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

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1 **Sleep disordered breathing in Silver-Russell syndrome patients: a new outcome.**

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25 **Abbreviated title:** Sleep disordered breathing in Silver-Russell syndrome

26 **Keywords:** Silver-Russell syndrome, sleep disordered breathing, growth hormone, sleep apnea  
27 syndrome, sleep recording

28 **Declaration of interests:** none.

29 **Abstract**

30 *Context:* Imprinting disorders (ID), such as Prader-Willi syndrome (PWS), are associated with sleep-  
31 disordered breathing (SDB). No data are available for Silver-Russell syndrome (SRS), another ID  
32 which shares clinical features with PWS, although many patients describe excessive daytime  
33 sleepiness, disturbed sleep, and snoring.

34 *Objective:* to characterize sleep in children with SRS and evaluate the impact of recombinant growth  
35 hormone (rGH) therapy.

36 *Patients and Methods:* we performed a retrospective analysis of sleep recordings in 40 patients with  
37 molecularly-proven SRS (methylation anomaly in 11p15 (n=32) or maternal uniparental disomy of  
38 chromosome 7 (n=16)). Sleep recordings were either polygraphy or polysomnography (n=16). 34  
39 patients received rGH therapy.

40 *Results:* We collected 61 sleep recordings. The mean apnea-hypopnea index (AHI) was 3.4  
41 events/hour (0-12.4), with a mean central AHI of 0.5 events/hour (0-2.4). SDB was identified in  
42 73.8% (n=45) of the recordings and was severe in 4.9%. SDB was present in 86.4% of patients before  
43 rGH therapy and was severe in 13.6%. AHI worsened for five of 12 patients with sleep recordings  
44 before and after rGH therapy initiation, reaching mild impairment. The mean rGH dose was  
45 32.3µg/kg/day (12.9-51.4), with a mean IGF-I plasma levels of 1.7 SDS (-1.9-6.6).

46 *Conclusion:* Most patients with SRS present SDB with an obstructive profile, possibly explained by  
47 narrowing of the airways and lymphoid organ hypertrophy. We recommend systematic ear-nose-throat  
48 evaluation of SRS patients and polysomnography if there are clinical anomalies, preferably before  
49 initiating rGH therapy, to monitor and adapt the management of patients with SDB.

50

## 51 **Introduction**

52 Imprinting disorders (IDs) are caused by the disruption of epigenetic marks (mainly DNA  
53 methylation) in crucial regions where, normally, they allow gene expression from only one allele,  
54 depending on the paternal or maternal origin. Some patients with IDs show a clinical overlap with  
55 growth failure, metabolic issues (obesity, glucose intolerance, inappropriate body mass composition),  
56 and impaired neurodevelopment (1). Recent studies suggest that these imprinted regions work together  
57 as a network to explain these overlapping phenotypes (1,2). Prader-Willi syndrome (PWS) is due to  
58 the loss of paternal expression of chromosome 15q11-13, resulting in severe hypothalamo-pituitary  
59 dysfunction, severe hypotonia, and impaired neurodevelopment. Sleep disordered breathing (SDB)  
60 was first identified in patients with PWS, although its prevalence appears to be widely variable (3–7).  
61 A recent multicentric study of a large cohort reported a prevalence of 51% (4). These patients showed  
62 both obstructive apnea syndrome and central apneas, although less common, which could be involved  
63 in sudden death during sleep (3,8). Such obstructive apneas may be due to tonsil hypertrophy and/or  
64 pharyngeal muscle hypotonia, but they appear to be independent of body mass index (BMI) (6).  
65 Central apneas with sleep-related alveolar hypoventilation may reflect hypothalamic dysfunction, as  
66 observed in PWS patients experiencing satiety dysregulation (9,10). Furthermore, 73% of PWS  
67 patients have impaired sleep, even without clinical signs of sleep-apnea syndrome (SAS) (6). Some  
68 studies have evaluated the impact of recombinant growth hormone (rGH) on sleep features and  
69 showed possible worsening of sleep polysomnography parameters six to nine months after treatment  
70 initiation, but no long-term effect (4,7,11–13). This could be explained by tonsil hypertrophy  
71 subsequent to the introduction of rGH, which rapidly stabilizes. Thus, a score for the risk of rGH  
72 therapy initiation has been proposed, taking into account polysomnographic data, tonsil size, and  
73 circulating insulin-like growth factor 1 (IGF-I) levels (14). Other studies have reported improved  
74 breathing parameters and better day activity levels with rGH therapy in PWS patients, probably due to  
75 an improvement in airway muscular tonus (12,13). Some of these patients required nocturnal non-

76 invasive ventilation, leading to an improvement in SDB parameters (15). The results of these studies  
77 and the possible risk of sudden death led to the recommendation of performing a sleep recording of all  
78 PWS patients before initiating rGH therapy (3,16).

79 Silver-Russell syndrome (SRS) is an imprinting disorder that results in intrauterine growth restriction  
80 (IUGR), poor postnatal growth, with feeding difficulties (often requiring early nutritional support),  
81 and facial dysmorphism (relative macrocephaly at birth, protruding forehead, body asymmetry)  
82 (17,18). The clinical diagnosis may be challenging because of non-specific signs. Azzi *et al.* thus  
83 developed a clinical score (Netchine-Harbison clinical scoring system, NH-CSS), which has been  
84 validated in a recent international consensus, to prompt genetic investigation (17,19). Molecular  
85 abnormalities are identified in approximately 60% of the patients and can consist of either  
86 chromosome 7 maternal uniparental disomy (upd(7)mat) or loss of methylation (LOM) in the  
87 *H19/IGF2* intergenic differentially methylated region (IG-DMR) in 11p15 (2,17). rGH therapy is  
88 recommended to increase their height and muscle mass and improve body composition (17).

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

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

## 101 **Patients and methods**

### 102 **1. Patients**

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

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

### 117 **2 Methods**

#### 118 2.1 Sleep recordings

119 Polygraphy or polysomnography were performed in these patients, either before or during rGH  
120 therapy. Patients and their parents had a consultation concerning their sleep environment and sleep  
121 characteristics to assess the presence of clinical features consistent with SDB prior to the sleep  
122 recording. Sleep recordings were analyzed by trained doctors specialized in sleep disorders. A clinical  
123 evaluation was performed before the recording to rule out any acute upper airway infections. Data

124 were analyzed, taking into consideration the height, weight, and body mass index (BMI) of the  
125 patients.

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

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

#### 134 2.2 Interpretation of sleep parameters

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

142 Central AHI values over 0.45 events/hour in patients between three and five years of age, and over  
143 0.85 events/hour in patients older than six years were considered to be abnormal. No reference values  
144 have been validated for younger children (27).

145 Transcutaneous oxygen and carbon dioxide pressures were recorded and interpreted to be abnormal  
146 (*i.e.* hypoxemia and hypercapnia) if there was a difference of more than 10 mmHg between the  
147 pressures when asleep and awake (27).

148 Data are expressed as the mean (min-max). Distributions were compared using Student's test and  
149 correlations were performed with Pearson's test.

### 150 2.3 Biological assay

151 Serum IGF-I concentrations were measured using a specific immunoradiometric assay (IGF-I  
152 RIACT) purchased from CIS-BIO INTERNATIONAL ( Gif- sur- Yvette, FRANCE ). The sensitivity  
153 threshold was 1 ng/ml and the intra-assay and inter-assay coefficients of variation were 3.2- 3.8% and  
154 3.8- 8.2%, respectively. Data were transformed into age-related SDS values on the basis of previously  
155 obtained data on controls.

156

## 157 **Results**

### 158 1. Recordings

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

### 164 2. Patients

165 Data were available for 40 patients with SRS: 32 with LOM in the 11p15 region and eight with  
166 upd(7)mat. The sex ratio was 0.5. All but one (with upd(7)mat) had a NH-CSS of SRS score of  $\geq 4$ .  
167 The mean age at the first polygraphy was 6.0 years (1.7-15.3). We performed 21 sleep recordings in 20  
168 patients without rGH therapy and sleep recording before and during rGH therapy in 12 patients. Most  
169 patients received rGH therapy (n = 30) with a mean age at initiation of 3.6 years (1.5-7.5). Eight  
170 patients had two sleep recordings during rGH therapy and two had sleep recording after rGH therapy  
171 cessation. All but three patients were born small for gestational age (with birth weight and/or length

172 below -2SDS at 37 (28-41) weeks of amenorrhea: birth weight was -2.8 SDS (-5.8;-0.3), birth length -  
173 4.1 SDS (-8.0;-0.9), and head circumference -1.0 SDS (-4.0;1.2) (28).

### 174 3. Clinical features

175 Twenty patients were screened for SDB with a questionnaire before the sleep recording (Table 1). All  
176 patients had a clinical gastro-intestinal evaluation and we found a high prevalence of reflux, even after  
177 24 months of age. The respiratory, ENT and maxillo-facial features, known to affect sleep quality, are  
178 shown in Table 2.

### 179 4. Sleep recordings

180 The sleep recording parameters are shown in Table 3. The AHI for overall sleep recordings was 3.4  
181 events/hour (0.0-12.4) with a central AHI of 0.5 events/hour (0.0-2.4). SDB was identified in 45  
182 recordings (73.8%) and classified as mild for 33 (54.1%), moderate for nine (14.8%), and severe for  
183 three (4.9%). The central AHI was abnormal in 22 recordings (36.0%) for 17 patients (42.5%). There  
184 was no difference in the AHI between patients with upd(7)mat and those with 11p15 ( $p = 0.94$ ). We  
185 found mild negative correlation between age and AHI ( $\rho = -0.37$ ,  $p = 0.003$ ). Before rGH treatment,  
186 only three patients (14.3%) had a normal sleep recording; 13 had mild SDB (61.9%), three had  
187 moderate SDB (14.3%), and two had severe SDB (9.5%). See Figure 2 for the complete data.

188 Concerning snoring, four patients (20.0%) had a pathological snoring index ( $\geq 50$ ) before rGH  
189 therapy, and one a severe index ( $\geq 300$ ); none had tonsil or adenoid hypertrophy. During rGH therapy,  
190 10 patients (27.8%) had a pathological index, with severe SDB for two. Among them, eight (80%) had  
191 a normal ENT examination, one had a tonsillectomy three months before, and one had adenoid  
192 hypertrophy (with a snoring index of 68). There was no statistical difference of the AHI between  
193 patients with adenoid or tonsil hypertrophy and those with a normal ENT examination (mean of 3.2  
194 events/hour (0.1;11.5) and 3.2 events/hour (0.0,12.4), respectively,  $p = 0.59$ ).

195 There was no difference in the AHI in patients without treatment (before rGH therapy onset or after  
196 cessation) and those during rGH therapy (mean of 4.1 events/hour (0.3;12.4) and 3.1 events/hour  
197 (0.1,11.5), respectively,  $p = 0.18$ ).

198 Transcutaneous carbon dioxide and oxygen pressures were measured in 30 recordings. Nine patients  
199 (30.0%) had hypoxemia and five had hypercapnia (16.7%). Minimal oximetry was under 90% in 25  
200 recordings (45.5%) and minimal transcutaneous oxygen pressure was under 70 mmHg for 11 patients  
201 (36.7%). The maximal transcutaneous carbon dioxide pressure during sleep was above 45 mmHg in 12  
202 recordings (40.0%). The time below 80 mmHg for transcutaneous oxygen pressure was null for all  
203 patients and only one patient under rGH therapy had a transcutaneous carbon dioxide pressure above  
204 50 mmHg during 7% of the time recorded.

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

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

## 215 5. IGF-I serum levels

216 We found spontaneously elevated IGF-I serum levels before rGH therapy, with a mean of 1.3 SDS (-  
217 1.9; 4.5) and nine patients (45.0%) had IGF-I serum levels above 2 SDS. These levels rose to 2.0 SDS  
218 (-0.6; 6.6) with rGH treatment and the IGF-I serum levels were above 2 SDS for 20 patients (50.0%).

219 There was no significant difference in IGF-I serum levels before or during rGH therapy, with a mean  
220 daily dose of 32.3 µg/kg (12.9-51.4). We failed to find a correlation between plasma IGF-I levels and  
221 AHI.

## 222 **Discussion**

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

227 We observed mainly obstructive apnea in these children, suggesting that their SDB may be due to  
228 narrowing of the upper airways and reflux. There was no direct link between lymphoid tissue  
229 hypertrophy and SDB in our patients. Only one patient had an adenotonsillectomy between the first  
230 and second polygraph, her AHI worsening from 1.5 to 11.5 after surgery. This finding suggests that  
231 adenotonsillectomy may be less successful in SRS patients than in the general population, as already  
232 reported for PWS patients (29–31). Furthermore, an ENT intervention concerning tonsils in SRS  
233 patients can result in a voice change and worsen a preexisting high-pitched voice, quite common in  
234 these patients. Such velopharyngeal insufficiency is well described in PWS and must be explored in  
235 SRS. For maxillofacial malformations (skeletal class II, supraclulsion, upper and lower crowding)  
236 orthodontic treatment is possible, and some patients had symphyseal distraction osteogenesis for severe  
237 lower crowding and bilateral scissor bite. Changes in SDB after such interventions have yet to be  
238 evaluated (21,30). In addition, we found the AHI to be no different between patients with clinical  
239 signs of reflux and those without ( $p = 0.14$ ). Hypotonia and constitutional narrowness of the upper  
240 airways appear to be the best explanation for the obstructive features in SRS patients during sleep.

241 The observed short-term worsening of SDB in PWS patients following the initiation of rGH therapy  
242 can be explained by rapid elevation of serum IGF-I levels, resulting in tonsil hypertrophy, which

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

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

266         Several studies have shown the benefit of nocturnal intermittent positive pressure ventilation  
267 (IPPV) on central alveolar hypoventilation in PWS patients. The presence of central apneas is the main

268 feature which determines nocturnal IPPV, whereas continuous positive airway pressure (CPAP) is  
269 preferred in cases of obstructive SAS (4). None of our patients had nocturnal ventilation but it has  
270 since been introduced for case 5 (table 4). In cases of obstructive SDB without tonsil hypertrophy or  
271 persistent obstructive SDB after tonsillectomy, transient nocturnal CPAP is a therapeutic option, while  
272 waiting for the growth of the head to enlarge the narrowness of the upper airways caused by  
273 maxillofacial anomalies, combined with rGH to improve hypotonia.

274 PWS patients experience abnormalities in the organization of REM sleep during polysomnography  
275 (32). Although we had only a small number of polysomnographies, we identified a high micro-  
276 awakening index in our patients. As mentioned in the methods, AHI is underestimated in polygraphies  
277 since micro-awakening is not monitored. Consequently together the high micro-awakening index we  
278 found in polysomnographies and the high prevalence of SDB we identified in polygraphies (even with  
279 an underestimated AHI) should drive us exclusively assess sleep parameters with polysomnographies  
280 for a more accurate diagnosis of SDB. Now that polysomnography is more widely available, it would  
281 be informative to gather sufficient data to study this tendency, depending on the acceptance of younger  
282 of this more uncomfortable method.

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

292 **Conclusion**

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

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412

### 413 **Figures and tables**

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

415 Table 2. Main clinical features of the cohort.

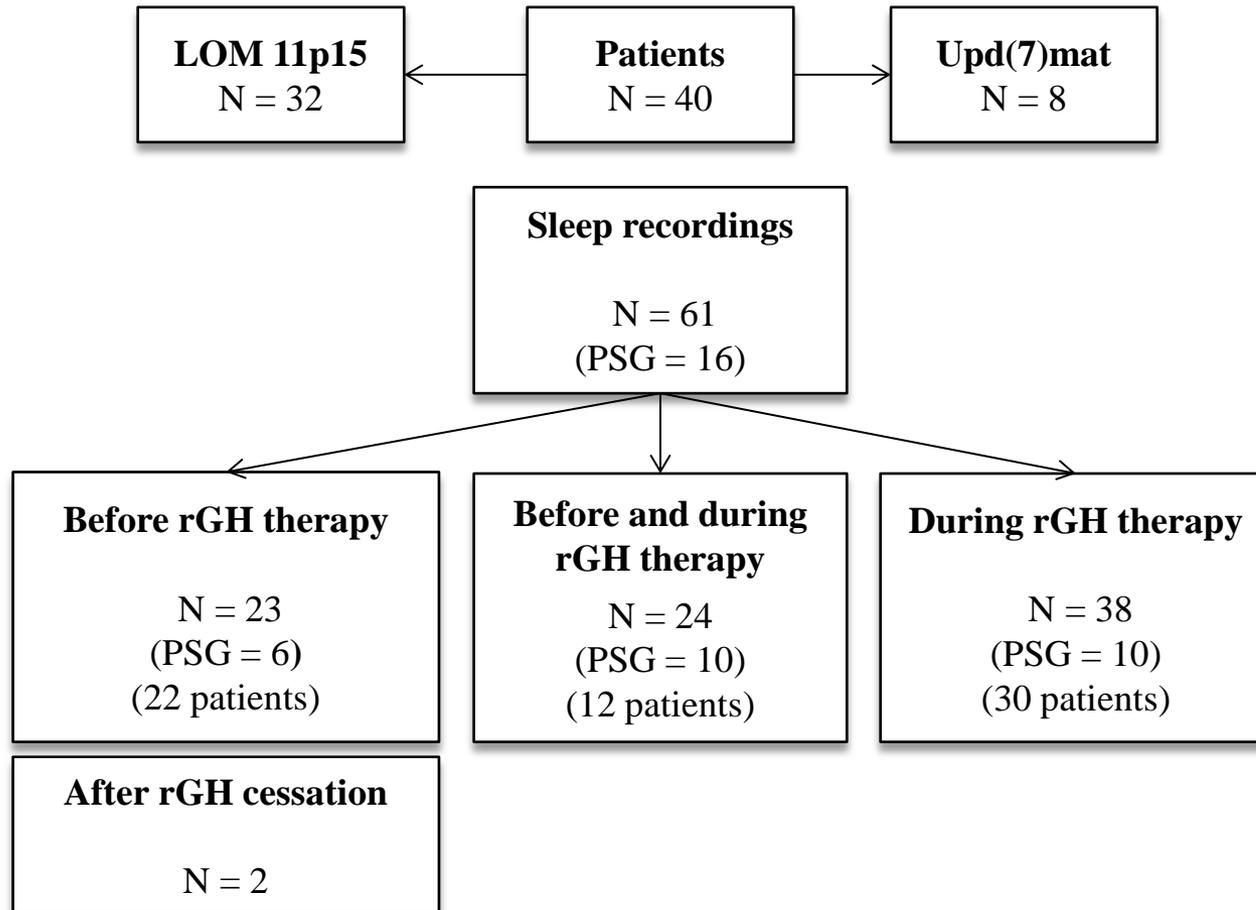
416 Table 3. Main sleep recording parameters of the cohort. rGH: recombinant growth hormone. SpO2:  
417 pulse oximetry. TcPO2: transcutaneous oxygen pressure. TcPCO2: transcutaneous carbon dioxide  
418 pressure. REM: rapid eye movement.

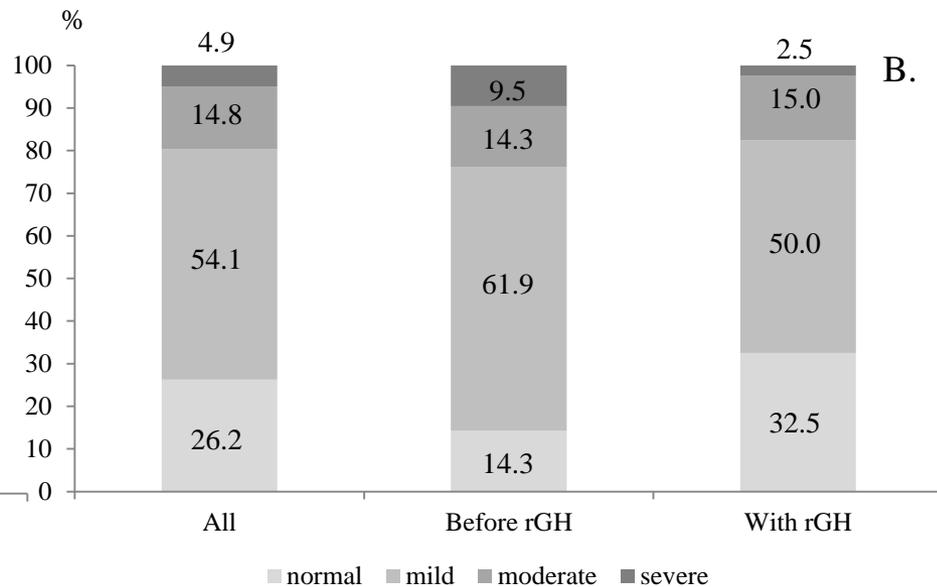
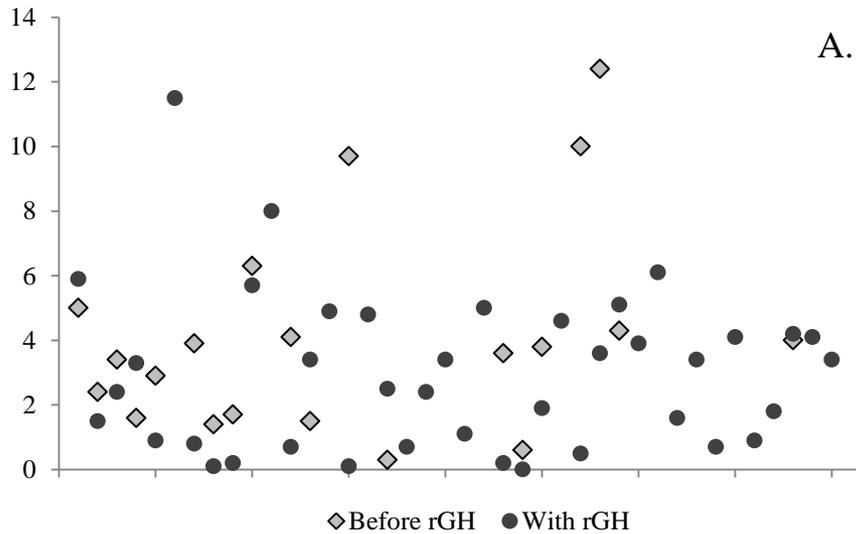
419 Table 4. Data for 12 patients before and after the initiation of rGH therapy. ♂ indicates that the sleep  
420 recording was a polysomnography. \* Delay between rGH therapy onset and second sleep recording.

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

424 Figure 2. A) Representation of each sleep recording AHI in the entire cohort. B) Repartition of the  
425 AHI depending on the corresponding SDB level (in percentage) in the entire cohort, before and during  
426 rGH therapy.

427





	Prior rGH therapy						During rGH therapy					
	PG n=17			PSG n=6			PG n=28			PSG n=10		
	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max
<b>AHI (events/h)</b>	3.0	0.0	10.0	5.9	1.6	12.4	3.2	0.1	11.5	2.9	0.5	6.1
<b>Obstructive AHI (events/h)</b>	2.5	0.0	9.1	4.8	1.5	10.2	2.9	0.0	9.6	10.6	0.4	4.7
<b>Central AHI (events/h)</b>	0.5	0.0	1.7	1.2	0.0	2.4	0.4	0.0	1.8	0.5	0.0	1.9
<b>Sleep efficiency</b>				87.1	83.0	93.0				76.4	66.0	91.0
<b>Percentage of time in slow sleep (%)</b>				27.8	18.0	37.0				21.1	11.6	27.0
<b>Percentage of time in REM sleep (%)</b>				16.0	10.0	26.0				23.8	17.0	36.4
<b>Micro-awakenings</b>				10.6	10.0	21.0				9.2	3.0	17.0

SDTable 1: Comparison of AHI values obtained with polygraphies (PG) or polysomnographies (PSG) before and during rGH treatment.

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

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

	<b>Without rGH therapy n= 23</b>			<b>During rGH therapy n=38</b>		
	<b>Mean</b>	<b>Min</b>	<b>Max</b>	<b>Mean</b>	<b>Min</b>	<b>Max</b>
<b>AHI (events/h)</b>	4.1	0.3	12.4	3.1	0.1	11.5
<b>Obstructive AHI (events/h)</b>	3.4	0.0	10.2	2.7	0.0	10.6
<b>Central AHI (events/h)</b>	0.7	0.0	2.4	0.4	0.0	1.9
<b>Minimum sleeping SpO2 (%)</b>	90.0	80.0	96.0	91.0	82.0	96.0
<b>Percentage of time with sleeping SpO2&lt;90% (%)</b>	0.1	0.0	1.0	0.05	0.0	1.0
<b>TcPO2 difference between sleep and arousal (mmHg)</b>	-6.4	-14.0	0.0	-4.9	-17.0	7.0
<b>Maximal TcPCO2 during sleep (mmHg)</b>	43.6	39.0	49.0	43.8	34.0	51.0
<b>TcPCO2 difference between sleep and arousal (mmHg)</b>	5.8	2.0	10.0	7.2	3.0	12.0
<b>Minimal TcPO2 during sleep (mmHg)</b>	71.7	57.0	89.0	74.7	64.0	91.0
<b>Snoring index</b>	105.6	0.0	1582.0	60.4	0.0	545.0

Cases	Sex	Genetic	Age (years)		AHI (events/h)		Obstructive AHI (events/h)		Central AHI (events/h)		IGF1 (SDS)		rGH therapy		
			1st recording	2nd recording	1st recording	2nd recording	1st recording	2nd recording	1st recording	2nd recording	1st recording	2nd recording	Age (years)	Dose (mg/kg/week)	Delay* (years)
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 $\alpha$	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 $\alpha$	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 $\alpha$	6.6 $\alpha$	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 $\alpha$	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 $\alpha$	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 $\alpha$	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 $\alpha$	5.0 $\alpha$	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 $\alpha$	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
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