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Original Article

Sleep disordered breathing in Silver–Russell syndrome patients: a new outcome

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ABSTRACT

Objective: Imprinting disorders (ID), such as Prader–Willi syndrome (PWS), are associated with sleep-disordered breathing (SDB). No data are available for Silver–Russell syndrome (SRS), another ID that shares clinical features with PWS, although many patients describe excessive daytime sleepiness, disturbed sleep, and snoring. The aim of this study was to characterize sleep in children with SRS and to evaluate the impact of recombinant growth hormone (rGH) therapy.
Methods: We performed a retrospective analysis of sleep recordings in 40 patients with molecularly proven SRS (methylation anomaly in 11p15 [n = 32] or maternal uniparental disomy of chromosome 7 [n = 16]). Sleep recordings were either by means of polygraphy or polysomnography (PSG) (n = 16). A total of 34 patients received rGH therapy.
Results: We collected 61 sleep recordings. The mean apnea–hypopnea index (AHI) was 3.4 events/h (0–12.4), with a mean central AHI of 0.5 events/h (0–2.4). SDB was identified in 73.8% (n = 45) of the recordings and was severe in 4.9%. SDB was present in 86.4% of patients before rGH therapy and was severe in 13.6%. AHI worsened for 5 of 12 patients with sleep recordings before and after rGH therapy initiation, reaching mild impairment. The mean rGH dose was 32.3 μg/kg/(12.9–51.4), with a mean insulin-like growth factor 1 plasma level of 1.7 SDS (−1.9 to 6.6).
Conclusion: Most patients with SRS present with SDB with an obstructive profile, possibly explained by narrowing of the airways and lymphoid organ hypertrophy. We recommend systematic ear–nose–throat evaluation of SRS patients and PSG if there are clinical anomalies, preferably before initiating rGH therapy, to monitor and adapt the management of patients with SDB.
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1. Introduction

Imprinting disorders (IDs) are caused by the disruption of epigenetic marks (mainly DNA methylation) in crucial regions where, normally, they allow gene expression from only one allele, depending on the paternal or maternal origin. Some patients with IDs show a clinical overlap with growth failure, metabolic issues (obesity, glucose intolerance, inappropriate body mass composition), and impaired neurodevelopment [1]. Recent studies suggest that these imprinted regions work together as a network to explain these overlapping phenotypes [1,2]. Prader–Willi syndrome (PWS) is due to the loss of paternal expression of chromosome 15q11–13, resulting in severe hypothalamo–pituitary dysfunction, severe hypotonia, and impaired neurodevelopment. Sleep disordered breathing (SDB)

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was first identified in patients with PWS, although its prevalence appears to be widely variable [3–7]. A recent multicentric study of a large cohort reported a prevalence of 51% [4]. These patients showed both obstructive apnea syndrome and central apneas, albeit less common, which could be involved in sudden death during sleep [3,8]. Such obstructive apneas may be due to tonsil hypertrophy and/or pharyngeal muscle hypotonia, but they appear to be independent of body mass index (BMI) [6]. Central apneas with sleep-related alveolar hypoventilation may reflect hypothalamic dysfunction, as observed in PWS patients experiencing satiety dysregulation [9,10]. Furthermore, 73% of PWS patients have impaired sleep, even without clinical signs of sleep apnea syndrome (SAS) [6]. Some studies have evaluated the impact of recombinant growth hormone (rGH) on sleep features and showed possible worsening of sleep PSG parameters 6–9 months after treatment initiation, but no long-term effect [4,7,11–13]. This could be explained by tonsil hypertrophy subsequent to the introduction of rGH, which rapidly stabilizes. Thus, a score for the risk of rGH therapy initiation has been proposed, taking into account PSG data, tonsil size, and circulating insulin-like growth factor 1 (IGF-I) levels [14]. Other studies have reported improved breathing parameters and better day activity levels with rGH therapy in PWS patients, probably due to an improvement in airway muscular tonus [12,13]. Some of these patients required nocturnal noninvasive ventilation, leading to an improvement in SDB parameters [15]. The results of these studies and the possible risk of sudden death led to the recommendation of performing a sleep recording of all PWS patients before initiating rGH therapy [3,16].

Silver–Russell syndrome (SRS) is an imprinting disorder that results in intrauterine growth restriction (IUGR), poor postnatal growth, feeding difficulties (often requiring early nutritional support), and facial dysmorphism (relative macrocephaly at birth, protruding forehead, body asymmetry] [17,18]. The clinical diagnosis may be challenging because of nonspecific signs. Azzi et al., thus developed a clinical score (Netchine–Harbison Clinical Scoring System [NH-CSS]), which has been validated in a recent international consensus, to prompt genetic investigation [17,19]. Molecular abnormalities are identified in approximately 60% of the patients and can consist of either chromosome 7 maternal uniparental disomy (upd(7)mat) or loss of methylation (LOM) in the *H19/IGF2* intergenic differentially methylated region (IG-DMR) in 11p15) [2,17]. rGH therapy is recommended to increase their height and muscle mass and to improve body composition [17].

No data on sleep have been reported for SRS patients before rGH therapy, but, in our clinical experience, these patients often present with excessive daytime sleepiness, snoring, and nocturnal sweating. Furthermore, frequent maxillofacial abnormalities, such as vertical and horizontal mandibular hypoplasia, retrognathia, maxillary hypoplasia, or high arched palate, which result in narrowing of the upper airways, could affect the sleep of SRS patients [20,21]. These possibly obstructive features may be worsened by gastric reflux, which is frequently experienced by these patients [22]. They also experience an impaired sensation of satiety, which may be the manifestation of a hypothalamic dysfunction mechanism that could also be responsible for central apneas [9]. Several publications have shown a link between deep sleep and reduced GH secretion [23]. SDB could thus directly impair GH secretion in these patients.

Here we investigated, for the first time, whether SRS patients experience SDB. Our objectives were to retrospectively assess sleep features in patients with SRS and to see the possible impact of rGH therapy.

2. Patients and methods

2.1. Patients

We performed a monocentric, retrospective study of molecularly proven SRS patients, either upd(7)mat or LOM of 11p15. For one patient with typical clinical SRS but no methylation abnormalities in leukocytes, we performed a skin biopsy and identified LOM in *H19/IGF2*:IG-DMR in her fibroblasts. All patients had at least one clinical evaluation in the unit to assess their NH-CSS [19]. All patients regularly followed in our clinic between January 2010 and June 2015 underwent at least one sleep recording, regardless of the presence of clinical symptoms or the treatment that they received.

rGH therapy was initiated in most of the patients, and the dose was adjusted to growth velocity. IGF-I levels were monitored before and during treatment. IGF-I is known to be spontaneously elevated in these patients (despite their poor nutritional status), consistent with an IGF-I insensitivity profile [24]. Thus, rGH doses were not adapted to IGF-I serum levels, as recommend by the international consensus [25]. Most patients had a gastroenterological, maxillofacial, and ear–nose–throat (ENT) clinical evaluation by specialists experienced with SRS. Some patients also had an evaluation by a pulmonologist, depending on the results of their sleep recording results or if they had respiratory symptoms.

2.2. Methods

2.2.1. Sleep recordings

Either polygraphy or PSG was performed in these patients, either before or during rGH therapy. Patients and their parents had a consultation concerning their sleep environment and sleep characteristics to assess the presence of clinical features consistent with SDB prior to the sleep recording. Sleep recordings were analyzed by trained doctors specialized in sleep disorders. A clinical evaluation was performed before the recording to rule out any acute upper airway infections. Data were analyzed taking into consideration the height, weight, and body mass index (BMI) of the patients.

Polygraphies were recorded during a night's sleep while the patient was hospitalized. When impossible, a nap recording was performed for younger children. PSG (polygraphy with electroencephalographic data) was available only for the most recent recordings. Nasal pressure, thoraco-abdominal movement, tracheal sound, pulse oximetry (PSG CID102L8 by CIDELEC), and transcutaneous carbon dioxide pressure (Radiometer TINA) were recorded.

Polysomnography recordings allowed the evaluation of sleep efficiency, the micro-awakening index, and the duration of both slow and rapid eye movement (REM) sleep (as a percentage of the whole sleep period).

2.2.2. Interpretation of sleep parameters

The classification of respiratory events was consistent with pediatric scoring rules of the American Academy of Sleep Medicine for the scoring of sleep and associated events [26]. The apnea-hypopnea index (AHI) was calculated as the sum of apnea and hypopnea events per hour of total sleep for all the recordings. We mainly performed polygraphies, meaning that the AHI is possibly underestimated in our recordings, as we did not include hypopnea associated with micro-awakening (see Table 1 in Supplemental Data). The AHI was considered to be mild between 1.5 and 5 events/h, moderate between 5 and 10 events/h, and severe above 10 events/h [27].

Table 1
Clinical features of sleep apnea syndrome collected at the sleep consultation (n = 20).

	n	%
Asthenia	5	25
Snoring	7	35
Apnea	2	10
Disturbed sleep	7	35
Nocturnal sweat	10	50
Nightmares	8	40
Enuresia	4	20
Morning headaches	2	10
Excessive daytime sleepiness	2	10

Central AHI values over 0.45 events/h in patients between three and five years of age, and more than 0.85 events/h in patients older than six years, were considered to be abnormal. No reference values have been validated for younger children [27].

Transcutaneous oxygen and carbon dioxide pressures were recorded and interpreted to be abnormal (ie, hypoxemia and hypercapnia) if there was a difference of more than 10 mm Hg between the pressures when asleep and awake [27].

Data are expressed as the mean (min–max). Distributions were compared using the Student test, and correlations were performed with the Pearson test.

2.2.3. Biological assay

Serum IGF-I concentrations were measured using a specific immunoradiometric assay (IGF-I RIACT) purchased from CIS-BIO International (Gif-sur-Yvette, France). The sensitivity threshold was 1 ng/mL, and the intra-assay and interassay coefficients of variation were 3.2–3.8% and 3.8–8.2%, respectively. Data were transformed into age-related SDS values on the basis of previously obtained data on controls.

3. Results

3.1. Recordings

A total of 61 sleep recordings (45 polygraphies and 16 PSGs) were analyzed, all but two (for the same patient) in our hospital (Fig. 1). Recordings were performed between January 1, 2010, and June 30, 2015.We excluded one recording due to lack of quality (loss of electrodes). Night recordings lasted 481 min (210–654) and those for two naps lasted 70 and 84 min for one young patient at 1.7 and 2.8 years of age.

3.2. Patients

Data were available for 40 patients with SRS: 32 with LOM in the 11p15 region, and eight with upd(7)mat. The sex ratio was 0.5. All but one patient (with upd(7)mat) had a NH-CSS of SRS score of ≥4. The mean age at the first polygraphy was 6.0 years (1.7–15.3). We performed 21 sleep recordings in 20 patients without rGH therapy and sleep recording before and during rGH therapy in 12 patients. Most patients received rGH therapy (n = 30), with a mean age at initiation of 3.6 years (1.5–7.5). Eight patients had two sleep recordings during rGH therapy, and two had sleep recording after rGH therapy cessation. All but three patients were born small for gestational age (with birth weight and/or length below −2SDS at 37 (28–41) weeks of amenorrhea: birth weight was −2.8 SDS (−5.8 to −0.3), birth length −4.1 SDS (−8.0 to −0.9), and head circumference −1.0 SDS (−4.0 to 1.2) [28].

3.3. Clinical features

Twenty patients were screened for SDB with a questionnaire before the sleep recording (Table 1). All patients had a clinical gastrointestinal evaluation, and a high prevalence of reflux, even after 24 months of age, was observed. The respiratory, ENT, and maxillo-facial features known to affect sleep quality are shown in Table 2.

3.4. Sleep recordings

The sleep recording parameters are shown in Table 3. The AHI for overall sleep recordings was 3.4 events/h (0.0–12.4), with a central AHI of 0.5 events/h (0.0–2.4). SDB was identified in 45 recordings (73.8%) and classified as mild for 33 (54.1%), moderate for 9 (14.8%), and severe for 3 (4.9%). The central AHI was abnormal in

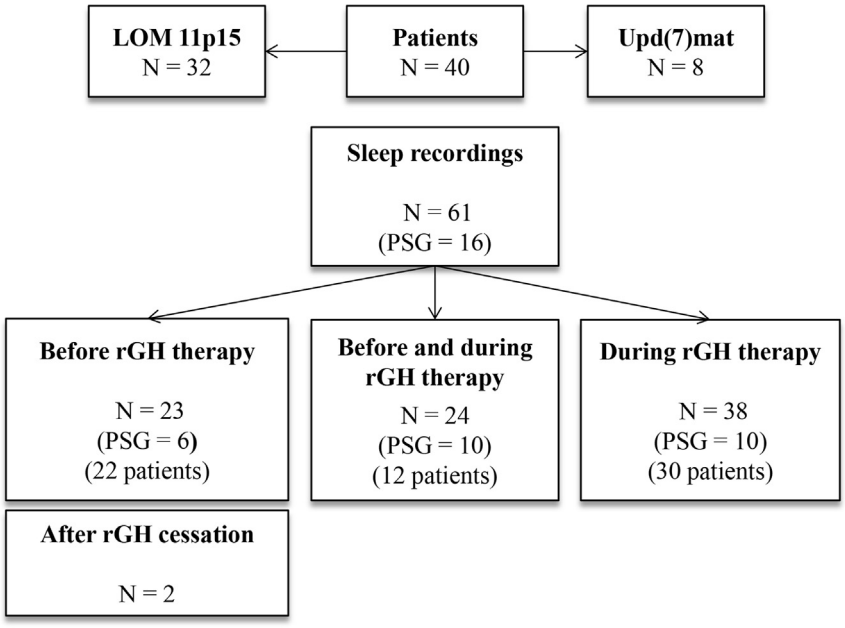

Fig. 1. Repartition of the patients and the sleep recordings regarding molecular anomalies, type of recording and recombinant growth hormone therapy (rGH). LOM, loss of methylation; PSG, polysomnography; upd(7)mat, maternal uniparental disomy of chromosome 7.

Table 2
Main clinical features of the cohort.

	n	%
Respiratory		
Asthma	13/36	36.1
Treatment of asthma	8/13	61.5
Ear–nose–throat		
Tonsil hypertrophy	11/33	33.3
Adenotonsillectomy	6/11	54.5
Maxillofacial		
Abnormalities	30/31	96.8
Orthodontic treatment	8/30	26.7
Surgical treatment	3/30	10.0
Nutrition		
Gastric reflux	25/40	62.5
Enteral nutrition	16/40	40.0
Feeding difficulties	24/40	60.0

22 recordings (36.0%) for 17 patients (42.5%). There was no difference in the AHI between patients with upd(7)mat and those with 11p15 ($P = 0.94$). We found mild negative correlation between age and AHI ($\rho = -0.37$, $P = 0.003$). Before rGH treatment, only three patients (14.3%) had a normal sleep recording; 13 had mild SDB (61.9%), three had moderate SDB (14.3%), and two had severe SDB (9.5%). Fig. 2 provides the complete data.

Concerning snoring, four patients (20.0%) had a pathological snoring index (≥50) before rGH therapy, and one a severe index (≥300); none had tonsil or adenoid hypertrophy. During rGH therapy, 10 patients (27.8%) had a pathological index, with severe SDB for two. Among them, eight (80%) had a normal ENT examination, one had a tonsillectomy three months before, and one had adenoid hypertrophy (with a snoring index of 68). There was no statistical difference of the AHI between patients with adenoid or tonsil hypertrophy and those with a normal ENT examination (mean of 3.2 events/h [0.1–11.5] and 3.2 events/h [0.0–12.4], respectively, $P = 0.59$).

There was no difference in the AHI in patients without treatment (before rGH therapy onset or after cessation) and those during rGH therapy (mean of 4.1 events/h [0.3–12.4] and 3.1 events/h [0.1–11.5], respectively, $P = 0.18$).

Transcutaneous carbon dioxide and oxygen pressures were measured in 30 recordings. Nine patients (30.0%) had hypoxemia, and five had hypercapnia (16.7%). Minimal oximetry was under 90% in 25 recordings (45.5%), and minimal transcutaneous oxygen pressure was under 70 mm Hg for 11 patients (36.7%). The maximal transcutaneous carbon dioxide pressure during sleep was above 45 mm Hg in 12 recordings (40.0%). The time below 80 mm Hg for transcutaneous oxygen pressure was null for all patients, and only one patient on rGH therapy had a transcutaneous carbon dioxide pressure above 50 mm Hg during 7% of the time recorded.

The results for sleep parameters of the 12 patients recorded before and during rGH therapy are shown in Table 4. All but one patient showed SDB at baseline, and there was one case of relevant worsening of the AHI (case 4) after 13 months of rGH therapy, going from mild to moderate SDB. The mild SDB of two patients normalized after 21 and 22 months (cases 7 and 12, respectively), whereas one patient (case 1) showed a marked improvement of his severe SDB to a moderate level after nine months of treatment. These patients showed no difference in the AHI before and during rGH therapy ($P = 0.52$).

We collected 16 PSGs for 14 patients; six were performed before rGH therapy (Table 1 in Supplementary Data). Among them, the proportion of deep sleep for the entire duration of sleep was 23.3% (11.6–37.0), REM sleep represented 21.2% (10–36.4), and the micro-awakening index was 9.2 (1.0–21.0). The mean sleep efficiency was 83% (66–93).

3.5. IGF-I serum levels

We found spontaneously elevated IGF-I serum levels before rGH therapy, with a mean of 1.3 SDS (−1.9 to 4.5), and nine patients (45.0%) had IGF-I serum levels above 2 SDS. These levels rose to 2.0 SDS (−0.6 to 6.6) with rGH treatment, and the Insulin-like growth factor 1 (IGF-I) serum levels were above 2 SDS for 20 patients (50.0%). There was no significant difference in IGF-I serum levels before or during rGH therapy, with a mean daily dose of 32.3 μg/kg (12.9–51.4). We did not find a correlation between plasma IGF-I levels and AHI.

4. Discussion

Here, we show that SRS patients frequently exhibit SDB, as 24 patients (60.0%) in our cohort had mild to severe SDB. This is the first time that such data on the sleep of SRS patients have been collected and published. Although the data are retrospective and preliminary, this study highlights a previously unknown feature of SRS.

We observed mainly obstructive apnea in these children, suggesting that their SDB may be due to narrowing of the upper airways and reflux. There was no direct link between lymphoid tissue hypertrophy and SDB in our patients. Only one patient had an adenotonsillectomy between the first and second polygraph, her AHI worsening from 1.5 to 11.5 after surgery. This finding suggests that adenotonsillectomy may be less successful in SRS patients than in the general population, as already reported for PWS patients [29–31]. Furthermore, an ENT intervention concerning tonsils in SRS patients can result in a voice change and worsen a pre-existing high-pitched voice, which is quite common in these patients. Such

Table 3
Main sleep recording parameters of the cohort.

	Without rGH therapy n = 23			During rGH therapy n = 38		
	Mean	Min	Max	Mean	Min	Max
AHI (events/h)	4.1	0.3	12.4	3.1	0.1	11.5
Obstructive AHI (events/h)	3.4	0.0	10.2	2.7	0.0	10.6
Central AHI (events/h)	0.7	0.0	2.4	0.4	0.0	1.9
Minimum sleeping SpO_2 (%)	90.0	80.0	96.0	91.0	82.0	96.0
Percentage of time with sleeping SpO_2 <90% (%)	0.1	0.0	1.0	0.05	0.0	1.0
$TcPO_2$ difference between sleep and arousal (mm Hg)	−6.4	−14.0	0.0	−4.9	−17.0	7.0
Maximal $TcPCO_2$ during sleep (mm Hg)	43.6	39.0	49.0	43.8	34.0	51.0
$TcPCO_2$ difference between sleep and arousal (mm Hg)	5.8	2.0	10.0	7.2	3.0	12.0
Minimal $TcPO_2$ during sleep (mm Hg)	71.7	57.0	89.0	74.7	64.0	91.0
Snoring index	105.6	0.0	1582.0	60.4	0.0	545.0

REM, rapid eye movement; rGH, recombinant growth hormone; SpO_2, pulse oximetry; $TcPCO_2$, transcutaneous carbon dioxide pressure; $TcPO_2$, transcutaneous oxygen pressure.

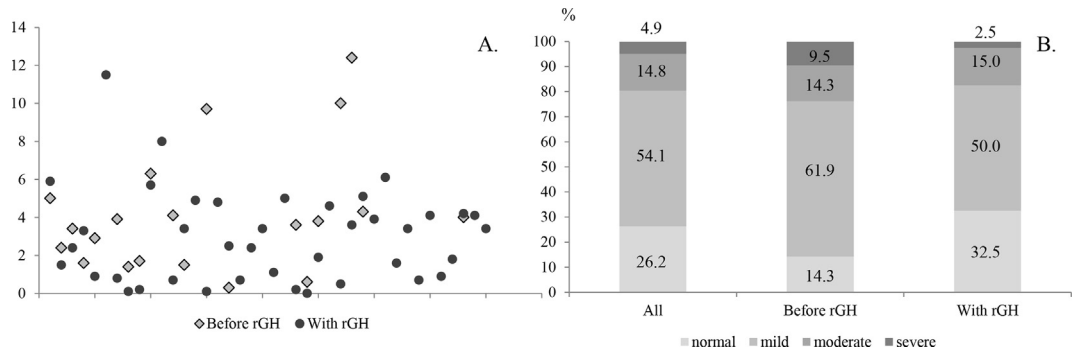

Fig. 2. (A) Representation of each sleep recording apnea–hypopnea index (AHI) in the entire cohort. (B) Repartition of the AHI depending on the corresponding sleep-disordered breathing (SDB) level (in percentage) in the entire cohort, before and during recombinant growth hormone (rGH) therapy.

Table 4
Data for 12 patients before and after the initiation of recombinant growth hormone (rGH) therapy.

			Age (yr)		AHI (events/h)		Obstructive AHI (events/h)		Central AHI (events/h)		IGF-1 (SDS)		rGH therapy		
Case	Sex	Genetic	1st recording	2nd recording	1st recording	2nd recording	1st recording	2nd recording	1st recording	2nd recording	1st recording	2nd recording	Age (yr)	Dose (mg/kg/wk)	Delay [a] (yr)
1	M	Upd(7)mat	3.6	5.4	10	5.1	9.1	3.3	0.9	1.8	0.1	1.8	4.6	0.26	0.8
2	F	Upd(7)mat	2.8	5.7	4.1	3.4	4.1	3.0	0.0	0.4	0.3	–0.6	2.8	0.28	2.9
3	F	11p15	1.7	2.8	1.4	3.4	0.0	3.4	1.4	0.0	–1.9	0.4	2.2	0.26	0.6
4	F	11p15	3.3	4.6[b]	3.4	6.1	1.7	4.7	1.7	1.4	1.0	2.8	3.5	0.22	1.1
5	M	11p15	2.1	3.3[b]	2.9	3.9	2.1	3.9	0.8	0.0	3.2	2.3	0.4	0.25	2.9
6	M	11p15	6.1[b]	6.6[b]	4.3	0.7	3.4	0.4	0.9	0.3	0.9	1.8	6.3	0.23	0.3
7	M	11p15	4.1	6.1[b]	3.9	0.9	3.9	0.8	0.0	0.1	–1.7	0.7	4.3	0.22	1.8
8	M	11p15	4.9	7.4[b]	3.8	1.6	3.2	1.5	0.6	0.1	2.2	2.2	6.9	0.21	0.5
9	F	11p15	3.2	6.4[b]	2.4	4.2	2.1	3.7	0.3	0.5	2.9	2.6	3.7	0.13	2.7
10	M	Upd(7)mat	4.1[b]	5.0[b]	4.0	4.1	–	–	–	–	1.2	3.8	4.3	0.19	0.7
11	M	11p15	3.2	4.7	3.6	1.8	3.5	1.8	0.1	0.0	2.2	2.9	3.1	0.36	1.6
12	M	Upd(7)mat	2.3	4.6¤	1.7	4.1	1.3	3.9	0.4	0.2	3.7	2.5	2.7	0.21	1.9

normal mild moderate severe

F, female; IGF-1, insulin-like growth factor 1; M, male; SDS, sleep disordered breathing.
[a] Delay between rGH therapy onset and second sleep recording.
[b] Indicates that the sleep recording was a polysomnography.

velopharyngeal insufficiency is well described in PWS and must be explored in SRS. For maxillofacial malformations (skeletal class II, supraclusion, upper and lower crowding), orthodontic treatment is possible, and some patients had symphyseal distraction osteogenesis for severe lower crowding and bilateral scissor bite. Changes in SDB after such interventions have yet to be evaluated [21,30]. In addition, we found the AHI to be no different between patients with clinical signs of reflux and those without ($P = 0.14$). Hypotonia and constitutional narrowness of the upper airways appear to be the best explanation for the obstructive features in SRS patients during sleep.

The observed short-term worsening of SDB in PWS patients following the initiation of rGH therapy can be explained by rapid elevation of serum IGF-I levels, resulting in tonsil hypertrophy, which worsens their obstructive SDB [3]. Our work confirms spontaneously high serum IGF-I levels in SRS patients and their increase with rGH therapy. These paradoxical findings in patients with malnutrition suggest at least partial IGF-I insensitivity [24]. Although rGH therapy can induce tonsil hypertrophy, it is more likely to act merely as an aggravating factor rather than being completely responsible for the worsening of SDB. We found no correlation between plasma IGF-I levels and AHI. Our data of 12 patients with sleep recordings before and after rGH therapy do not show major worsening of SDB with rGH therapy. These data, however, are difficult to analyze because of the different time intervals between the initiation of rGH therapy and the second sleep recording. We found no correlation between either plasma IGF-I levels or the time after initiating rGH therapy and changes in the AHI between the two sleep recordings. The only significant correlation was AHI decreasing with age as already described. A larger standardized, longitudinal, prospective study will be necessary to properly investigate the impact of rGH on SDB in these patients.

In our cohort, 17.5% of patients presented with pathological central apneas. Among them, all but one had either enteral nutrition (n = 3) or feeding disorders (n = 3). The one patient without nutritional or feeding disorders had an almost normal central AHI of 0.5 at 6.7 years of age. These data support the hypothesis of hypothalamic dysfunction, which could alter the control of both satiety/hunger and breathing [9,10]. Involvement of the hypothalamus in the regulation of appetite, mediated by oxytocin neurons, has been described in PWS, and, according to some authors, almost all PWS symptoms are caused by dysfunction of the hypothalamus [9]. More recent work suggests direct imprinting mechanisms in the regulation of hypothalamic function [10]. These new insights suggest that hypothalamic disturbances could be responsible for feeding difficulties in SRS patients. Hence, both satiety and breathing hypothalamic centers could be impaired in these patients with imprinting diseases.

Several studies have shown the benefit of nocturnal intermittent positive pressure ventilation (IPPV) on central alveolar hypoventilation in PWS patients. The presence of central apneas is the main feature that determines nocturnal IPPV, whereas continuous

positive airway pressure (CPAP) is preferred in cases of obstructive SAS [4]. None of our patients had nocturnal ventilation, but it has since been introduced for case patient five (Table 4). In cases of obstructive SDB without tonsil hypertrophy or persistent obstructive SDB after tonsillectomy, transient nocturnal CPAP is a therapeutic option while waiting for the growth of the head to enlarge the narrowness of the upper airways caused by maxillofacial anomalies, combined with rGH to improve hypotonia.

PWS patients experience abnormalities in the organization of REM sleep during PSG [32]. Although we had only a small number of PSGs, we identified a high micro-awakening index in our patients. As mentioned in the Patients and Methods section, AHI is underestimated in polygraphies, as micro-awakening is not monitored. Consequently, together the high micro-awakening index that we found in polysomnographies and the high prevalence of SDB that we identified in polygraphies (even with an underestimated AHI) should drive us exclusively to assess sleep parameters with PSGs for a more accurate diagnosis of SDB. Now that PSG is more widely available, it would be informative to gather sufficient data to study this tendency, depending on the acceptance of younger patients of this more uncomfortable method.

These data are preliminary and need to be validated to recommend guidelines for sleep evaluation in SRS patients in the future [17]. Our results should be confirmed in another cohort with a prospective protocol, a standardized method (PSG), and longer recordings (avoiding short naps when possible), based on the limitations encountered here. Sleep quality should be investigated because of the proven negative effect on psychological, behavioral, and global functioning of PWS patients with sleep disorders [33]. rGH therapy should have a positive effect on daytime sleepiness in SRS patients, as shown for PWS patients [11,34]. It may be informative to evaluate the effects of various types of treatment, such as nocturnal CPAP or IPPV, orthodontic devices, distraction osteogenesis, or adenotonsillectomy, on the sleep of SRS patients and their global well-being.

5. Conclusion

Patients with SRS frequently present with SDB. Apneas are mainly obstructive and could be caused by hypotonia and narrowing of the upper airways because of their known maxillofacial abnormalities. Sleep features were not worsened by rGH therapy for 11 of 12 patients. We thus recommend an ENT evaluation of SRS patients before rGH therapy and, when possible, polysomnography. Clinical signs of SAS should be screened in consultation and, if present, should prompt a sleep recording. Persistent obstructive anomalies after ENT intervention should prompt the pulmonologist to consider the need for nocturnal ventilation.

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Conflict of interest

The authors declare that they have no conflict of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.05.020.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2019.05.020.

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