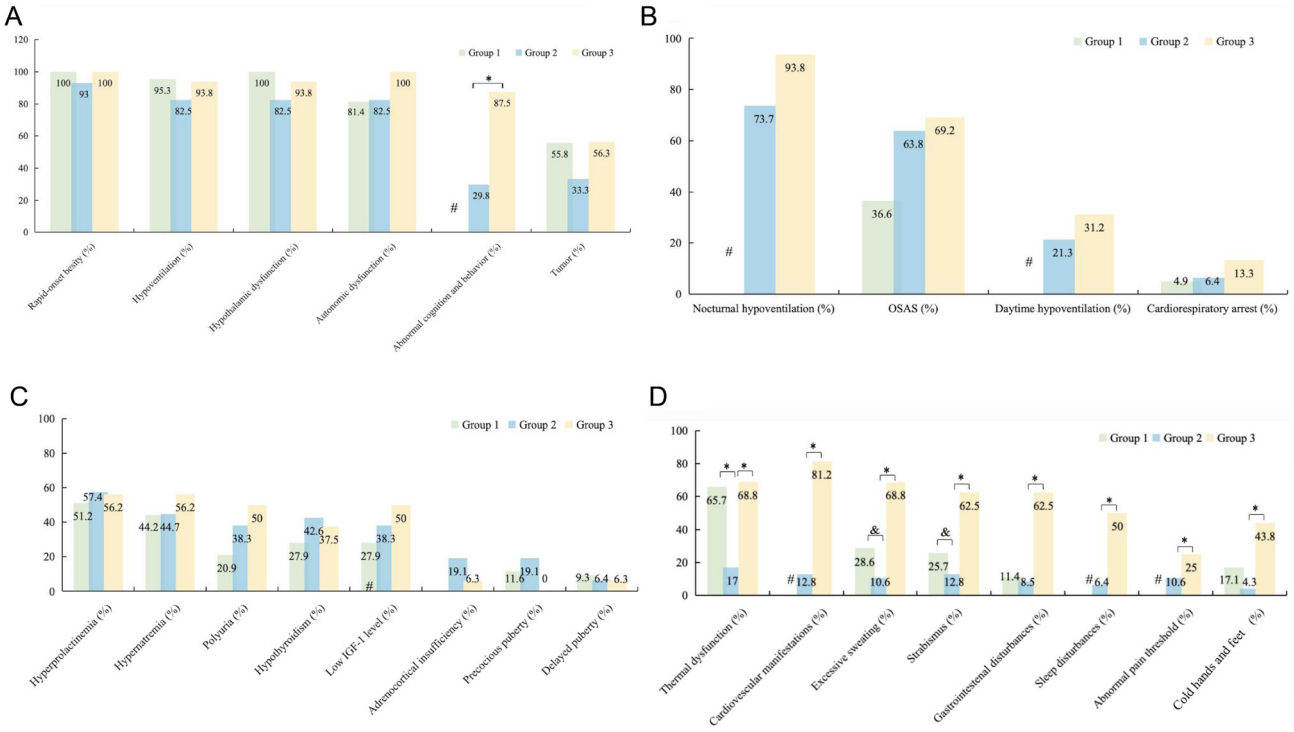

Figure 4

The frequency of different components in various dimensions of ROHHAD syndrome. (A) The percentage for the main hypothalamic disorders reported in ROHHAD syndrome in three groups. (B) The percentage of different types of hypoventilation in three groups. (C) The percentage of different manifestations of hypothalamic dysfunction in three groups. (D) The percentage of different manifestations of autonomic dysfunction in three groups. #, Not available; **P* < 0.01; and *P* < 0.05.

Discussion

The diagnosis of ROHHAD syndrome is challenging, owing to a lack of specific markers. While clinical criteria offer clues for its diagnosis, not all symptoms occur concurrently, making missed diagnoses common. With an increasing number of cases being reported in recent years, the descriptions have become more comprehensive. Therefore, the age and order of occurrence of different ROHHAD symptoms, as well as the definitions of their specific phenotypes, should be reconsidered. Our review of data from our cohort and previously reported cases revealed that rapid weight gain is not always the first sign. We observed higher rates of autonomic dysregulation and cognitive and behavioral abnormalities in our cohort, with multiple coexisting manifestations of autonomic dysregulation. This suggests that strengthening evaluations of autonomic function and the limbic system may facilitate earlier diagnosis. Furthermore, autonomic dysregulation markers could serve as indicators of effective treatment.

Overall, obesity was most often the earliest symptom to appear, followed by cognitive and behavioral abnormalities, autonomic dysregulation, hypothalamic dysfunction, neurogenic tumors, and finally central hypoventilation. Among 116 reported cases, only four had normal BMIs, while the rest were obese and experienced rapid weight gain (96.6%). The median age at which rapid-onset obesity occurred was 3.17 (range:1.67–10.00) years in 47 cases. Autonomic dysregulation followed at a median age of 4.00 years (range: 1.83–14.60) years in 33 cases, approximately ~0.83 years after the onset of obesity. These were followed by hypothalamic dysregulation at a median age of 4.92 (range: 1.83–10.00) years in 33 cases, 1.75 years after the onset of obesity. Central hypoventilation manifested at a median age of 5.09 (range: 2.20–14.68) years in 34 cases, 1.92 years after the onset of obesity – thus occurring in the same order as that observed in our cohort. However, the age range of symptom onset has further expanded, indicating that the age of onset of the disease is not limited to the preschool age. Healthcare providers should therefore remain vigilant regarding the possibility of later ROHHAD onset in some patients.

Hypoventilation represents a key symptom of ROHHAD syndrome. A previous follow-up study of four non-obese ROHHAD patients found all exhibited symptoms of sleep apnea and hypopnea, with three requiring ventilation support, suggesting that the hypopnea associated with the disease is not solely

caused by obesity (6). Nocturnal hypoventilation is central to ROHHAD; however, sleep-disordered breathing often continues to develop over time. In the largest reported case series of ROHHAD to date, Ludlow *et al.* reported that all 15 of their patients had evidence of nocturnal hypoventilation, and 53% had co-existent OSAS. In another study, 2/6 patients had nocturnal hypoventilation at baseline, and 5/6 patients had OSAS (2). In this study, nocturnal hypoventilation was present in 57/73 (78.1%) of the cases, OSAS occurred in 54/101 (53.5%), and 15/64 (23.4%) of the cases experienced daytime hypoventilation (32). These data indicated that OSAS and nocturnal hypoventilation may coexist in patients with ROHHAD syndrome. For previously healthy children experiencing sudden rapid-onset obesity, hypothalamic dysregulation, or autonomic dysregulation without OSAS, sleep monitoring is recommended. Some researchers have suggested that early intervention using nocturnal noninvasive ventilation may improve daytime hypoxemia. In our cohort, case 7 had no nocturnal hypoventilation or OSAS, and seven cases (46.7%) required non-invasive ventilation.

Hypothalamic dysfunction is a major clinical feature of ROHHAD. The most frequently reported form of hormonal dysfunction in previous studies, as well as in our cohort, was hyperprolactinemia. This occurred to varying degrees, however, as few patients experienced only a slight increase of 23.28–44.7 ng/mL. In previous studies and our cohort, approximately 33% of patients experienced symptoms of hyperprolactinemia, hypernatremia, central hypothyroidism, low IGF-1 levels, and polyuria (7). Five patients with low IGF-1 levels had short stature and low growth rate, they were suspected of growth hormone deficiency. While all patients had so many symptoms, height was not a significant issue, all patients did not perform growth hormone (GH) stimulation test.

Most of the patients presented with rapid-onset obesity as their first symptom, whereas we found that other symptoms such as tumors, autonomic dysregulation, or abnormal behavior – which are often overlooked – may occur first. Comparing our cohort with cases reported between 2007–2019 and 2019 onward, we found that the authors paid more attention to symptoms of obesity, hypothalamic function, hypoventilation, and tumors. There were no statistically significant differences in terms of the occurrence rate of these symptoms among the three groups—but higher rates of autonomic dysregulation, as well as cognitive and behavioral abnormalities, were observed in our cohort, with over 93.8% of patients having ≥4 symptoms of autonomic dysregulation. Although autonomic dysregulation poses less of a threat to patients' lives, as it is relatively mild compared to hypoventilation, hypothalamic dysregulation, or tumors, it can nevertheless severely impact quality of life. Therefore, careful and comprehensive inquiries are crucial to achieving early diagnosis, intervention, and adequate responses during subsequent follow-ups with patients.

Different from the other two groups, ganglioneuroblastoma accounts for the main type of neuronal tumor in our cohort. The reason is unclear. According to the experience of the pathologist of our hospital, ganglioneuroblastoma is indeed more common. However, we need more cases to further study the issue.

The pathophysiology and genetic mechanisms of ROHHAD remain unclear. The *ABCL1* gene mutation found in one of our patients was associated with hypopnea syndrome (33, 34); however, this could not explain the other phenotypic abnormalities. Several studies have suggested autoimmunity involvement in the pathogenesis of ROHHAD syndrome. Some patients with the condition have received immunomodulatory treatments, including glucocorticoids, globulin, cyclophosphamide, and rituximab (35). Cyclophosphamide plays a positive role in stabilizing BMI and improving neuropsychological cognition, but long-term follow-up data regarding this treatment are lacking. A 5-year-old girl with ROHHAD syndrome treated with rituximab experienced a decrease in her interleukin-6 levels until they reached normal levels, and her weight reduced significantly, from above the 99th percentile to the 50th percentile within 12 months (9). Previous studies on patients with obesity, Prader–Willi syndrome (PWS), and autism have found that oxytocin nasal spray treatment can effectively help patients lose weight and improve mental and behavioral abnormalities (36). However, there have been no reports of the use of this treatment approach in patients with ROHHAD syndrome. Intranasal oxytocin proved effective in our case 10, suggesting a potential new alternative for ROHHAD syndrome treatment.

This study analyzed the clinical characteristics of 16 patients with ROHHAD syndrome and compared them with data from other similar cases reported over varying periods. Our results revealed a 100% incidence of autonomic dysregulation in our cohort, with multiple coexisting manifestations. The incidence of emotional, cognitive, and behavioral abnormalities was significantly higher than reported in other periods, indicating the need for strengthened evaluation of autonomic dysregulation and the limbic system. A small number of patients experienced rapid weight gain without obesity. The age spectrum of onset ranged from very young children to 10 years of age. Notable, not all patients presented with obesity as the first manifestation; some initially exhibited tumors, autonomic dysregulation, or abnormal behavior. The pathogenesis of ROHHAD remains unknown, and effective treatment methods are lacking. New treatments are therefore worth investigating, and further research on ROHHAD syndrome is warranted.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-24-0189.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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Author contribution statement
YW, YX, BC, YD, XL, and LC collected the patients' data. YW analyzed the data and wrote the manuscript. CG revised the manuscript. LL provided suggestions for the revision of the manuscript. JG helped analyzed the data. XN and ZY helped revise the language. All authors approved the final version of the manuscript.

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