

## Research Article

# Rapid-Onset Obesity with Hypoventilation, Hypothalamic, Autonomic Dysregulation, and Neuroendocrine Tumors (ROHHADNET) Syndrome: A Systematic Review

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Received 14 May 2018; Revised 24 September 2018; Accepted 28 October 2018; Published 21 November 2018

Academic Editor: Sheba Mohankumar

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**Background and Aim.** ROHHADNET (rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation, neuroendocrine tumor) syndrome is a rare disease with grave outcome. Although early recognition is essential, prompt diagnosis may be challenging due to its extreme rarity. This study aimed to systematically review its clinical manifestation and to identify genetic causes. **Materials and Methods.** We firstly conducted a systematic review on ROHHAD/NET. Electronic databases were searched using related terms. We secondly performed whole exome sequencing (WES) and examined copy number variation (CNV) in two patients to identify genetic causes. **Results.** In total, 46 eligible studies including 158 patients were included. There were 36 case reports available for individual patient data (IPD; 48 patients, 23 ROHHAD, and 25 ROHHADNET) and 10 case series available for aggregate patient data (APD; 110 patients, 71 ROHHAD, and 39 ROHHADNET). The median age at onset calculated from IPD was 4 years. Gender information was available in 100 patients (40 from IPD and 60 from APD) in which 65 females and 35 males were showing female preponderance. Earliest manifestation was rapid obesity, followed by hypothalamic symptoms. Most common types of neuroendocrine tumors were ganglioneuromas. Patients frequently had dysnatremia and hyperprolactinemia. Two patients were available for WES. Rare variants were identified in *PIK3R3*, *SPTBN5*, and *PCFII* in one patient and *SRMS*, *ZNF83*, and *KMT2B* in another patient, respectively. However, there was no surviving variant shared by the two patients after filtering. **Conclusions.** This study systematically reviewed the phenotype of ROHHAD/NET aiming to help early recognition and reducing morbidity. The link of variants identified in the present WES requires further investigation.

## 1. Introduction

Rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation (ROHHAD) syndrome is a rare disorder of respiratory failure and autonomic dysregulation with endocrine abnormalities [1]. The suffix -NET was later added to describe a subset of patients with ROHHAD who were found with neuroendocrine tumors (NET) as ROHHADNET [2].

ROHHAD or ROHHADNET may mimic genetic obesity syndromes and present with hypothalamic-pituitary dysfunctions which are not fully investigated [3]. Since the central respiratory control becomes progressively impaired in the patients, the outcome is often fatal and associated with cardiopulmonary arrest [4]. Prompt diagnosis based on early recognition is essential to provide timely respiratory support and to minimize morbidity and mortality. We thereby sought to systematically review the clinical manifestation, laboratory profiles, and treatment strategies of patients with ROHHAD/NET to help understanding and managing the disease. In addition, we performed whole exome sequencing (WES) in 2 patients with ROHHADNET in the attempt to identify the genetic causes.

## 2. Methods

**2.1. Search Methods.** We conducted a systematic review of the medical literature to identify all published cases of ROHHAD and/or -NET using the online databases of MEDLINE/PubMed, EMBASE, and Google Scholar, until July 7th, 2018. There were no language restrictions; non-English language articles were translated and included. The broad search query was designed to include “ROHHADNET” OR “ROHHAD”; OR “obesity” AND two of the following terms; “hypoventilation” OR “hypothalamic” OR “autonomic” OR “tumor” OR “neural crest tumor” OR “neuroendocrine tumor.” We reviewed the titles, abstracts, and full texts adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) individual patient data (IPD) guidelines (Figure 1; Supplementary Table S1) [5].

**2.2. Eligibility Criteria.** The basic criteria for consideration of the diagnosis of ROHHAD had been published by Ize-Ludlow et al. [6]. The criteria briefly included the following: (1) onset of rapid and extreme weight gain after an age of 1.5 years (typically 2–7 years) in a previously nonobese and seemingly normal child, (2) evidence of hypothalamic dysfunction, (3) alveolar hypoventilation, and (4) features of autonomic dysregulation. We collected published case reports and case series which contained data on clinical manifestations fulfilling the criteria of ROHHAD/NET. Due to the extreme paucity of data, congress abstracts were also included. All cases from the literature were included as applicable.

**2.3. Exclusion Criteria.** Duplicates, letters, commentaries, or replies were excluded. Original articles not containing patient data, such a review articles, were also excluded.

**2.4. Selection of Studies.** Two reviewers (J.M.L, and S.K.) working independently considered the potential eligibility of

each abstract and title that resulted from the initial search. The full-text versions of the eligible studies were reviewed. Disagreements were harmonized by consensus and, if not possible, through arbitration by a third reviewer (J.I.S.).

**2.5. Data Extraction.** Data were extracted from all of the case reports and case series which were included in the systematic review. Demographic information included age, gender, and ethnicity. Clinical manifestation included presence of symptoms, such as hypothalamic dysfunction, hypoventilation, autonomic dysregulation, neuroendocrine tumors, and neurologic or other remarkable reports. Data regarding the laboratory findings, management strategy, and clinical outcomes were also examined.

**2.6. DNA Preparation, Whole Exome Sequencing, Sequence Alignment, and Variant Calling.** This study was approved by the institutional review board of the Severance Hospital, Yonsei University Health System (IRB No.2017-2991-001). There were two patients with ROHHADNET with available samples, Case 1 [7] and Case 2 [8] (Supplementary Table S2). After obtaining informed consent, whole blood (3 ml) was collected from the two individuals with ROHHADNET. Genomic DNA was extracted using RBC Lysis Solution, Cell Lysis Solution, and Protein Precipitation Solution (iNtRon Biotechnology, Inc). Whole exome capture was performed using the Agilent SureSelect V5 enrichment capture kit (Agilent Technologies). The enriched library was then sequenced using the HiSeq 2500 sequencing system (Illumina; 101-base paired-end sequencing). Image analysis and base calling were performed with the Pipeline software (Illumina) using default parameters. Sequence reads were mapped to the human reference genome assembly (GRCh37/hg19) using the CLC Genomic Workbench (version 9.0.1) software (QIAGEN). Mapping was performed using the “Map Reads to Reference” function of the CLC Genomic Workbench software with the following settings: mismatch cost, 2; insertion cost, 3; deletion cost, 3; length fraction, 0.5; similarity fraction, 0.9; and map to nonspecific reads, random. Nonspecific reads were ignored for count and coverage. All variants with a minimum coverage of 2 were called using the “Basic Variant Caller” function of the CLC Genomic Workbench and annotated.

**2.7. Filtering and Evaluation of Variants.** Whole exome sequencing was analyzed as previously described [9]. Briefly, variants with minor allele frequencies >1% in the single nucleotide polymorphism (dbSNP; version 138) or 1000 genomes (2504 individuals; phase 3 data) databases were excluded. In the second step, variants present in the homozygous or hemizygous state in 59 healthy individuals without ROHHAD syndrome (internal control WES data) were excluded. In step 3, synonymous variants and intronic variants not located within splice site regions were excluded. In step 4, a recessive inheritance pattern was assumed on the basis of the pedigree of affected individuals. Therefore, homozygous and biallelic compound heterozygous variants were retained, while single heterozygous variants were excluded from further evaluation. In Case 1 who was a male, hemizygous variants were also considered. De novo

variants could not be evaluated because parental DNAs were not available. In the final step, the remaining variants were ranked based on conservation of the mutated amino acid residue across species and their probable impact on the function of the encoded protein. The remaining variants were confirmed in the original participant DNA samples by Sanger sequencing.

**2.8. Copy Number Variant (CNV) Analysis.** Analysis of CNV was performed using the paired-end WES data using the EXCAVATOR version 2.2 [10] and ExomeDepth version 1.1.10 tools [11] with default settings. The GRCh37/hg19 database was used as the reference assembly for calculation of GC content. The WES dataset of 11 internal control subjects was compared with that of the study participants. Copy number variations at specific target regions were estimated according to different CNV detection algorithms using the Agilent SureSelect V5 kit.

### 3. Results

In total, 321 articles were identified using electronic and manual search methods (Figure 1). After serially reviewing the titles, abstracts, and full texts, 46 eligible studies including 158 patients were included. Among them, there were 36 case reports available for individual patient data (IPD; 48 patients, 23 ROHHAD and 25 ROHHADNET) [3, 4, 7, 8, 12–43]. The remaining ten studies were reporting patients in groups or cohorts and were therefore available for aggregate patient data (APD; 110 patients, 71 ROHHAD and 39 ROHHADNET) [6, 44–50].

Data regarding gender were available in 100 patients (40 from IPD and 60 from APD). There were 65 females and 35 males showing female preponderance, and female to male ratio was 1.9 to 1. Aside from gender, most of clinical information was extracted from 36 case reports where IPD were available. Limited information was retrievable from 10 studies with APD. Detailed profiles of the studies and patients' data are presented in Tables 1 and 2.

**3.1. Individual Patient Data (IPD) from Case Reports.** There were 48 patients in the 36 case reports, in which 100% were pediatric cases. The median age at the time of diagnosis was 4.0 years (range, 1–15). Twelve patients (12/40, 30 %) were boys, 28 (28/40, 70%) were girls, and no information could be retrieved in the 8 remainders. Female to male ratio from IPD was 2.3 to 1.

**3.1.1. Clinical Presentation.** The most common presentation of patients with ROHHAD/NET was rapid obesity and hypothalamic dysfunction found in 40 cases (83%) respectively, followed by hypoventilation reported in 36 cases (75%). Hypothalamic dysfunction presented in various forms of endocrine disorder, such as growth hormone deficiency (25%), diabetes insipidus (19%), and central precocious puberty (15%). Hypoventilation most commonly presented as obstructive sleep apnea (44%). For symptoms of autonomic dysregulation, ophthalmologic abnormality such as

blurred vision was most commonly reported (25%), followed by altered pain perception (13%) and gastrointestinal dysmotility (13%). Excessive sweating was noted in 10% of the patients. Behavioral change was a common (60%) form of cognitive dysfunction, and the symptoms included mood changes, fatigue, social withdrawal, poor school performance, and intellectual disability. Other neurologic manifestations majorly included seizures, altered consciousness, sleep disturbance, and developmental delay. The clinical presentations of the patients are summarized in Table 3.

**3.1.2. Laboratory Findings.** In 13 patients who had available datasets, all had hypoxemia at initial presentation and hypercapnia was also dominant (14/15, 93%; Table 4). Dysnatremia was accompanied in most of the patients (30/31, 97%): 25 hypernatremia and 5 hyponatremias. Hyperprolactinemia (27/28, 96%), decreased IGF-1 level (12/16, 75%), and hypothyroidism (18/30, 60%) were also common.

**3.1.3. Treatment Strategies and Survival.** At the time of diagnosis, high proportion of patients (21/48, 44%) required respiratory support: mechanical ventilation in 20 (42%) cases and tracheostomy in 6 (13%) cases (Table 5). Six of the 44 (14%) patients were treated with steroids, while other immunosuppressive measures including rituximab and/or cyclophosphamide were administered in 7 cases (7/48, 14%). There were 4 deaths (3 sudden cardiac arrests and 1 multiorgan failure after sepsis) out of the 48 cases (Table 1).

**3.1.4. Tumor Presentation.** Out of 48 patients, twenty-five had neuroendocrine tumors (52.1%). The features of the tumors are described in Table 6. The most common type was ganglioneuromas: 15 ganglioneuromas (60%), 9 ganglioneuroblastomas (36%), and 1 hamartoma with neural tissue (2%). Although the lesions usually presented as intra-abdominal mass, 2 cases with mediastinal masses were reported.

**3.2. Aggregate Patient Data (APD).** The 10 studies with APD included 110 patients (Figure 1; Table 2). Although limited data were available regarding age, all of the reported were pediatric cases. Sixty patients were available for gender information: 23 males (38%) and 37 females (62%). Female predilection was consistently noted. Rapid-onset obesity was observed in 65% (71/110) of the patients. Hypoventilation was reported in 51/110 (46%) patients, 63% of them (32/51) presented with sleep apnea, supporting the findings from IPD. Autonomic dysfunction was reported in 80/106 (75%) patients and behavioral changes were observed in 40/110 (36%). There were 46/110 (42%) patients who had neuroendocrine tumors and ganglioneuroma was the most common type as in IPD (12/46; the remaining 34 were not available for histology). In line with the IPD results, dysnatremia was the most commonly observed electrolyte imbalance (21/27, 78%). Information regarding treatment strategies was available in 51 patients and 100% of them eventually received artificial ventilation. There were 12 deaths (9 sudden cardiac arrests and 2 not available for cause of death) out of the 110 patients. The frequencies and characteristics of clinical manifestation generally conformed to those from IPD.

TABLE I: Summary profiles of individual patient data (IPD) of ROHHADNET syndrome (case-reports).

| Patient No. | Authors, year         | Age/Sex | Height (cm)/Weight (kg)/BMI  | Presenting symptoms                                                          | Rapid obesity | Hypothalamic dysfunction | Hyperventilation | Autonomic dysregulation | Behavioral changes            | Neurologic findings | Neural crest tumor     | Other findings       | Na (mmol/L) | Prolactin (ng/mL)   | fT4 (ng/dL)             | Treatment                    | Outcome |
|-------------|-----------------------|---------|------------------------------|------------------------------------------------------------------------------|---------------|--------------------------|------------------|-------------------------|-------------------------------|---------------------|------------------------|----------------------|-------------|---------------------|-------------------------|------------------------------|---------|
| 1           | Park, 2010 [7]        | 13/M    | 161/70.6/28                  | Pain on both thighs, gait disturbance, general weakness, cold/body sensation | No            | Yes                      | Yes              | Yes                     | No                            | Seizure             | Ganglio-neuroma        | Rhabdo-myolysis      | 198         | 35.8 > 13.          | 0.5 > 0.8               | Hydration, IVIG              | Alive   |
| 2           | Thaker, 2015 [12]     | 2/M     | 163 (11 yr)/166.3 (11 yr)/62 | -                                                                            | No            | No                       | No               | Yes                     | Yes                           | No                  | No                     | No                   | Normal      | -                   | 1.04                    | -                            | Alive   |
| 3           | Gordon, 2015 [13]     | 4/F     | -/-                          | -                                                                            | No            | DI                       | Sleep apnea      | Yes                     | No                            | No                  | Ganglio-neuroblast oma | No                   | -           | Hyper-prolactinemia | -                       | Caffeine                     | Alive   |
| 4           | Tellingen, 2015 [14]  | 4/F     | -/-                          | Rapid weight gain, growth retardation                                        | Yes           | DI                       | Yes              | No                      | No                            | No                  | Ganglio-neuroma        | No                   | -           | -                   | Hypo thyroidism         | -                            | Alive   |
| 5           | Grudnikoff, 2013 [15] | 4/F     | -/-                          | Weight gain, growth retardation, irritability, aggression                    | Yes           | Yes                      | Sleep apnea      | No                      | Yes                           | No                  | Ganglio-neuroma        | No                   | -           | -                   | -                       | -                            | Alive   |
| 6           | Patwara, 2011 [16]    | 8/F     | 150/45>80/36                 | -                                                                            | Yes           | Precocious puberty       | Sleep apnea      | Pupil dilatation        | Yes                           | No                  | Ganglio-neuroblast oma | Pneumonia, scoliosis | 158         | 56                  | -                       | Artificial ventilation       | Alive   |
| 7           | Sarroti, 2012 [17]    | 4/M     | -/-                          | -                                                                            | Yes           | Polyuria, polydipsia     | Sleep apnea      | Yes                     | Yes                           | No                  | No                     | No                   | Normal      | Hyper-prolactinemia | -                       | IVIG, artificial ventilation | Alive   |
| 7           | Sarroti, 2012 [17]    | 5/F     | -/-                          | -                                                                            | Yes           | Yes                      | Yes              | No                      | Yes                           | No                  | No                     | No                   | -           | -                   | Central hypo-thyroidism | -                            | Alive   |
| 8           | Dhondt, 2013 [18]     | 3/F     | -/-                          | Stagnation of neurodevelopment, aggression, hyperphagia                      | Yes           | Precocious puberty       | Yes              | Yes                     | Yes                           | Yes                 | No                     | No                   | -           | -                   | -                       | Artificial ventilation       | Alive   |
| 9           | Bougrères, 2008 [19]  | 4/-     | -/22                         | -                                                                            | Yes           | Yes                      | Yes              | Yes                     | Mental retardation, psychosis | No                  | Ganglio-neuroma        | No                   | 156         | 19                  | 8.5                     | -                            | Alive   |

TABLE I: Continued.

| No. | Patient No. | Authors, year             | Age/Sex | Height (cm)/Weight (kg)/BMI               | Presenting symptoms                                                                                  | Rapid obesity | Hypothalamic dysfunction                               | Hypoventilation | Autonomic dysregulation                       | Behavioral changes  | Neurologic findings | Neural crest tumor    | Other findings                           | Na (mmol/L) | Prolactin (ng/mL)   | fT4 (ng/dL) | Treatment                                                                        | Outcome                       |
|-----|-------------|---------------------------|---------|-------------------------------------------|------------------------------------------------------------------------------------------------------|---------------|--------------------------------------------------------|-----------------|-----------------------------------------------|---------------------|---------------------|-----------------------|------------------------------------------|-------------|---------------------|-------------|----------------------------------------------------------------------------------|-------------------------------|
| 9   | 11          | Bougreres, 2008 [9]       | 3/-     | -/-/40                                    | -                                                                                                    | Yes           | Yes                                                    | Sleep apnea     | Yes                                           | Mental retardation  | No                  | Ganglio-neuroma       | No                                       | 161         | 39                  | 9.8         | -                                                                                | Alive                         |
| 9   | 12          | Bougreres, 2008 [9]       | 3/-     | -/-/29                                    | -                                                                                                    | Yes           | Yes                                                    | Yes             | Yes                                           | No                  | No                  | Ganglio-neuroma       | No                                       | 150         | 14                  | 171         | -                                                                                | Alive                         |
| 9   | 13          | Bougreres, 2008 [9]       | 3/-     | -/-/35                                    | -                                                                                                    | Yes           | Yes                                                    | Sleep apnea     | Yes                                           | No                  | No                  | Ganglio-neuroma       | No                                       | 151         | 22                  | 16          | -                                                                                | Alive                         |
| 9   | 14          | Bougreres, 2008 [9]       | 2/-     | -/-/24                                    | -                                                                                                    | No            | Yes                                                    | Yes             | Yes                                           | No                  | No                  | Ganglio-neuroma       | No                                       | 145         | 31                  | 16          | -                                                                                | Alive                         |
| 9   | 15          | Bougreres, 2008 [9]       | 2/-     | -/-/44                                    | -                                                                                                    | No            | Yes                                                    | Yes             | Yes                                           | No                  | No                  | Ganglio-neuroma       | No                                       | 149         | 34                  | 12.4        | -                                                                                | Alive                         |
| 10  | 16          | Paz-Priel, 2011 [20]      | 5/F     | -/-/17 > 25                               | -                                                                                                    | Yes           | Yes                                                    | No              | Left exotropia                                | Aggressive behavior | No                  | Ganglio-neuroblastoma | No                                       | -           | 76.5                | Normal      | Cyclophosphamide, IVIG, prednisone, rituximab                                    | Alive                         |
| 11  | 17          | Chandrasekaran, 2012 [21] | 5/F     | 108/29/25                                 | -                                                                                                    | Yes           | DI                                                     | Yes             | Pupil dilatation, pupillary response decrease | No                  | No                  | Ganglio-neuroblastoma | No                                       | Hyper Na    | Hyper-prolactinemia | -           | Artificial ventilation, tracheostomy                                             | Alive                         |
| 11  | 18          | Chandrasekaran, 2012 [21] | 9/F     | 137/54/29                                 | -                                                                                                    | Yes           | DI                                                     | Yes             | Chronic constipation, neurogenic bladder      | No                  | Developmental delay | No                    | No                                       | Hyper Na    | -                   | -           | Noninvasive mask                                                                 | Alive                         |
| 12  | 19          | Kocay, 2004 [22]          | 13/F    | 145/69/32 (10 yrs)                        | Respiratory distress, cyanosis                                                                       | Yes           | Hypogonadism, secondary amenorrhea, precocious puberty | Yes             | No                                            | Social withdrawal   | Drowsiness          | No                    | acanthosis nigricans, Raynaud phenomenon | 151         | 1.044 (10 yrs)      | 0.88        | -                                                                                | Alive                         |
| 13  | 20          | Sumanasekera, 2012 [23]   | 10/F    | -/35/-                                    | Progressive respiratory difficulty, edema                                                            | Yes           | No                                                     | Yes             | No                                            | Hallucination       | Drowsiness          | Ganglio-neuroma       | No                                       | 167         | Normal              | -           | -                                                                                | Alive                         |
| 14  | 21          | Abadi, 2013 [3]           | 3/M     | 92 > 96.8 (9 mo)/20 > 25.7 (9 mo)/24 > 28 | Cyanosis, recent onset dyspnea                                                                       | Yes           | Polyuria, polydipsia                                   | Yes             | No                                            | Yes                 | No                  | Uroblastoma           | No                                       | 143         | 44.7                | 0.75        | Cyclophosphamide, IVIG, dexamethasone, rituximab                                 | Alive                         |
| 15  | 22          | Atapattu, 2015 [24]       | 4/F     | -/-/-                                     | Excessive weight gain, increase food seeking, daytime somnolence                                     | Yes           | No                                                     | Yes             | No                                            | Yes                 | No                  | Ganglio-neuroma       | Celiac disease                           | -           | -                   | -           | Hypertension medication                                                          | Alive                         |
| 16  | 23          | Ucar, 2013 [8]            | 6/F     | -/-/-                                     | Blurring of consciousness, recurrent fever                                                           | No            | GH deficiency                                          | Yes             | No                                            | No                  | Yes                 | Hamartoma tonsil      | No                                       | 152         | 89                  | -           | Dexamethasone, ventilatory support                                               | Alive                         |
| 17  | 24          | Sethi, 2004 [25]          | 5/F     | 117/25 > 37/14 > 28                       | Behavior outbursts, poor school performance, hyperphagia, fever, abdominal pain with rectal prolapse | Yes           | Bilateral tonic pupils                                 | No              | Bilateral tonic pupils                        | Yes                 | No                  | Ganglio-neuroblastoma | Metabolic alkalosis                      | HypoNa      | -                   | Normal      | Endotracheal intubation, risperidone, benzodiazepines, antipsychotic medications | Multifactorial failure, death |

TABLE I: Continued.

| Patient No. | Authors, year        | Age/Sex | Height (cm)/Weight (kg)/BMI | Presenting symptoms                                                                                                                                 | Rapid obesity | Hypothalamic dysfunction  | Hypoventilation | Autonomic dysregulation                                           | Behavioral changes                 | Neurologic findings          | Neural crest tumor | Other findings       | Na (mmol/L) | Prolactin (ng/mL)   | fT4 (ng/dL) | Treatment                                                                  | Outcome |
|-------------|----------------------|---------|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|---------------|---------------------------|-----------------|-------------------------------------------------------------------|------------------------------------|------------------------------|--------------------|----------------------|-------------|---------------------|-------------|----------------------------------------------------------------------------|---------|
| 18          | Galizia, 2012 [26]   | 3/F     | -/-                         | Rapid weight gain, polyuria, sleep apnea                                                                                                            | Yes           | Yes                       | Sleep apnea     | No                                                                | No                                 | No                           | No                 | No                   | -           | Hyper-prolactinemia | Normal      | -                                                                          | Alive   |
| 18          | Galizia, 2012 [26]   | 3/F     | -/-                         | Rapid weight gain, fatigue, polydipsia, syncope episodes, strabismus, behavioral problems                                                           | Yes           | Yes                       | No              | Strabismus                                                        | Yes                                | Yes                          | No                 | No                   | -           | Hyper-prolactinemia | Normal      | Mechanical ventilation                                                     | Alive   |
| 19          | Baronío, 2013 [27]   | 1/M     | -/-                         | Severe obesity, hyperreninemic hypertension                                                                                                         | Yes           | No                        | No              | No                                                                | No                                 | No                           | Ganglioneuroma     | No                   | -           | -                   | 0.62        | Mechanical ventilation, brain hypothermia, steroid pulse                   | Alive   |
| 19          | Baronío, 2013 [27]   | 2/F     | -/-                         | Severe obesity, hyperreninemic hypertension                                                                                                         | Yes           | GH deficiency             | No              | No                                                                | No                                 | No                           | Ganglioneuroma     | No                   | -           | Hyper-prolactinemia | 0.17        | Mechanical ventilation, brain hypothermia, steroid pulse                   | Alive   |
| 20          | Chow, 2014 [28]      | 15/M    | 174/87/29                   | Fever, headache, vomiting, weight gain                                                                                                              | Yes           | No                        | No              | No                                                                | Irritability, lethargy, somnolence | No                           | No                 | No                   | 150>123     | -                   | -           | Mechanical ventilation, IVIG, methylprednisolone                           | Alive   |
| 21          | Kot, 2012 [29]       | 9/M     | short stature/-/-           | Weight gain, short stature, hyperphagia, hypodipsia, thermal dysregulation, excessive perspiration, cold extremity, livedo reticularis, sleep apnea | Yes           | Hypodipsia, GH deficiency | Sleep apnea     | Yes                                                               | No                                 | No                           | No                 | No                   | 161         | Hyper-prolactinemia | Normal      | GH replacement                                                             | Alive   |
| 22          | Cemeroglu, 2015 [30] | 5/-     | -/-                         | Short stature, obesity                                                                                                                              | Yes           | DI, GH deficiency         | Sleep apnea     | Yes                                                               | Flat affect                        | No                           | No                 | Scoliosis            | 157>153     | -                   | 0.9>0.5     | GH replacement, levodopa, desmopressin, tonsillectomy, adenoidectomy, CPAP | Alive   |
| 23          | Chew, 2011 [31]      | 11/M    | -/35/26                     | Fever, drowsiness, shallow breathing                                                                                                                | No            | DI, hypogonadism          | Sleep apnea     | Thermal dysregulation, excessive sweating, right divergent squint | 0                                  | Seizure, developmental delay | No                 | Respiratory acidosis | 192         | Hyper-prolactinemia | Normal      | Anti-epileptics                                                            | Alive   |

TABLE I: Continued.

| No. | Patient No. | Authors, year                 | Age/Sex | Height (cm)/Weight (kg)/BMI | Presenting symptoms                                      | Rapid obesity | Hypothalamic dysfunction           | Hyperventilation                 | Autonomic dysregulation                                                           | Behavioral changes                                                                         | Neurologic findings | Neural crest tumor | Other findings                | Na (mmol/L)  | Prolactin (ng/mL)  | fT4 (ng/dL)                                          | Treatment                                                                       | Outcome                       |
|-----|-------------|-------------------------------|---------|-----------------------------|----------------------------------------------------------|---------------|------------------------------------|----------------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|---------------------|--------------------|-------------------------------|--------------|--------------------|------------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------|
| 24  | 33          | Petty, 2014 [32]              | -/M     | -/-/-                       | Weight gain, enuresis, sleep apnea, fever                | Yes           | No                                 | Yes                              | Transient visual loss                                                             | Hallucination                                                                              | No                  | No                 | Thrombocytopenia              | -            | -                  | -                                                    | IVIG, CPM, rituximab                                                            | Alive                         |
| 25  | 34          | Maksood, 2015 [33]            | 6/F     | 119/38/27                   | Abdominal mass, rapid onset obesity                      | Yes           | Premature thelarche, GH deficiency | Sleep apnea                      | Urinary incontinence                                                              | No                                                                                         | No                  | Ganglioneuroma     | Hepatitis C                   | 156          | -                  | 0.79                                                 | -                                                                               | Alive                         |
| 26  | 35          | Sinklecha, 2016 [34]          | 2/F     | -/-/-                       | Gait disturbance, head jerky movement, nystagmus         | Yes           | DI, polyuria, polydipsia           | Yes                              | No                                                                                | Aggressiveness                                                                             | Seizure             | Ganglioneuroma     | No                            | 189>115      | -                  | -                                                    | Chemotherapy, mechanical ventilation, tracheostomy, nasal BIPAP, rituximab, CPM | Cardiac arrest, sudden demise |
| 27  | 36          | Erenow, 2016 [35]             | 8/F     | -/-/-                       | Overweight, recession, fatigue, decreased school success | Yes           | No                                 | No                               | No                                                                                | Poor school performance, MDD, ADHD                                                         | No                  | No                 | No                            | -            | -                  | -                                                    | Fluoxetine, methylphenidate                                                     | Alive                         |
| 28  | 37          | Al-Harbi, 2016 [36]           | 8/F     | 126/45/28                   | Progressive fatigue, skin bluish discoloration, fever    | Yes           | Breast enlargement                 | Shortness of breath, sleep apnea | Cold intolerance, excessive sweating, altered pain sense                          | Slow mental function, poor school performance, sleepiness                                  | No                  | No                 | No                            | 186          | Hyperprolactinemia | Normal                                               | BIPAP                                                                           | Alive                         |
| 29  | 38          | Aljabban, 2016 [37]           | 4/F     | 110/25/-                    | Rapid weight gain, excessive eating                      | Yes           | Polyuria, polydipsia               | Sleep apnea                      | Cold extremity, GI dysmotility                                                    | Mood alteration, anxiety, aggressiveness, recurrent fatigue, social withdrawal, sleepiness | Seizure             | Ganglioneuroma     | No                            | Normal > 162 | Normal             | Antipsychotics, mechanical ventilation, tracheostomy | Cardiac arrest, death                                                           |                               |
| 30  | 39          | Bagheri, 2017 [4]             | 5/F     | 120/40/-                    | Cough, cyanosis                                          | Yes           | Central hypothyroidism             | Sleep apnea                      | Cold extremities, hyperhidrosis, constipation                                     | Mood change                                                                                | Seizure             | Ganglioneuroma     | Facial plethora, buffalo neck | 125          | Hyperprolactinemia | 0.8                                                  | Mechanical ventilation, tracheostomy                                            | Alive                         |
| 31  | 40          | Galewicz-Zielinska, 2012 [38] | 9/-     | -/-/-                       | -                                                        | No            | No                                 | Mixed sleep apnea                | No                                                                                | Yes                                                                                        | No                  | No                 | Tonsillar hypertrophy         | -            | -                  | -                                                    | BIPAP                                                                           | Alive                         |
| 32  | 41          | Jacobson, 2016 [39]           | 2/F     | -/-/40                      | Hyperphagia, weight gain (16.8 > 35.5 kg)                | Yes           | Partial DI                         | Sleep apnea                      | Reduced pain perception, strabismus                                               | Social withdrawal, autism                                                                  | No                  | Ganglioneuroma     | Papular rash                  | -            | -                  | -                                                    | Rituximab, cyclophosphamide                                                     | Alive                         |
| 32  | 42          | Jacobson, 2016 [39]           | 3/M     | -/-/34                      | Hyperphagia, weight gain (18 kg for 3 mo)                | Yes           | Yes                                | Sleep apnea                      | excessive sweating, thermal dysregulation, emesis, altered pain sense, strabismus | Social withdrawal                                                                          | No                  | No                 | No                            | -            | Hyperprolactinemia | -                                                    | Rituximab, CPM                                                                  | Alive                         |

TABLE I: Continued.

| Patient No. | Authors, year           | Age/Sex | Height (cm)/Weight (kg)/BMI | Presenting symptoms         | Rapid obesity | Hypothalamic dysfunction                                                                                                        | Hyperventilation                                | Autonomic dysregulation         | Behavioral changes                     | Neurologic findings | Neural crest tumor | Other findings                        | Na (mmol/L) | Prolactin (ng/mL) | fT4 (ng/dL) | Treatment                                      | Outcome      |
|-------------|-------------------------|---------|-----------------------------|-----------------------------|---------------|---------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|---------------------------------|----------------------------------------|---------------------|--------------------|---------------------------------------|-------------|-------------------|-------------|------------------------------------------------|--------------|
| 33          | Lucas-Herald, 2012 [40] | 1/F     | -/32 (3 yr)/22              | Hyperphagia, food stealing  | Yes           | Hyperprolactinemia, GH deficiency, water imbalance                                                                              | Sleep apnea                                     | Altered pain perception         | No                                     | No                  | No                 | Renal failure                         | 184         | -                 | -           | BIPAP                                          | Alive        |
| 33          | Lucas-Herald, 2012 [40] | 2/M     | -/33/29                     | Obesity                     | Yes           | Hyperprolactinemia, failed GH                                                                                                   | Mixed sleep apnea                               | No                              | No                                     | No                  | No                 | No                                    | -           | -                 | -           | BIPAP                                          | Alive        |
| 34          | Ibanez-Mico, 2017 [41]  | 2/F     | -/-/-                       | Obesity, increased appetite | Yes           | Hyperprolactinemia, Central hypothyroidism                                                                                      | Sleep apnea                                     | Yes                             | Aggression, hyperactivity, impulsivity | Yes                 | No                 | Altered pain sense, GI dysmotility    | 175         | 166               | 1.05        | IVIG, steroids, cyclophosphamide, Tracheostomy | Sudden death |
| 35          | Issas, 2018 [42]        | 10/M    | 136/66.5/34.92              | Seizures (hyponatremia)     | Yes           | Hyperprolactinemia, Central hypothyroidism                                                                                      | Central hyperventilation, Thermal dysregulation | Polydipsia                      | Aggressiveness                         | Yes                 | No                 | No                                    | Hyper/hypo- | -                 | -           | -                                              | Alive        |
| 36          | Siraz, 2018 [43]        | 7/F     | 130/61/36.0                 | obesity                     | Yes           | Central hypothyroidism, DI, MDD, Central precocious puberty, GH deficiency, Hyperprolactinemia, Secondary/adrenal insufficiency | No                                              | Excessive sweating, hypothermia | No                                     | No                  | No                 | Pulmonary hyper-tension IQ 65         | 156         | 33                | 0.7         | -                                              | Alive        |
| 36          | Siraz, 2018 [43]        | 5/F     | 101/31/30.4                 | Obesity, seizure            | Yes           | Central hypothyroidism, Hyperprolactinemia                                                                                      | Central hyperventilation                        | Yes                             | Aggressiveness                         | Yes                 | No                 | Central cyanosis IQ of 3 years of age | 164         | 56                | 0.8         | Tracheostomy                                   | Alive        |

ADHD, attention deficit hyperactivity disorder; BIPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CPM, cyclophosphamide; DM, diabetes mellitus; DI, diabetes insipidus; IVIG, intravenous immunoglobulin; IQ, intellectual quotient; GH, growth hormone; GI, gastrointestinal; OCD, obsessive-compulsive disorder; SIADH, syndrome of inappropriate antidiuretic hormone secretion.



TABLE 2: Summary profiles of aggregate patient data of ROHADNET syndrome (case-series and cohorts).

| Author, year           | N° patients | Age (yr)       | Sex (M/F) | Rapid obesity | Hypothalamic dysfunction (N° patients)                                                                                                                                                                                          | Hypoventilation (N° patients)                              | Autonomic dysregulation (N° patients)                                                                                                                  | Behavioral changes (N° patients)                                                                                                                                                                     | Neurologic symptoms (N° patients)                                            | Neuroendocrine tumors (N° patients) | Other findings (N° patients)                                                         | Na (mmol/L) (N° patients) | Treatment (N° patients)     | Outcome (N° patients) |
|------------------------|-------------|----------------|-----------|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|-------------------------------------|--------------------------------------------------------------------------------------|---------------------------|-----------------------------|-----------------------|
| Gil, 2012 [44]         | 5           | -              | -         | Yes           | Yes(5), hypothalamic dysfunction(1), adrenal insufficiency(1), precocious puberty(1)                                                                                                                                            | Central apnea(2), transient obstructive apnea(2)           | Yes(5)                                                                                                                                                 | Yes(2)                                                                                                                                                                                               | No                                                                           | Ganglioneuroma (3)                  | No                                                                                   | -                         | -                           | Death(1)              |
| Reppucci, 2014 [45]    | 7           | 8.3 (4.7~10.1) | -         | Yes           | No                                                                                                                                                                                                                              | Yes(3), sleep apnea(5)                                     | No                                                                                                                                                     | No                                                                                                                                                                                                   | No                                                                           | Yes                                 | No                                                                                   | -                         | -                           | Alive                 |
| Barclay, 2016 [51]     | 16          | 4.3            | -         | No            | Yes(16)                                                                                                                                                                                                                         | Yes(16),                                                   | Yes(16)                                                                                                                                                | No                                                                                                                                                                                                   | No                                                                           | Yes(7)                              | No                                                                                   | -                         | Artificial ventilation(16)  | Alive                 |
| Biancheri, 2013 [46]   | 6           | -              | 2/4       | Yes           | Hypothyroidism(5), adrenal insufficiency(2), precocious puberty(2)                                                                                                                                                              | Central apnea(4)                                           | No                                                                                                                                                     | Yes(6)                                                                                                                                                                                               | No                                                                           | No                                  | No                                                                                   | Electrolyte imbalance (6) | -                           | Alive                 |
| Napoli, 2014 [47]      | 6           | 2~4            | -         | Yes           | Hypothyroidism(5), adrenal insufficiency(3), precocious puberty(2)                                                                                                                                                              | Central apnea(4)                                           | No                                                                                                                                                     | Yes(6)                                                                                                                                                                                               | No                                                                           | No                                  | No                                                                                   | Electrolyte imbalance (6) | Non-invasive ventilation    | Alive                 |
| Napoli, 2014 [47]      | 7           | -              | -         | Yes(7)        | Hypothyroidism(6), adrenal insufficiency(4), precocious puberty(2)                                                                                                                                                              | Sleep apnea(7)                                             | No                                                                                                                                                     | Yes(7)                                                                                                                                                                                               | No                                                                           | Ganglioneuroma (3)                  | No                                                                                   | -                         | -                           | Alive                 |
| Ize-Ludlow, 2007 [6]   | 15          | -              | 6/9       | Yes(8)        | Hypothyroidism(5), adrenal insufficiency(4), precocious puberty(2), delayed puberty(2), amenorrhea(1), irregular menstruation(1), premature adrenarche(2), hypogonadism(1), SIADH(2), polydipsia(8), hypodipsia(4), polyuria(4) | Alveolar hypoventilation (15), sleep apnea(8), cyanosis(4) | Ophthalmologic manifestations (13), thermal dysregulation (11), GI dysmotility(10), Altered pain perception(8), altered sweating(8), cold extremity(6) | Depression(2), flat effect(2), psychosis(2), behavioral outbursts(1), bipolar disorder(1), emotional lability(1), OCD(1), oppositional-defiant disorder(1), Tourette's syndrome(1), hallucination(1) | Syncope(1), developmental delay(3), regression(3), seizure(5), hypotonia (4) | Yes(5)                              | Scoliosis(3), type 2 DM(2), enuresis(4), asthma(3), hypersomnolence(2), pneumonia(2) | HyperNa (7), hypona (2)   | -                           | Cardiac arrest(9)     |
| Barclay, 2015 [48]     | 35          | -              | 14/21     | Yes           | Yes(35)                                                                                                                                                                                                                         | Yes(35)                                                    | Yes(35)                                                                                                                                                | No                                                                                                                                                                                                   | No                                                                           | Yes(15)                             | No                                                                                   | -                         | Artificial ventilation (35) | Alive                 |
| Gueorguieva, 2011 [49] | 9           | 0~4            | -         | No            | Hypogonadism(4)                                                                                                                                                                                                                 | Yes(9)                                                     | Yes(9)                                                                                                                                                 | Mental retardation(4)                                                                                                                                                                                | No                                                                           | Ganglioneuroma (6)                  | No                                                                                   | Mean 150                  | -                           | Death (2)             |
| Abel, 2010 [50]        | 4           | -              | 1/3       | Yes           | No                                                                                                                                                                                                                              | Alveolar hypoventilation                                   | Thermal dysregulation, cold extremity, altered pain perception                                                                                         | Emotional lability, behavioral outburst                                                                                                                                                              | No                                                                           | No                                  | No                                                                                   | -                         | -                           | Alive                 |

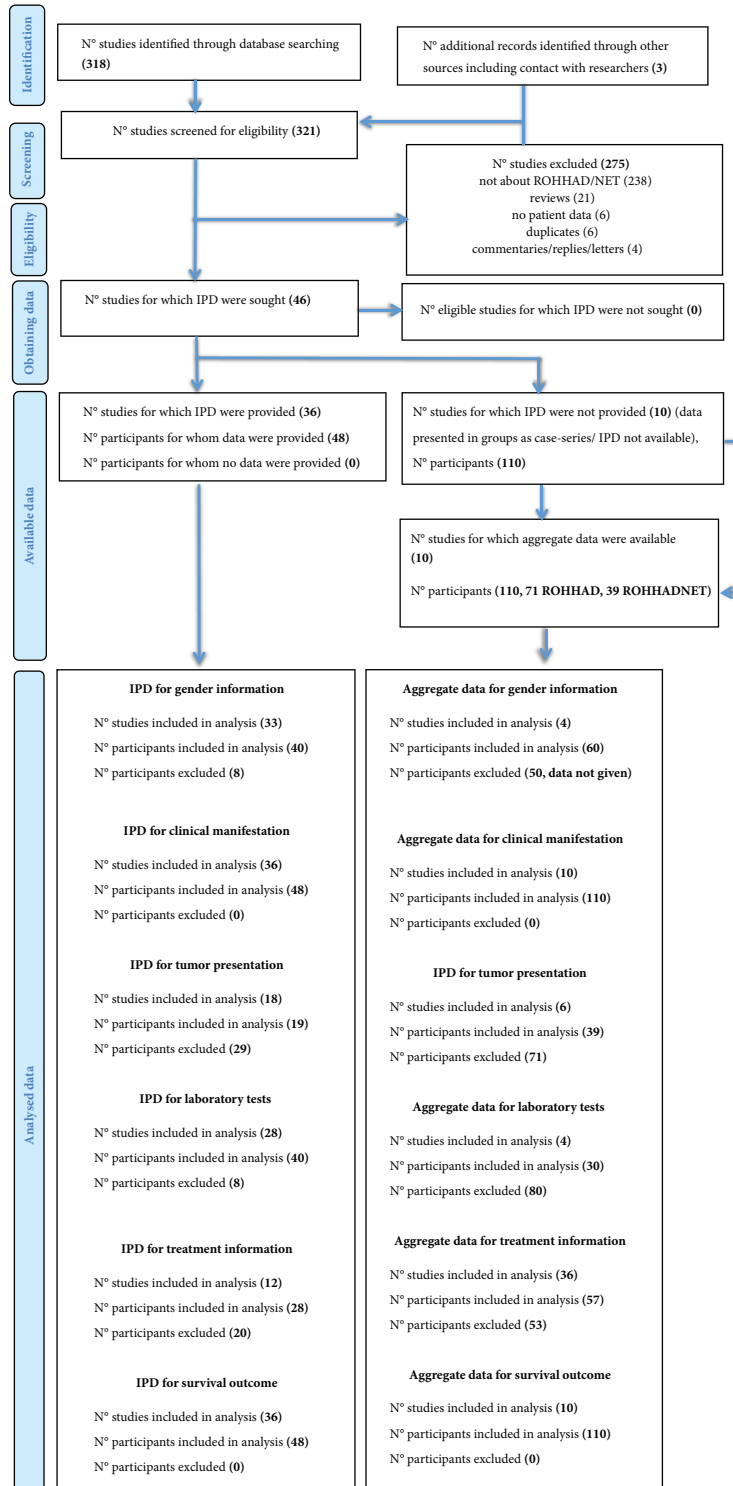


FIGURE 1: PRISMA IPD flow diagram.

3.3. *Next Generation Sequencing.* We described previously reported human candidate genes [6, 12, 51–54] for ROHHAD/NET in Table 7. None of these, however, have been identified in the patient cases to date. In our study, there were two ROHHADNET patients with available samples for whole exome sequencing: Case 1, a 15-year-old Korean boy

[7]; and Case 2, a 5-year-old Turkish girl [8]. Details with regard to these two patients are briefed in Supplementary Table S2. Currently, there is no known genetic cause for ROHHAD or ROHHADNET [55]. To identify genetic variants related to ROHHAD syndrome, we performed WES for Case 1 and Case 2. Since ROHHAD syndrome in

TABLE 3: Clinical presentations of patients with ROHHADNET syndrome (IPD).

| Clinical findings               | Total number of patients (n=48) |                |
|---------------------------------|---------------------------------|----------------|
|                                 | Number of patients              | (%)            |
| <b>Rapid obesity</b>            | <b>40</b>                       | <b>(83.3%)</b> |
| <b>Hypoventilation</b>          | <b>36</b>                       | <b>(75.0%)</b> |
| Obstructive sleep apnea         | 21                              | (43.8%)        |
| Respiratory distress            | 5                               | (10.4%)        |
| Cyanotic episodes               | 4                               | (8.3%)         |
| <b>Hypothalamic dysfunction</b> | <b>40</b>                       | <b>(83.3%)</b> |
| Growth hormone deficiency       | 13                              | (25.3%)        |
| Diabetes insipidus              | 9                               | (18.8%)        |
| Polyuria/polydipsia             | 8                               | (16.7%)        |
| Central precocious puberty      | 7                               | (14.6%)        |
| Hypogonadotropic hypogonadism   | 2                               | (4.2%)         |
| Premature thelarche             | 2                               | (4.2%)         |
| <b>Autonomic dysregulation</b>  | <b>32</b>                       | <b>(66.7%)</b> |
| Ophthalmologic abnormality      | 12                              | (25.0%)        |
| Altered perception of pain      | 6                               | (12.5%)        |
| Gastrointestinal dysmotility    | 6                               | (12.5%)        |
| Cold extremity                  | 4                               | (8.3%)         |
| Neurogenic bladder              | 4                               | (8.3%)         |
| Excessive sweating              | 5                               | (10.4%)        |
| Thermal dysregulation           | 3                               | (6.3%)         |
| Syncope                         | 1                               | (2.1%)         |
| Urinary incontinence            | 1                               | (2.1%)         |
| <b>Behavioral disorders</b>     | <b>29</b>                       | <b>(60.4%)</b> |
| Irritability & aggression       | 10                              | (20.8%)        |
| Fatigue                         | 4                               | (8.3%)         |
| Social withdrawal               | 4                               | (8.3%)         |
| Poor school performance         | 3                               | (6.3%)         |
| Intellectual disability         | 2                               | (4.2%)         |
| Mood change                     | 2                               | (4.2%)         |
| Flat affect                     | 2                               | (4.2%)         |
| Hallucination                   | 2                               | (4.2%)         |
| Major depressive disorder       | 1                               | (2.1%)         |
| Attention deficit disorder      | 1                               | (2.1%)         |
| Psychosis                       | 1                               | (2.1%)         |
| <b>Neurologic abnormality</b>   | <b>16</b>                       | <b>(33.3%)</b> |
| Seizure                         | 7                               | (14.6%)        |
| Blurring of consciousness       | 4                               | (8.3%)         |
| Sleep disturbance               | 3                               | (6.3%)         |
| Developmental delay             | 3                               | (6.3%)         |
| Gait disturbance                | 2                               | (4.2%)         |
| Nystagmus                       | 1                               | (2.1%)         |
| General weakness                | 1                               | (2.1%)         |

TABLE 3: Continued.

| Clinical findings      | Total number of patients (n=48) |         |
|------------------------|---------------------------------|---------|
|                        | Number of patients              | (%)     |
| <b>Other findings</b>  |                                 |         |
| Fever                  | 6                               | (12.5%) |
| Papular rash           | 3                               | (6.3%)  |
| Enuresis               | 2                               | (4.2%)  |
| Scoliosis              | 2                               | (4.2%)  |
| Rhabdomyolysis         | 1                               | (2.1%)  |
| Pneumonia              | 1                               | (2.1%)  |
| Headache               | 1                               | (2.1%)  |
| Megaloblastic anemia   | 1                               | (2.1%)  |
| Thrombocytopenia       | 1                               | (2.1%)  |
| Acanthosis nigricans   | 1                               | (2.1%)  |
| Raynaud phenomenon     | 1                               | (2.1%)  |
| Celiac disease         | 1                               | (2.1%)  |
| Metabolic alkalosis    | 1                               | (2.1%)  |
| Hepatitis C            | 1                               | (2.1%)  |
| Buffalo neck           | 1                               | (2.1%)  |
| Tonsillar hypertrophy  | 1                               | (2.1%)  |
| Abdominal mass         | 1                               | (2.1%)  |
| Renal failure          | 1                               | (2.1%)  |
| Edema                  | 1                               | (2.1%)  |
| Pulmonary hypertension | 1                               | (2.1%)  |
| Cough                  | 1                               | (2.1%)  |

these individuals was sporadic and had childhood onset, we assumed the following inheritance patterns: (1) biallelic variants in recessive genes and (2) hemizygous variants in X-chromosome genes in Case 1. Variant filtering reduced the number of candidate genes to five in Case 1 and three in Case 2, respectively, as outlined in Supplementary Table S3. In Case 1, variant filtering was begun with 188,415 variants from the normal reference sequence. This number was reduced to 1,914 upon exclusion of homozygous and hemizygous variants in healthy domestic individuals, common variants (minor allele frequencies >1% in public databases), and synonymous variants. Upon considering only those genes with hemizygous variants or more than two variants in the same gene, the number of variants was further reduced to 50 variants (14 genes). Exclusion of artefacts by direct inspection of sequence alignment and exclusion of variants with minor allele frequencies < 0.005 in public databases left six variants in three candidate genes—*PIK3R3*, *SPTBN5*, and *PCF11* (Supplementary Table S4). These variants were predicted likelihood to be deleterious for the function of the encoded protein in some prediction tools and *PIK3R3*, *SPTBN5*, and *PCF11* are not linked to any disease phenotype in human yet. The WES of Case 2 was analyzed in the same manner to identify candidate variants (Supplementary Table S4), but

TABLE 4: Laboratory findings of patients with ROHHADNET syndrome (IPD).

| Laboratory findings        | Total number of patients (n=48) |         |
|----------------------------|---------------------------------|---------|
|                            | Number of patients (%)          |         |
| <b>ABGA</b>                |                                 |         |
| Hypoxemia <sup>†</sup>     | 13/13                           | (100%)  |
| Hypercapnia <sup>‡</sup>   | 14/15                           | (93.3%) |
| Normal                     | 0/15                            | (0%)    |
| No information             | 34/48                           | (70.8%) |
| <b>Dysnatremia</b>         |                                 |         |
| Hypernatremia              | 25/31                           | (80.6%) |
| Hypонатremia               | 5/31                            | (16.1%) |
| Normal                     | 2/31                            | (6.5%)  |
| No information             | 17/48                           | (35.4%) |
| <b>Prolactin</b>           |                                 |         |
| Hyperprolactinemia         | 27/28                           | (96.4%) |
| Normal                     | 1/28                            | (3.6%)  |
| No information             | 19/48                           | (39.6%) |
| <b>Thyroid dysfunction</b> |                                 |         |
| Hypothyroidism             | 18/30                           | (60.0%) |
| Normal                     | 12/30                           | (40.0%) |
| No information             | 17/48                           | (35.4%) |
| <b>IGF-1 level</b>         |                                 |         |
| Low                        | 12/16                           | (75.0%) |
| Normal                     | 4/16                            | (25.0%) |
| No information             | 31/48                           | (64.6%) |

ABGA: Arterial blood gas analysis, IGF-1: Insulin-like growth factor-1.

<sup>†</sup>Hypoxemia is defined in terms of reduced partial pressure of oxygen below 80 mmHg or decreased oxygen saturation less than 90%.

<sup>‡</sup>Hypercapnia is defined in terms of elevated carbon dioxide above 45 mmHg.

none of them overlapped with variants identified in Case 1; *SRMS* and *ZNF4* were not linked to any disease phenotypes, whereas mutations in *KMT2B*, which encodes lysine-specific methyltransferase 2B, cause childhood-onset dystonia [56]. All variants were confirmed by Sanger sequencing of the DNA of the affected individuals.

In addition, we analyzed CNVs; has been previously abbreviated using WES in Case 1 and Case 2. The CNVs detected by both EXCAVATOR and ExomeDepth tools were 38 in Case 1 and 48 in Case 2, respectively. We specifically focused on deletion or duplication of alleles in an AR pattern; however, there was no surviving CNV upon manual inspection of WES data.

#### 4. Discussion

ROHHAD/NET is a rare disease and differential diagnosis from other obesity syndromes or neuroendocrine disorders requires clinical suspicion based on its phenotype. The genetic basis of this syndrome is still unknown.

The first part of this study is a systematic review on phenotypes of ROHHAD/NET involving 46 studies with 158 patients. Clinical manifestation, laboratory findings, tumor characteristics, and patient courses were reviewed. The results

TABLE 5: Treatment of case-reported patients with ROHHADNET syndrome (IPD).

| Treatment                          | Total number of patients (n = 48) |         |
|------------------------------------|-----------------------------------|---------|
|                                    | Number of patients (%)            |         |
| <b>Respiratory support</b>         |                                   |         |
| Mechanical ventilation             | 20                                | (41.7%) |
| BIPAP                              | 7                                 | (14.6%) |
| CPAP                               | 1                                 | (2.1%)  |
| Noninvasive mask                   | 1                                 | (2.1%)  |
| Tracheostomy                       | 6                                 | (12.5%) |
| <b>Steroids</b>                    |                                   |         |
| Methylprednisolone                 | 2                                 | (4.2%)  |
| Steroid pulse therapy              | 2                                 | (4.2%)  |
| Prednisolone                       | 2                                 | (2.1%)  |
| Dexamethasone                      | 1                                 | (2.1%)  |
| <b>Fluid resuscitation</b>         |                                   |         |
|                                    | 4                                 | (8.3%)  |
| <b>Intravenous immunoglobulins</b> |                                   |         |
|                                    | 7                                 | (14.6%) |
| <b>Immunosuppressive agents</b>    |                                   |         |
| Rituximab                          | 5                                 | (10.4%) |
| Cyclophosphamide                   | 6                                 | (12.5%) |
| <b>Other agents</b>                |                                   |         |
| Antipsychotics                     | 3                                 | (6.3%)  |
| Desmopressin acetate               | 2                                 | (4.2%)  |
| GH replacement                     | 2                                 | (4.2%)  |
| Anti-epileptics                    | 2                                 | (4.2%)  |
| Levothyroxine                      | 4                                 | (8.3%)  |
| Caffeine                           | 1                                 | (2.1%)  |
| Hypertensive medication            | 1                                 | (2.1%)  |
| <b>Procedure</b>                   |                                   |         |
| Brain hypothermia                  | 1                                 | (2.1%)  |
| Tonsillectomy                      | 1                                 | (2.1%)  |

BIPAP: bilevel positive airway pressure; CPAP: Continuous Positive Airway Pressure; GH: growth hormone.

showed that it has a pediatric onset and it is noteworthy that no adult case has been reported to date. There was a female preponderance, with the girls being twice as often affected than the boys, consistently in both IPD and APD. This finding is in contrast to what has been reported on acquired sleep disorders with a 2:1 predominance of males in the reported frequency of obstructive sleep apnea [57]. Rapid obesity may often be the first recognizable sign, since other endocrine dysfunctions are gradually present. The results implicated that common endocrine disorders such as hypothyroidism or precocious puberty may be early signs for recognition. In addition, it has been reported that one of the major effects of hypothyroidism is its influence on the central ventilatory control and that both hypoxic and hypercapnic ventilatory impairment are significantly present in untreated thyroid insufficiency [58]. Such impaired ventilatory responses are thought to be related to the decrease in oxygen consumption associated with hypothyroidism [59]. In that, it is tempting to speculate that disturbance of thyroid function may be in part responsible for respiratory distress

TABLE 6: Tumor presentation of patients with ROHHADNET syndrome (IPD and aggregate data).

| Author, year [ref]       | Type/histology                                              | Location/size                                                 | Associated symptoms/signs            | Treatment                                        |
|--------------------------|-------------------------------------------------------------|---------------------------------------------------------------|--------------------------------------|--------------------------------------------------|
| Park, 2010 [7]           | Ganglioneuroma                                              | Right adrenal                                                 | N/A                                  | IVIg                                             |
| Gordon, 2015 [13]        | Ganglioneuroblastoma                                        | Left adrenal                                                  | N/A                                  | N/A                                              |
| Tellingen, 2015 [14]     | Ganglioneuroma                                              | N/A                                                           | N/A                                  | N/A                                              |
| Grudnikoff, 2013 [15]    | Ganglioneuroma                                              | N/A                                                           | N/A                                  | resection                                        |
| Patwari, 2011 [16]       | Ganglioneuroblastoma                                        | Right paraspinal                                              | N/A                                  | N/A                                              |
| Bougnères, 2008 [19]     | Ganglioneuroma (6 patients)                                 | 1 mediastinal<br>2 right adrenal<br>3 left adrenal            | N/A                                  | N/A                                              |
| Paz-Priel, 2011 [20]     | Ganglioneuroblastoma                                        | Retroperitoneal mass                                          | Opsoclonus-myoclonus-ataxia syndrome | resection, cyclophosphamide, IVIG                |
| Chandrakantan, 2012 [21] | Ganglioneuroblastoma                                        | Left adrenal                                                  | N/A                                  | resection                                        |
| Sumanasena, 2012 [23]    | Ganglioneuroma                                              | Left adrenal                                                  | N/A                                  | resection                                        |
| Abaci, 2013 [3]          | Ganglioneuroma/<br>intermixed type with favorable histology | Retroperitoneal mass (6.5 × 3.5 × 2.0 cm)                     | N/A                                  | Resection, cyclophosphamide, IVIG, dexamethasone |
| Atapattu, 2015 [24]      | Ganglioneuroma                                              | Right adrenal                                                 | N/A                                  | resection                                        |
| Ucar, 2013 [8]           | Hamartomatous mass with neural elements of benign nature    | Parahilar mass (2.5 cm)                                       | N/A                                  | Resection                                        |
| Sethi, 2014 [25]         | Ganglioneuroblastoma                                        | Right adrenal mass (4.0 × 3.0 × 4.0 cm)                       | N/A                                  | N/A                                              |
| Baronio, 2013 [27]       | Ganglioneuroblastoma intermixed                             | N/A                                                           | Hypertension, Cushing syndrome       | Resection                                        |
| Maksoud, 2015 [33]       | Ganglioneuroma                                              | Paravertebral mass (8.0 × 3.5cm) compressing the right ureter | Right hydronephrosis                 | Resection                                        |
| Sanklecha, 2016 [34]     | Ganglioneuroblastoma                                        | Paravertebral mass                                            | Gait disturbance                     | Resection, chemotherapy (not specified)          |
| Aljabban, 2016 [37]      | Ganglioneuroma                                              | Posterior mediastinal mass (10 × 10 cm)                       | N/A                                  | resection                                        |
| Bagheri, 2017 [4]        | Ganglioneuroblastoma                                        | Mediastinal mass (1.5 cm)                                     | N/A                                  | N/A                                              |
| Jacobson, 2016 [39]      | Ganglioneuroma                                              | N/A                                                           | N/A                                  | resection                                        |

IVIg, intravenous immunoglobulin; N/A, not available for information.

TABLE 7: Reported human candidate genes for ROHHAD/NET.

| Gene                    | Location  | Protein                                                   | Function                                                                                                                                    | Reference Number                                |
|-------------------------|-----------|-----------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| <i>RAI1</i>             | 17p11.2   | p.R1089X<br>p.P204H                                       | Craniofacial and nervous system development                                                                                                 | Thaker et al. [12]                              |
| <i>NTRK2</i>            | 9q21.33   | Tropomyosin receptor kinase B (TrkB),<br>Necdin (p.V318A) | Neuroendocrine / synaptic plasticity                                                                                                        | Ize-Ludlow et al. [6]                           |
| <i>NECDIN</i>           | 15q11-q13 |                                                           | Hypothalamic/respiratory                                                                                                                    | De Pontual et al. [52]                          |
| <i>ASCL1</i>            | 12q23.2   | Human achaete-scute homolog 1 (hASH1)                     | Neuroendocrine                                                                                                                              | De Pontual et al. [52]                          |
| <i>PHOX2B</i>           | 4p13,     | Paired mesoderm homeobox protein 2B (NBPhox)              | Respiratory/autonomic                                                                                                                       | Ize-Ludlow et al. [6]<br>De Pontual et al. [52] |
| <i>BDNF</i>             | 11p14.1   | Brain-derived neurotrophic factor (BDNF)                  | Neuronal development/synaptic plasticity                                                                                                    | Ize-Ludlow et al. [6]<br>Han et al. [53]        |
| <i>HCRT</i>             | 17q21.2   | Hypocretins                                               | Sleep/wake regulation, energy balance, and the control of breathing                                                                         | Barclay et al. [51]                             |
| <i>HCRT1</i>            | 1p35.2    | Hypocretin receptor type 1 (HcrtR1),                      | Sleep/wake regulation, energy balance, and the control of breathing                                                                         | Barclay et al. [51]                             |
| <i>HCRT2</i>            | 6p12.1    | Hypocretin receptor type 2 (HcrtR2),                      | Sleep/wake regulation, energy balance, and the control of breathing                                                                         | Barclay et al. [51]                             |
| <i>HTR<sub>1A</sub></i> | 5q12.3    | 5-hydroxytryptamine (serotonin) receptor 1A               | Appetite control, energy regulation, autonomic response to homeostatic stress                                                               | Rand et al. [54]                                |
| <i>OTP</i>              | 5q14.1    | Orthopedia (Otp) homeodomain protein                      | Hypothalamic expression, with an important role in hypothalamic cell specification in the developing hypothalamus                           | Rand et al. [54]                                |
| <i>ADCYAP1</i>          | 18p11.32  | Adenylate Cyclase Activating Polypeptide 1                | Maintenance of normal energy homeostasis, respiratory chemosensitivity and preventing neonatal hypoventilation at reduced body temperatures | Rand et al. [54]                                |

in patients with ROHHAD/NET. Electrolyte imbalance, especially dysnatremia, was present in a majority of the patients, requiring attention. Impaired water balancing condition such as polydipsia or diabetes insipidus due to hypothalamic dysfunction may have caused dysnatremia. Ganglioneuromas were the most common type of accompanied tumor and may presented not only as abdominal but also as mediastinal masses. We therefore suggest that suspected patients take both thoracic and abdominal imaging to screen for tumors. As ROHHAD/NET involves progressive impairment of the respiratory center, we observed that artificial ventilation was commonly initiated from the first place. Cardiac arrest probably due to preceding respiratory arrest was the major cause of deaths in these patients. We noted that all of the patients were already exposed to hypoxemia at the time of diagnosis. We believe that earlier recognition and timely application of pressure supporting devices during sleep may improve the quality of life and prevent sudden death.

The second part of this study was a WES which attempted to identify the genetic basis of ROHHAD/NET. It has been noted that central hypoventilation syndrome (CHS) resulting from *PHOX2B* mutations is associated with tumors of neural crest origin (neuroblastoma, ganglioneuroblastoma, and ganglioneuroma) in approximately 6% of cases [59]. However, the association of ROHHAD/NET and *PHOX2B* mutations has not been identified. Recently, several studies have made progress in investigating genetic basis of ROHHAD/NET (Table 7). Thaker et al. [12] identified a *de novo* retinoic acid-induced 1 (*RAI1*) gene mutation in a child with ROHHAD and proposed *RAI1* as a candidate gene for children with morbid obesity. Furthermore, there were studies which performed NGS in a set of ROHHAD/NET patients [6, 51, 52, 54]. Rand and colleagues [54] analyzed 5-hydroxytryptamine receptor 1A (*HTR1A*), orthopedia (*OTP*), and Adenylate Cyclase Activating Polypeptide 1 (*ADCYAP1*, formerly *PACAP*) genes which are involved in the embryologic development of the hypothalamus and autonomic nervous system in a set of 25 ROHHAD patients and 25 matched controls. Although there were no significantly correlating variations, this report provided evidence that variation of the *HTR1A*, *OTP*, and *ADCYAP1* genes are unlikely responsible for ROHHAD/NET. Barclay et al. [51] analyzed 16 ROHHAD patients using a combination of NGS and Sanger sequencing. They examined mutations in the exons of the genes for hypocretin and accompanying receptors, namely, *HCRT*, *HCRTR1*, and *HCRTR2*, and found no rare or novel mutations. In this study, we also identified rare variants in two ROHHAD/NET patients. However, the causality of these variants remains unclear and demands further investigation. Nevertheless, we believe that accumulation of these attempts would contribute to progress.

There are some limitations in our research. Firstly, we could not analyze the relationship between the treatments and the subsequent outcomes. Secondly, there remains the possibility of existing case reports or series that were not accessible. Thirdly, some studies only had grouped data where IPD were not available. Nevertheless, this study also has its strengths in that it provides a pooled data and combined evidence on a disease of extreme rarity.

ROHHAD/NET is a rare disease, which has pediatric onset and female preponderance. Rapid obesity and hypothalamic dysfunction are earliest detectable signs. Prompt recognition and timely application of respiratory support may prevent grave complications leading to unprepared mortality. WES on 2 ROHHAD/NET patients identified no significant mutations or copy number variations. Further analyses of patients in prospective studies are required.

## Data Availability

The data used to support the findings of this study are included within the main manuscript and the supplementary information file.

## Conflicts of Interest

The authors declare no conflicts of interest.

## Authors' Contributions

Jiwon M. Lee, Jaewon Shin, and Sol Kim contributed equally to the work

## Acknowledgments

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2015R1D1A1A01056685 to Heon Yung Gee), and by Chungnam National University Hospital Research Fund (2017-CF-023 to Jiwon M. Lee).

## Supplementary Materials

Supplementary Table S1: checklist summarizing compliance with PRISMA guidelines Supplementary Table S2: clinical details of the two patients included in WES. Supplementary Table S3: filtering process of whole exome sequencing analysis performed in two patients. Supplementary Table S4: possible variants identified in individuals with ROHHAD syndrome by WES. (*Supplementary Materials*)

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