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SCIENTIFIC INVESTIGATIONS

Altered slow-wave sleep activity in children with rapid-onset obesity with hypothalamic dysregulation, hypoventilation, and autonomic dysregulation syndrome

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Study Objectives: Rapid-onset obesity with hypothalamic dysregulation, hypoventilation, and autonomic dysregulation (ROHHAD) is a rare condition. Little is known about sleep/wake and slow-wave activity in this condition, although the central hypothalamic dysfunction associated with autonomic dysregulation would make the occurrence of SWA deregulation most likely.

Methods: Two children with clinical presentation of ROHHAD syndrome were evaluated, diagnosed, and treated. Their polysomnographic studies were compared with 4 matched children with obstructive sleep apnea and 6 controls.

Results: Children that were clinically diagnosed with ROHHAD exhibited significantly weaker slow-wave activity power and shallower slow-wave activity slopes during the first 2 sleep cycles compared with children with obstructive sleep apnea or controls.

Conclusions: This study shows that children with ROHHAD have suppressed slow-wave activity, possibly because of hypothalamic dysregulation that may contribute to their rapid-onset obesity and excessive daytime sleepiness.

Keywords: children; obesity; ROHHAD syndrome; slow-wave activity

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Little is known about sleep/wake disorders and slow-wave activity across the night in rapid-onset obesity with hypothalamic dysregulation, hypoventilation, and autonomic dysregulation syndrome.

Study Impact: This study shows suppression of sleep homeostasis that is associated with rapid-onset obesity in rapid-onset obesity with hypothalamic dysregulation, hypoventilation, and autonomic dysregulation syndrome.

INTRODUCTION

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) is an extremely rare pediatric syndrome, associated with hypothalamic obesity and a fatality rate of up to 60% because of cardiorespiratory arrest.[1,2] The vast majority of ROHHAD cases exhibit deranged function of hypothalamic centers involved in energy intake and obesity, followed by additional hypothalamic abnormalities (ie, impaired antidiuretic hormone secretion, hyperprolactinemia, central hypothyroidism, abnormal growth hormone homeostasis, and precocious or delayed puberty).[1,2] Autonomic nervous system symptoms may include hyper- or hypothermia, bradycardia, and/or constipation. Obstructive sleep apnea (OSA) may be manifested either gradually or abruptly after rapid weight gain, followed by late-onset central hypoventilation.

The hypothalamus plays a key role in the regulation of non–rapid eye movement sleep.[3] Spectral analysis makes possible the quantitative description of the time course of a sleep electroencephalogram (EEG) across the night. Slow-wave activity (SWA, the power in the Delta band, 0.75–4 Hz) is a quantitative measure of slow-wave sleep [SWS]) and represents a marker of homeostatic sleep regulation. Stronger cortical connections would produce stronger network synchronization and thus a higher level of SWA, whereas weaker connections would reduce network synchronization and thereby SWA level.[4,5] Disruption of SWA can lead to a shift in autonomic balance-associated changes in growth hormone, as well as cardiovascular and glucose homeostasis, and decreased SWS was observed in individuals who were obese.[5,6] Obesity is a major risk factor for OSA, a common condition characterized by sleep fragmentation and low amounts of Delta power. Treatment of OSA can restore a more physiologic decay of SWA across the night.[7,8]

Little is known about sleep/wake activity and SWA in ROHHAD, although the central hypothalamic dysfunction associated with autonomic dysregulation would make the occurrence of SWA deregulation most likely.

METHODS

The study was conducted in the university-affiliated sleep/wake disorder center.

The Institutional Review Committee of Soroka University Medical Center approved the study protocol (protocol no. 0024-17).

Participants

Two ROHHAD cases were retrospectively recruited from the Sleep-Wake Disorders Unit of Soroka Medical Center's medical records. Because of the rapid body weight gain, and parental report about snoring and excessive daytime fatigue and sleepiness, nocturnal polysomnography (PSG) was performed on both ROHHAD cases to exclude OSA. The control group (comparison group) included 6 typically developing children who were otherwise healthy (matched retrospectively by age and sex to the ROHHAD cases) identified retrospectively from study results that were normal. Reasons for initial referral of comparison group children included snoring or other sleep problems such as sleepwalking, bedwetting, and daytime sleepiness. The OSA group included 4 otherwise healthy children, matched retrospectively by age, sex, and OSA severity to ROHHAD cases that were referred for PSG and were diagnosed with OSA.

Polysomnography

All participants were instructed to maintain a regular sleep/wake schedule on the day of the study. PSG of ROHHAD cases was performed when the participants were at their most stable point. One day before PSG, we ruled out an intercurrent illness in the last 48 hours in all children. The PSG study started at 8:30 PM and ended on the following morning. The sleep technician connected 6 EEG electrodes, (C3, C4, O1, O2, A1, and A2 according to the international 10–20 system; sampling frequency: 128 Hz; resolution: 16 bit), electrooculography, electromyography, and electrocardiogram electrodes, abdomen, and chest effort belts to measure respiratory activity and an oxygen saturation sensor (SomniPro 19 PSG, Deymed Diagnostic, Hronov, Czech Republic). Sleep stage scoring was performed according to the American Academy of Sleep Medicine criteria.[9] Non–rapid eye movement sleep episodes were defined according to standard criteria[10] and adjusted for children[11] because of the frequent occurrence of a skipped rapid eye movement (REM) sleep episode after the first non–rapid eye movement sleep episode. The apnea-hypopnea index was calculated as the number of obstructed respiratory events resulting in either arousal or oxygen desaturation of >4% per hour of sleep.

EEG analysis

Signal analysis was performed as previously described by our laboratory.[7,12] Data were analyzed offline using MATLAB (MathWorks Inc., Tel Aviv, Israel) and the EEGLAB toolbox (Swartz Center for Computational Neuroscience, La Jolla CA). EEG data were referenced to the bilateral mastoids, filtered using a 0.75-Hz finite impulse response high-pass filter (cutoff frequency at −6 db: 0.37 Hz, transition band width: 0.75 Hz), and a 20-Hz finite impulse response low-pass filter (cutoff frequency at −6 db: 22.5, transition band width: 5 Hz), and then divided into consecutive 30-second epochs. Each 30-second epoch was subdivided into 4 consecutive second segments with a 2-second overlap, using a hamming window. The power spectrum was computed for each 4-second segment using the fast Fourier transform function, as implemented in MATLAB (MathWorks Inc.) at a frequency resolution of 0.25 Hz), and then averaged across segments of each 30-second epoch. Absolute power was calculated for the Delta (1–4 Hz), Theta (4–8 Hz), Alpha (8–13 Hz), and Beta (13–20 Hz) frequency bands as the sum of power across these frequencies. To compute the slope of the SWA, we refiltered the EEG data using a 0.75- to 4-Hz band-pass filter. Slow waves were identified in each 30-second epoch as negative peaks, with subsequent zero-crossings that were separated by 0.25–1 second. We calculated the slope of each wave as the amplitude of the negative peak divided by the time to the next zero crossing (ie, ascending slope) and then computed the mean slope across all waves in each epoch. Descending slopes were also computed as the negative peak divided by the time to the previous zero crossing. Both ascending and descending slope measures yielded equivalent results, and only ascending slopes are reported in the manuscript.

Statistical analysis

Statistical analysis was performed using MATLAB (MathWorks Inc.). The percentage of sleep at each sleep stage (ie, N2, N3, or REM) was compared using 1-way analyses of variance. SWS power and slope were compared using a 2-way analysis of variance.

RESULTS

Table 1 summarizes the anthropometric measures and PSG findings of all children.

In both cases, no evidence of central pauses of respiration while awake and/or asleep was found. Case 1 transcutaneous PCO_2 was 45 mm Hg. Mean SaO_2 was 98% and 97.8% during sleep and awake, respectively. Case 2 transcutaneous PCO_2 was measured twice (ie, 43 mm Hg during hospitalization and 50 mm Hg during PSG after admission). Mean SaO_2 was 99% and 96.8% during sleep and awake, respectively. Clinical assessment, laboratory findings, and treatments for the ROHAAD cases are summarized in the supplemental material.

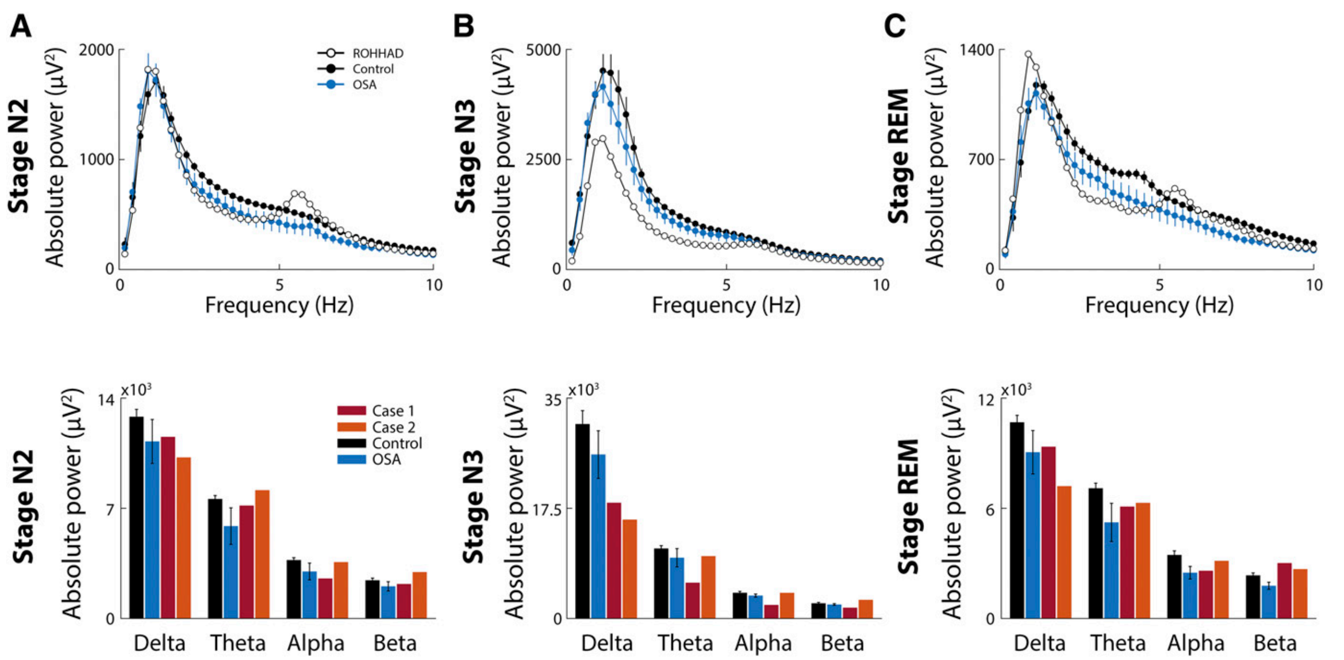
We computed mean power (in all artifact-free epochs) across all epochs of each sleep stage (ie, N2, N3, or REM) from the entire night. In comparison with the findings across groups, using the occipital electrodes, SWA at this age is maximal in the occipital cortex.[12,13] Both children with ROHHAD compared with OSA (and OSA compared with typically developing children) exhibited considerably lower power in the Delta during epochs of N3 sleep ($P < .004$; **Figure 1B**). Spectral power in N2 and REM epochs did not differ significantly across

Table 1—Anthropometric measures and sleep characteristics.

	Control (n = 6)	OSA (n = 4)	ROHHAD Case 1	ROHHAD Case 2
Height (cm)	107 ± 3.6	111 ± 5.3	103	116
Weight (kg)	17.4 ± 1.9	19.8 ± 3.8	26	34
BMI z-score	−0.53 ± 1.2	0.5 ± 1.7	4.55	3.33
Time in bed (min)	442.8 ± 26.5	416 ± 25.2	532.5	353.5
Total sleep time (min)	414.8 ± 20.4	385.3 ± 24.7	444.5	343.5
Sleep latency (min)	6.8 ± 4.4	6.5 ± 8.1	8.5	10.5
Sleep efficiency (%)	93.8 ± 1.7	92.6 ± 0.7	83.5	97.2
Arousal index (events\h)	11.4 ± 5.2	10.9 ± 5.5	16.1	13.3
N1 (%)	0.6 ± 0.8	0.1 ± 0.2	0	0
N2 (%)	54.3 ± 5.1	54.1 ± 3.2	57.8	67.5
N3 (%)	28.4 ± 3.8	29.5 ± 1.2	38.2	20.7
REM (%)	16.8 ± 1.7	16.3 ± 3.4	3.9	11.8
AHI (events\h)	0.43 ± 0.39	6.2 ± 0.9*	8.5	10.1
Nadir SaO_2 (%)	95 ± 0.5	90.5 ± 3	88	89
T_{90} (%)	0	0.6 ± 0.1	0.4	0.3

Values are mean ± standard deviation. *$P < .05$, control vs OSA. AHI = apnea-hypopnea index, BMI = body mass index, N1 = sleep stage 1, N2 = sleep stage 2, N3 = sleep stage 3, OSA = obstructive sleep apnea, REM = rapid eye movement, ROHHAD = rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation, T_{90} = percent sleeping time in which oxygen saturation was < 90%.

Figure 1—EEG power spectrum.

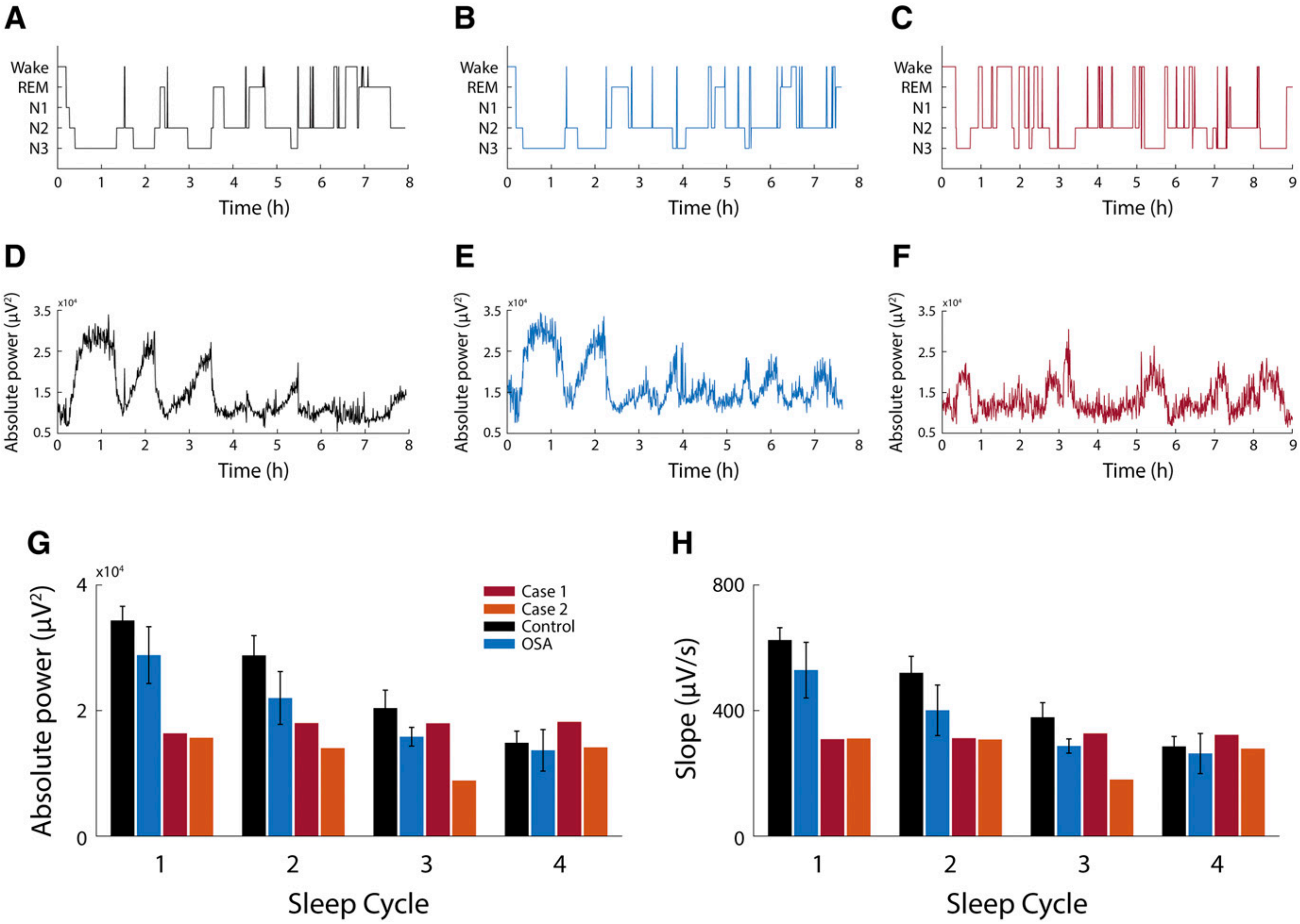


The upper panel represents the mean power across participants for the control and OSA groups and ROHHAD cases (error bars omitted) during N2 **(A)**, N3 **(B)**, and rapid eye movement sleep **(C)**. Power was computed as the mean across all artifact-free epochs from each sleep stage (lower panel, **(A–C)**) and plotted in 0.25-Hz bins or averaged within the Delta, Theta, Alpha, and Beta frequency. ROHHAD cases are presented individually. Error bar, standard error of the mean for control and OSA groups.

groups (Figure 1). Performing the same analyses with the central electrodes did not reveal any significant differences across groups in any of the sleep stages.

Sleep stages and SWA dynamics during the night are presented in Figure 2A–F. Children with ROHHAD had decreased SWA power (Figure 2G; $P < .003$) and slope (Figure 2H; $P < .004$) across the first 2 sleep cycles compared with children who were typically developing or had OSA. As expected, OSA was associated with decreased SWA across the first 2 sleep cycles compared with controls ($P < .003$).

Figure 2—Example sleep dynamics analysis.



Visually scored sleep stages from 1 control **(A)**, OSA **(B)**, and ROHHAD **(C)** participant in 30-second epochs. Example of slow-wave activity (occipital electrodes) across the night from 1 control **(D)**, obstructive sleep apnea **(E)**, and ROHHAD case 1 **(F)** (using data for cases presented in **(A–C)**). Mean time course of slow-wave activity power **(G)** and slope **(F)** for control (black) and obstructive sleep apnea (blue) groups and ROHHAD cases (ROHHAD cases are presented individually) for consecutive non–rapid eye movement sleep cycles across the night. ROHHAD = rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation.

DISCUSSION

Here, we describe the unique PSG findings for 2 patients with ROHHAD. We are able to show these findings after matching them to PSGs performed in age- and sex-matched children with and without OSA.

The clinical presentation in this extremely rare condition (only approximately 100 cases described thus far) is caused by a deranged function of hypothalamic centers that are responsible for antidiuretic hormone secretion, hyperprolactinemia, and autonomic changes. Little is known about sleep function in children with ROHHAD. Manual sleep staging that is a categorical measure of sleep has limited value in differentiating among groups. In our results, the proportion of all sleep stages was not significantly different across groups. In this study, we quantified SWA power in addition to traditional sleep staging throughout the night. SWA is less biased by potential differences in overall sleep duration and represents an objective and quantitative marker of sleep in children.[5,12] Both our cases exhibited decreased SWA power and SWA slopes during the first 2 sleep cycles. SWA is a reliable measure of mammalian sleep homeostasis and discharge of sleep need.[5,8,14] It is established that decreased sleep pressure can generate deeper SWS, which can be quantified by the power of SWA,[5] and reduced sleep pressure may lead to longer sleep latency.[15] Our finding suggests that a disruption in sleep homeostasis may reduce sleep pressure in children with ROHHAD and exacerbate difficulties with sleep maintenance. However, in our study, we did not find a difference in sleep latency between the children with ROHHAD and the comparison groups to support this claim, and further studies are needed to explore this issue. SWA intensity is regulated by the hypothalamic centers involved in the regulation of growth hormone release, energy consumption, and the autonomic nervous system.[3,5] It is possible that the marked and rapid weight gain in our cases was exacerbated by decreased SWA. This hypothesis is supported by earlier studies that found that disruption of deep SWS can shift the autonomic balance, suppress the response to glucose challenges, and increase the risk for obesity.[5,6] Our findings support the possibility that hypothalamic center dysfunction in ROHHAD is associated with suppression of SWA, which may accelerate weight gain.

The decline of SWA in our study indicates decreased cortical synaptic strength involved in generation of SWS.[14] The excessive daytime sleepiness in our cases could be attributed to decreased SWA during the first 2 sleep cycles.[5,8] Moreover, it is possible that the excessive daytime sleepiness can be attributed to moderate OSA in our cases. However, this possibility is unlikely; Gozal et al[16] reported that excessive daytime sleepiness, defined by average sleep latency in multiple sleep latency tests of <10 minutes, occurs in a small proportion of children with severe OSA. Our findings suggest that children with ROHHAD have a dysregulation of sleep homeostasis that is probably related to their hypothalamic dysfunction and may lead to excessive daytime sleepiness regardless of OSA severity.

CONCLUSIONS

This study shows that children with ROHHAD have suppressed SWA, possibly because of hypothalamic dysregulation that may contribute to their rapid-onset obesity and excessive daytime sleepiness.

ABBREVIATIONS

EEG, electroencephalogram
OSA, obstructive sleep apnea
PSG, polysomnography
REM, rapid eye movement
ROHHAD, rapid-onset obesity with hypothalamic dysregulation, hypoventilation, and autonomic dysregulation
SWA, slow-wave activity
SWS, slow-wave sleep

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