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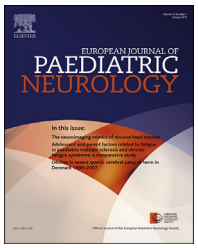

Original article

Polysomnographic findings in Rett syndrome

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ABSTRACT

Introduction: Rett syndrome (RS) is a severe neurodevelopment disorder associated with abnormal breathing during wakefulness and disturbed nocturnal behaviour. Breathing abnormalities during daytime have been extensively reported but polysomnographic (PSG) findings have been poorly studied.

Materials and methods: Consecutive patients with RS carrying distinct mutations in *MECP2* gene, who underwent a PSG between October 2014 and January 2018, were included in the study. Clinical and PSG data were collected.

Results: Seventeen RS girls, mean age 9.5 ± 2.8 years, were included in the study. Mean total sleep time was 366 ± 102 min. Mean sleep efficiency was reduced (66 ± 19%) with only 3 girls presenting a sleep efficiency above 80%. Wake after sleep onset was increased (33 ± 20%) with an arousal index of 7 ± 6 events/hour. Sleep stages were altered with a normal N1 (2 ± 3%), a decreased N2 (34 ± 20%), an increase of N3 (51 ± 23%) and a decrease of REM sleep (12 ± 9%). Mean apnea hypopnea index (AHI) was increased at 19 ± 37 events/hour, with a predominance of obstructive events. Thirteen patients had an AHI > 1.5 event/hour. Four patients had an obstructive AHI >10 events/hour with one patient having associated tonsillar hypertrophy. Two patients had predominant severe central apneas (central AHI 53 and 132 events/hour) which resolved with noninvasive ventilation and nocturnal oxygen therapy respectively.

Conclusion: Girls with RS have poor sleep quality with alterations in slow wave and REM sleep stages. Obstructive respiratory events are uncommon in patients without adenotonsillar hypertrophy. Central respiratory events are rare. Longitudinal studies should help understanding the natural history of sleep disturbances in RS and their relationship with the neurocognitive decline.

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1. Introduction

Rett syndrome (RS) is a severe neurodevelopment disorder affecting almost exclusively girls, with an estimated prevalence of almost 1 per 10,000 females.[1] RS is linked to mutations in the X-linked methyl-CpG-binding protein 2 gene (*MECP2*)[2] in more than 95% of classical RS cases.[3] Although the complex role of MECP2 is largely unknown, current knowledge highlights the importance of this protein for the expression of various genes involved in the normal neurodevelopmental process. Clinical course of patients with typical RS is characterized by rapid neurocognitive decline between the age of 12–18 months of age, during which girls lose acquired speech and purposeful hand use, develop autistic features and stereotypic hand movements, ataxia, gait apraxia, and typical breathing abnormalities after an apparent normal development in the early months of life.[4,5] These features may vary from one subject to another, but abnormal behaviour during sleep appears to be one of the prominent features of RS. Recent data from an Australian registry reported night screaming, laughing and waking in almost 80% of patients, with some differences related to age and type of mutation.[6,7] In addition, breathing abnormalities are common in RS and have been suggested to contribute to the high incidence of sudden death in this population.[8] Breathing profile in RS is characterized by periods of hyperventilation followed by apneas, shallow breathing and Valsalva's manoeuvres[9] during wakefulness, suggesting a cortical contribution to their pathophysiology.[10–12] Breathing disturbances have classically been described during wakefulness but some authors reported also a high prevalence of breathing and heart frequency abnormalities during sleep.[13]

Sleep architecture has been poorly described in RS. Studies showed a nearly normal sleep macro-architecture compared to healthy controls[10,14,15] with a moderate increase of the percentage of slow wave sleep (SWS) and a decrease of rapid eye movement (REM) sleep.[16] Obstructive and central sleep apneas, associated with oxygen desaturations, have also been reported, which may suggest a dysregulation of the cardiorespiratory system during sleep.[16–18] However, more extensive data on sleep in larger cohorts of patients with RS are lacking. The aim of the present study was to get further insight into the polysomnographic (PSG) pattern of RS in 17 patients with RS followed at a national RS reference centre.

2. Patients and methods

2.1. Patients

All consecutive patients with a typical RS who underwent a full overnight PSG at the sleep and noninvasive ventilation unit in Necker Children's Hospital between October 2014 and January 2018 were included in the study. Clinical data, including medical treatment and previous surgical interventions, were collected. PSG were always performed in a stable condition, and in particular when epilepsy, if present, was clinically controlled with antiepileptic treatment. The study was conducted in agreement with the French regulations and received appropriate legal and ethical approval from the ethical committee CPP Ile de France II, protocol 2013-A00374-41.

2.2. Polysomnography

All PSG started at patients' usual bedtime and continued until spontaneous morning awakening. PSG studies were performed using CID 102* (Cidelec, Saint Gemmes sur Loire, France) or Alice 6 LDxS (Philips Respironics, Carquefou, France) devices. Electroencephalographic (EEG) recordings were based on the international 10–20 system with the placement of electrodes in positions F1-A2, F2-A1, C3-A2, C4-A1, O1-A2, O2-A1, recording of eye movements, electromyography (EMG) of the chin, electrocardiogram and left and right tibialis EMG. Sleep stages were scored manually using standard criteria of the American Academy of Sleep Medicine (AASM).[19] Cardiorespiratory data included airflow (nasal pressure transducer and oronasal thermistor), body position, body movements, thoracic and abdominal movements assessed by inductance belts, and pulse oximetry (SpO_2) using the Nonin pulse oximeter (Nonin Medical, Inc., Plymouth, MN) for CID 102* and the Masimo pulse oximeter (Masimo SET LNCS pulse oximeters) for Alice 6 LDxS. Respiratory events were scored according to the AASM guidelines.[19,20] Oxygen desaturation index (ODI) was defined as the number of at least 3% oxygen desaturations (DS) per hour of total sleep time. Transcutaneous carbon dioxide ($PtcCO_2$) recordings were performed simultaneously with the SenTec Digital Monitor (SenTecInc, Therwil, Switzerland). Mean, maximal $PtcCO_2$ were recorded.

The following sleep parameters were evaluated:

- Time in bed (TIB): since all the girls were non-ambulatory TIB was considered as the time between light-off and light-on.
- Total sleep time (TST): the time in minutes from sleep onset to the end of the final sleep epoch minus the time awake.
- Sleep efficiency: the percentage ratio between total sleep time and time in bed (TST/TIB × 100).
- Wakefulness after sleep onset (WASO): the time spent awake after sleep onset.
- Arousal index: number of arousals per hour of TST
- Percentage of TST spent in sleep stages 1, 2, 3 and REM sleep
- Apnea-hypopnea index (AHI): number of apneas and hypopneas per hour of TST.

Sleep latency was not analysed because all the patients had altered wake-sleep cycles and therefore, several episodes of sleep during the recordings were registered. Given the different characteristics of nap sleep we arbitrarily decided to exclude all naps from analysis. Therefore, we chose the longest continuous period of night sleep for the analysis of sleep architecture and sleep-related respiratory events. All the recordings were scored by two of the investigators (AA and LDS).

2.3. Statistical analysis

All data are expressed as mean and standard deviation.

3. Results

3.1. Patients

Seventeen girls, mean age 9.5 ± 2.8 years and mean body mass index centile 38 ± 28 kg/m^2, were included in the study (Table 1). A known mutation of the *MECP2 gene* was present in 10 patients and a deletion in 5 patients. As the diagnosis was performed in another institution in patients #13 and #17, genetic data was not available at the time of the PSG. In 10 patients, the PSG was performed as part of the preoperative evaluation before spine surgery. The other 7 patients were referred because of suspected sleep-disordered breathing (SDB). Scoliosis was present in all patients and epilepsy in 15 patients. Four patients were receiving melatonin for difficulties in sleep initiation.

3.2. Polysomnographic data

Mean TST was 366 ± 102 min. Mean sleep efficiency was reduced at 66 ± 19%, with only 3 patients having a sleep efficiency above 80%. Patient #11 had the lowest sleep efficiency with a value of only 19%. Mean percentage of WASO was 33 ± 20% with a mean arousal index of 7 ± 6 events/hour. Sleep stages were altered with a decrease of N2 (34 ± 20%), an increase of N3 (51 ± 23%) and a decrease of REM (12 ± 9%). Seven patients had a percentage of REM sleep <10%. Detailed PSG results are shown in Table 2.

The mean AHI was increased at 19 ± 37 events/h, with a mean obstructive AHI (OAHI) of 9 ± 12 events/h and a mean central apnea index (CAI) of 11 ± 34 events/h. Only 4 patients had an OAHI ≤1 event/h, 7 patients had an OAHI between 1 and 5 events/h, 2 patients had an OAHI between 5 and 10 events/h, and 4 patients had an OAHI >10 events/h. Among these 4 patients, one (patient #16) had tonsillar hypertrophy with a tonsillectomy planned. One (patient #15) was started on CPAP because of the presence of pharyngomalacia associated with mild tonsillar hypertrophy.

The two other patients (patients #1 and #8) showed an association of obstructive and central apneas (patients #1 and #8). Patient #1 had an OAHI of 28 events/h and a CAI of 53 events/h, with events occurring mainly during REM sleep and which were associated with profound oxygen desaturations. As an arthrodesis was planned shortly, she was immediately started on NIV without a trial of oxygen therapy alone. A follow up PSG is planned 6 months after the arthrodesis Patient #8 had a CAI of 132 events/hour, with profound oxygen desaturations and a predominance of periodic breathing during N2 and N3 (Fig. 1A and B). Central and obstructive sleep apneas resolved completely with nocturnal oxygen therapy with an AHI of 1 event/h during oxygen therapy (Fig. 1C and D).

None of the other patients experienced epileptic seizures during the PSG. Abnormal nocturnal behaviours were not reported.

Abnormalities in sleep quality, sleep architecture and respiratory events were not related to age, type of mutation, and associated conditions such as epilepsy. Sleep quality and quantity were not better in the 4 patients treated with melatonin as compared to the other 13 patients. As an example, patient #11 was treated by melatonin and had the worst TST and sleep efficiency.

4. Discussion

Our study demonstrates that patients with RS have poor sleep quality with alterations in sleep stages. However, respiratory events are uncommon in those without adenotonsillar hypertrophy.

Table 1 – Demographic and clinical data of the 17 patients.

Patient	Mutation	Age (years)	BMI kg/m^2, centile	Associated conditions	Previous surgery	Antiepileptic treatment	Melatonine
1	Deletion	6	N/A	S, E, G, O	None	Valproate	Yes
2	p.(Arg255*)	6	54	S, G, O	Adenoidectomy and Nissen fundoplicature	None	None
3	p.(Arg168*)	6	8	S, E, G, O	None	None	None
4	p.(Arg168*)	6.8	63	S,E, G, O	None	Valproate	Yes
5	p.(Arg168*)	6.8	93	S, E, G	None	Carbamazepine	None
6	Deletion	8	33	S, E, G	None	Carbamazepine	None
7	p.(Arg133Pro)	8.7	53	S, G	Adenotonsillectomy	None	None
8	Deletion	9.4	69	S, E, G	None	Valproate	Yes
9	Deletion	9.4	0	S, E, G, O	None	Carbamazepine	None
10	Deletion	10	7	S, G, O	Scoliosis surgery	None	None
11	p.(Arg294*)	10	12	S, E, G, O	None	Topiramate	Yes
12	p.(Arg306Cys)	11	29.5	S, E, G, O	None	Topiramate	None
13	Unknown	11	0	S, E, G, O	Adenotonsillectomy	Valproate	None
14	p.(Arg168*)	11	53	S, E, G, O	Adenotonsillectomy	Valproate	None
15	p.(Thr158Met)	12	31	S, E, G	None	Valproate	None
16	p.(Tyr141*)	13	31	S, E, G	Adenotonsillectomy	Valproate	None
17	Unknown	16	76	S, E, G, O	None	Topiramate	None

Abbreviations: N/A: not available, S: Scoliosis, E: Epilepsy, G: chronic gastro-oesophageal reflux, O: osteoporosis.

Table 2 – Polysomnographic data.

Patient	TST (min)	Sleep efficiency %	WASO (%)	N1 (%)	N2 (%)	N3 (%)	REM (%)	Arousal index (events/h)	AHI (events/h)	OAHI (events/h)	CAI (events/h)	Mean SpO_2 (%)	Minimal SpO_2 (%)	ODI (events/h)	Mean $PtcCO_2$ (mmHg)	Maximal $PtcCO_2$ (mmHg)
1	300	35	64	3	17	60	20	5	81	28	53	95	82	94	42	51
2	391	78	22	1.5	27	57	14	3	8	7	1	96	88	7	44	47
3	320	71	29	0	31	68	0	2	15	5	1.5	94	87	9	46	50
4	255	65	34	0	22	45	28	4	10	8	0	96	90	3.5	45	54
5	384	59	41	1	12	78	10	3	4	4	0	93	78	11	40	43
6	396	99	0	1	3	96	0	3	4	4	0	98	87	4	44	48
7	378	77	23	1	54	30	15	12	2	1	0	98	94	1	45	48
8	435	67	32	1	21	56	22	1	140	34	132	95	70	134	36	46
9	507	50	50	5	48	41	5	7	4	3	1	99	89	4	42	46
10	448	92	8	1	34	37	27	8	1	0	0	98	90	2	38	44
11	137	19	81	3	47	47	3	3	0	0	0	99	93	0	33	50
12	446	75	25	0	51	30	19	6	1	3	0	99	94	3	N/A	N/A
13	513	83	17	0	15	68	16	7	3	3	0	97	100	0	45	48
14	368	65	35	5	57	20	17	2	0	0	0	98	93	2	43	48
15	386	71	28	3	19	72	5	13	33	33	0	95	81	37	46	53
16	372	66	34	0	44	54	2	6	13	12	1.5	95	58	21	39	42
17	183	54	46	12	81	0	7	27	4	4	0	98	86	32	46	52
Mean ± SD	366 ± 102	66 ± 19	33 ± 20	2 ± 3	34 ± 20	51 ± 23	12 ± 9	7 ± 6	19 ± 37	9 ± 11	11 ± 34	97 ± 2	86 ± 10	21 ± 37	42 ± 4	48 ± 3

Abbreviations: N/A = not available; Total Sleep Time = TST; WASO = wake after sleep onset; REM: rapid eye movement, AHI = apnea-hypopnea index; OAHI: obstructive apnea-hypopnea index, CAI = central apnea index; SpO_2 = pulse oximetry; ODI = oxygen desaturation index; $PtcCO_2$ = transcutaneous carbon dioxide.

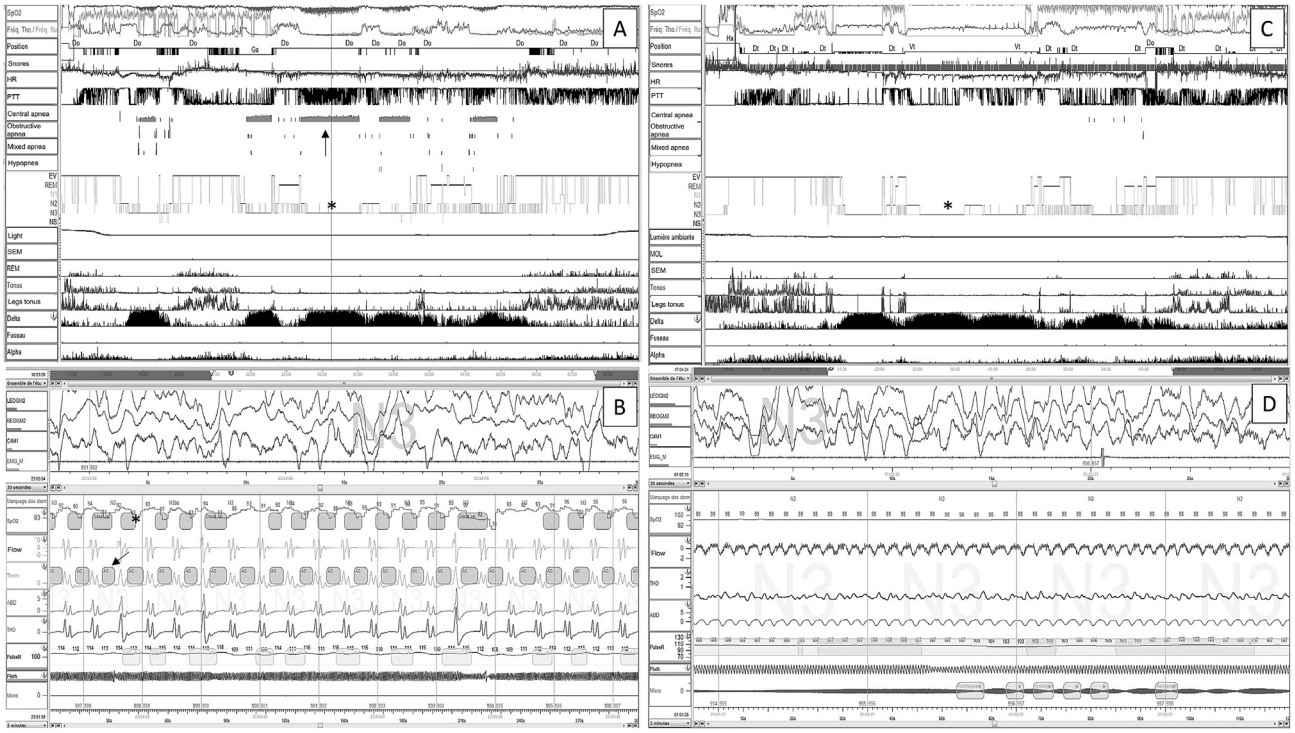

Fig. 1 – Efficacy of oxygen therapy on central apneas syndrome in patient #8. Abbreviation: HR = heart rate, PTT = pulse transit time, SEM = slow eye movements, REM = rapid eye movements, LEOGM2 = left ocular electromyogram, REOGM2 = right ocular electromyogram, C4M1 = central 4- mastoid 1 derivation, EMG_M = mandibular muscle electromyogram, THO = thoracic movements, ABD = abdominal movements, PulseR = heart rate, Therm = oronasal thermistance, SpO_2 = peripheral oxygen saturation, Pleth = pulse plethysmography, Micro = microphone. A. Whole night recording during spontaneous ventilation in room air. Central apnoeas (arrows) occurred almost exclusively in N3 sleep stages (*). B. Detailed EEG and respiratory parameters during N3 sleep. Epoch of 30 s for EEG recording, epoch of 5 min for respiratory parameters. The patient had periodic breathing with central pauses (arrows), characterised by lack of thoraco-abdominal movements and airway flow, associated with profound desaturations (*). C. Whole night recording during spontaneous ventilation with oxygen 1 l/min. Central apnoeas resolved almost completely in N3 sleep stages (*). D. Detailed EEG and respiratory parameters during N3 sleep. Epoch of 30 s for EEG recording, epoch of 5 min for respiratory parameters. The patient had normal and regular respiration with no central apnoeas nor desaturations.

The impairment of sleep quality is a major observation of the present study which showed a mean sleep efficiency of 66 ± 19%. Only 3 patients had a sleep efficiency of more than 80%, and only 2 patients had a value above 90%, which is considered as normal in children and adolescents.[21] This poor sleep efficiency is mainly explained by the high percentage of WASO which reached about 33%. Night awakenings are reported in almost 80% of girls with RS,[7] and are a major determinant of poor sleep quality. Circadian rhythm has been shown to be disrupted in a mouse model of RS,[22] suggesting a potential role of exogenous melatonin as a treatment. The only placebo-controlled trial evaluating the efficacy of melatonin in RS patients found an improvement in sleep latency and sleep efficiency but only in the girls with the most severe sleep disruption.[23] In the present study, according to their parents or caregivers the 4 patients treated with melatonin had persistent problems in sleep latency despite treatment, independently from the dosage used. These data are in accordance with the results of Wong et al.[7] on the reduced efficacy of sleep medications for improving sleep efficiency in RS. These results do not demonstrate that melatonin is ineffective in RS but rather that medications alone without an individually-targeted sleep strategy may not be sufficient for treating sleep disorders in patients with RS.

Sleep macrostructure was also impaired in our study, with a relative increase in N3 sleep and a decrease of REM sleep. A previous study did not find any difference in sleep stages in a series of 30 patients with RS as compared to healthy controls.[10] A more recent study found comparable abnormalities in percentages of sleep stages as in the present study, namely 43 ± 16% of N3 and 12 ± 7% of REM, in 13 patients with RS.[16] These alterations may be explained by alterations of thalamo-cortical connections, as reported in children with mental retardation.[24] Alteration of N3 architecture in RS has also been recently reported by Ammanuel et al.,[25] who observed a significant heightened delta wave power, mainly in young patients. This may be explained by a relative lack of synaptic maturation in the RS brain.[26] Further cases-controls studies, with more patients, may help confirm these findings.

Obstructive respiratory events were the most common respiratory events with 4 patients having an OAHI >5 events/h without associated central events. Obstructive sleep apnea

(OSA) was explained by a hypertrophy of the adenoids and/or tonsils, despite a history of adenoidectomy in one patient (patient #2) and adenoidectomy with partial tonsillectomy in another patient (patient #16). Similar cases of OSA related to adenotonsillary hypertrophy in patients with RS have been reported in the literature.[16,18] OSA related to adenotonsillary hypertrophy does not seem to be a specific feature of RS. OSA is relatively common in the general paediatric population with an estimated prevalence between 2 and 5%. The small number of patients does not allow any comparison or conclusion on a potential increased prevalence of OSA in RS. Surgical treatment should not differ from children with RS except for a thorough pre-operative anaesthetic evaluation and the contraindication of ambulatory surgery.

A combination of central sleep apneas (CSA) and OSA were observed in 2 patients (patient #1 and #8), with all other patients having a CAI $\leq$ 1.5/h, which is considered as within the normal range.[27] CSA has been reported in RS.[10,13,16] CSA is supposed to be related with an instability of central respiratory drive, with dysfunction of the central chemoreceptors or of the respiratory integrative systems of the brainstem. This mechanism is the hallmark of congenital central hypoventilation syndrome, a disorder related to mutation of the *PHOXB2* gene,[28] and probably of primary idiopathic central apnoeas.[29] In our cases, a *PHOXB2* mutation was not explored due to the lack of other suggestive signs or symptoms. Other diseases that may be associated to CSA are Prader Willi syndrome,[30,31] hypothyroidism,[32] and anatomical brainstem alterations such Arnold Chiari malformation[27,33] or achondroplasia[34,35] which were ruled out clinically or with brain imaging. Interestingly, in patient #8, sleep apnea resolved with oxygen therapy alone. Similar results have been reported in 10 patients with Prader Willi syndrome and CSA in whom a significant decrease of CSA was observed during oxygen therapy.[36] In Prader Willi syndrome, CSA has been linked to an abnormal response to hypoxia and hypercapnia,[37,38] probably due to a deficient development of the pre-Botzinger complex in the brainsteam.[39] A disruption of norepinephrine circuits in the brainstem has been described in RS[40] along with other abnormalities of the respiratory network.[41] These data may therefore suggest an abnormal ventilatory control during sleep in both diseases with a potential benefit of oxygen therapy. Our finding, along with that observed in Prader Willi syndrome, pleads for a trial of oxygen therapy as a first line therapy of CSA in RS.

Patients #11 and 17 had a dramatic reduction of their TST that was related to a particular alteration of wake-sleep pattern in both girls. Despite the dramatic short TST in these patients we decided to maintain them in our study, as these patients may reflect an extreme alteration of sleep-wake pattern in RS. Moreover, sleep architecture and respiratory events of patient #11 were similar to those observed in the other patients. Concerning patient #17 we observed a complete absence of N3 stage, which is indeed a finding that deserves further explication. We were not able to find any other external cause that may explain this difference, except for the older age of this patient. Further PSG in adult patients with RS may increase the understanding of the role of ageing on sleep changes in this population.

Our study has some limitations. Of these, a control group is lacking. However, normative values for sleep macrostructure and sleep respiratory parameters for children are widely available,[21,42,43] and PSG were scored following the American Academy of Sleep Medicine rules[19] by two well trained investigators. Information on sleep latency was not available and TIB could not be correctly assessed. Video recording was performed as a support for the analysis of respiratory events but detailed analysis of abnormal behaviour during the night, such as screaming or laughing, was not done. Finally, no follow up is available at the moment for all the patients, but as these patients are all followed in the national RS reference centre, this is actually underway. Finally, we did not perform an analysis of sleep microstructure in our patients. Indeed, cyclic alternating pattern (CAP) has been shown to provide interesting information about sleep instability and sleep microstructure in patients with intellectual disability or autism[44,45] and in children with neuromuscular disorders.[46,47] It may thus be worth studying CAP in future studies performed in patients with RS.

In conclusion, patients with RS have poor sleep quality with alterations in sleep stages. OSA is uncommon in patients without adenotonsillar hypertrophy. CSA is rare but may be improved by oxygen therapy. Longitudinal studies should help understanding the natural history of sleep disturbances in RS and their relationship with the neurocognitive decline.

Conflict of interest

All the authors declare that they have no conflict of interest with this manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejpn.2018.09.003.

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