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Sleep breathing and periodic leg movement pattern in Angelman Syndrome: A polysomnographic study

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Abstract

Objective: The aim of this study was to evaluate the sleep breathing patterns and to detect the eventual presence of periodic leg movements (PLMs) in patients affected by Angelman syndrome (AS).

Methods: Ten children with AS were recruited to participate in the study; the clinical diagnosis was confirmed by the genetic analysis (maternal 15q deletion, uniparental paternal disomy, or mutation of the UBE3A gene). All patients but two had presented epileptic seizures. Two age-matched groups of patients with mental retardation (MR) associated (MRE+) or not (MRE−) to epilepsy were used as control groups. All subjects underwent one polysomnographic recording, after one adaptation night. Sleep stages were scored according to standard criteria slightly modified in order to take into account the specific EEG patterns of AS, also the apnea/hypopnea index (AHI) was quantified; PLMs were identified and the PLM index (PLMI) was computed. The statistical analysis was carried out by means of the one-way ANOVA, followed by the Fisher LSD post-hoc test, when appropriate, and by means of the linear correlation coefficient between AHI and PLMI.

Results: Sleep macrostructure showed only few significant differences between children with AS and the other two groups of subjects: AS patients showed higher percentage of wakefulness after sleep onset and sleep onset latency; moreover, the percentage of REM sleep was reduced in AS and in MRE+ subjects. A tendency for AS subjects to present a higher PLMI than the other two groups was also found. AHI >5 was found in 30% of AS subjects, in 30.8% of MRE+, and only in 20% of MRE− patients ($\chi^2=2.359$, NS); 70% of AS patients, 38.5% of MRE+, and 46.7% of MRE− subjects had PLMI >5 ($\chi^2=3.088$, NS).

Conclusions: These results confirm our previous questionnaire-based findings of a high prevalence of sleep breathing disorder and important PLMs in AS and allow us to hypothesize that epilepsy, rather than mental retardation, might exacerbate these sleep disorders.

Significance: Sleep breathing disorder and PLMs might contribute to the cognitive impairment and to the worsening of life quality of subjects with AS and with MR (mostly those with epilepsy). Therefore, our findings suggest the need to explore these sleep disorders in children affected by MR and to set up a correct treatment.

Keywords: Angelman syndrome; Mental retardation; Epilepsy; Sleep; Sleep apnea; Periodic leg movements

1. Introduction

Angelman syndrome (AS) is a genetic neurodevelopmental disorder, characterized by mental retardation, severe speech impairment, ataxia of gait and/or tremulous movement of limbs, behavioral specificity as frequent laughter, jerky (puppet-like) movements, microcephaly, abnormal

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EEG features, epilepsy and dysmorphic craniofacial features.

Sleep disturbances are part of associated clinical characteristics of AS, with a prevalence ranging from 20 to 80% (Williams et al., 1995). The few studies investigating sleep disorders in AS, by means of questionnaires or polysomnographic recordings, showed that AS patients suffered from sleep/wake rhythm disorders, multiple nocturnal awakenings or difficulties in falling asleep (Didden et al., 2004; Guerrini et al., 1996; Smith et al., 1996; Summers et al., 1995; Viani et al., 1995; Zhdanova et al., 1999).

In our previous study (Bruni et al., 2004), we assessed the prevalence of sleep disorders in a relatively large group of AS subjects, compared to an age-matched normal healthy control group, by means of a comprehensive sleep questionnaire. In agreement with the previous literature data, we found a high frequency of disorders of initiating and maintaining sleep; however, we also detected a high frequency of different types of sleep disorders never reported before in AS: movement disorders during sleep (nocturnal hyperkinesias, restless sleep and unusual movements during sleep), enuresis, bruxism, sleep terrors, sleepwalking, sleep breathing difficulties, excessive daytime sleepiness, hypersomnia and sleep paralysis.

Contemporarily, we analyzed sleep structure of AS children by means of polysomnography (Miano et al., 2004), in comparison to age-matched normal subjects and children with epilepsy/mental retardation; we found sleep structure abnormalities in AS which were in agreement with the sleep maintenance disorders detected by the questionnaire (Bruni et al., 2004). The questionnaire study indicated the existence of other additional sleep problems, such as sleep breathing and movement disorders.

Sleep breathing disorders (SBD) are commonly reported in some specific genetic syndromes, such as Down syndrome, Prader–Willi syndrome and several craniofacial syndromes (Ferri et al., 1997, 1998; Harvey and Kennedy, 2002; Levanon et al., 1999; Manni et al., 2001; Pijpers et al., 2004; Richdale et al., 1999; Stores, 2001; Vgontzas et al., 1996; Zucconi and Bruni, 2001) and in children with epilepsy (Becker et al., 2003). Moreover, periodic leg movements (PLMs) during sleep have already been reported in Williams syndrome (Arens et al., 1998) and in mentally retarded children with ADHD (Chervin et al., 2002).

The typical craniofacial dysmorphic features of AS (microbrachycephaly, mid-facial hypoplasia, deep set eyes, macrostomia and prominent mandible) might be considered as risk factors for the occurrence of sleep breathing disorders. Moreover, daytime movement disorders such as dyskinesia, tremors and cortical myoclonus (Guerrini et al., 1996; Viani et al., 1995) have been already reported in AS; it is not known if this condition is also characterized by the presence of disturbed movements during sleep or not.

For these reasons, the aim of our study was to evaluate the sleep breathing patterns and to detect the eventual presence of PLMs in AS, by recording a complete sleep polygraphy (PSG).

2. Subjects and methods

2.1. Subjects

Ten children with AS (five males and five females, mean age 5.8 years, range 2–16 years), attending the Sleep Research Centre of the Oasi Institute of Troina (Italy) were recruited to participate in the study.

The clinical diagnosis in AS subjects was based on the presence of the physical, behavioral and EEG features described by Williams et al. (1995). The genetic analysis showed a deletion of Prader–Willi Syndrome/AS region with absence of the maternal allele in six patients; uniparental paternal disomy in one patient and mutation of the UBE3A gene in three.

All patients but two (both with UBE3A mutation) had presented epileptic seizures of different types (atonic, myoclonic, generalized tonic–clonic, partial, febrile convulsions); control of seizures was only partial in six cases and good in two cases (one with uniparental paternal disomy, one with 15q11-13 deletion). The antiepileptic drugs more frequently used were valproic acid, clobazam and clonazepam (Table 1).

Two age-matched groups of patients with mental retardation associated or not to epilepsy were used as control groups (Table 1):

(a) Patients with mental retardation without epilepsy (MRE−) (nine males and six females, mean age 7.6 years, range 3–10).
(b) Patients with mental retardation and epilepsy (MRE+) (five males and eight females, mean age 6.8 years, range 3–9).

2.2. Procedure

All subjects underwent hematologic screening in order to rule out anemia or deficit of ferritin level. All subjects underwent one PSG in the sleep laboratory, after one adaptation night in order to avoid the first-night effect. No hypnotic drugs were taken for at least 2 weeks before sleep recording in all subjects participating in the study.

PSG montage included at least three EEG channels—frontal (F3 or F4), central (C3 or C4) and occipital (O1 or O2) leads—referred to the contralateral mastoid, left and right electro-oculogram (EOG), chin electromyogram (EMG), electrocardiogram (ECG), electromyogram of left and right tibialis anterior muscles, oral and nasal airflow (thermistor), thoracic and abdominal respiratory effort (strain gauge) and oxygen saturation (pulse-oxymetry),

Table 1
Clinical characteristics of the three groups

	Age	Sex	MR	Diagnosis	Epilepsy	Drug therapy
AS patients						
1	4.05	F	Severe	AS (deletion)	FC	VPA
2	16.08	F	Severe	AS (deletion)	FC	VPA, CLB
3	4.01	M	Severe	AS (deletion)	ME	VPA
4	4.01	F	Moderate	AS (UBE3A mutation)	No	No
5	10.01	M	Severe	AS (deletion)	TCGS	VPA, CLN
6	4.01	M	Moderate	AS (UBE3A mutation)	FC	VPA
7	2	F	Not spec.	AS (deletion)	AE, ME	VPA; CLN
8	6.04	M	Severe	AS (deletion)	ME	VPA; DZP
9	2.9	F	Not spec.	AS (uniparental disomy)	ME	VPA
10	4.5	M	Moderate	AS (UBE3A mutation)	No	No
MRE+ patients						
11	6	F	Not spec.	Lafora disease	ME	No
12	4.07	F	Moderate	CP	PE	VPA
13	5.05	F	Severe	Not spec.	PE	VPA, PHE, ETS
14	8.03	M	Mild	CP	FC	VPA
15	9.01	F	Moderate	Not spec.	PE	VPA
16	7.07	M	Severe	CP, autism	TCGS	PHE, LTG
17	5.05	F	Not spec.	CP	PE	VPA
18	9.06	F	Mild	Not spec.	PE	VPA, PHE, ETS
19	9.01	M	Moderate	Not spec.	PE	VPA
21	3.25	M	Severe	CP	PE	TP
22	5.92	F	Severe	Rett syndrome	AE	VPA
23	7.25	F	Borderline	Not spec.	PE	VPA
24	9.02	M	Mild	Not spec.	PE	VPA
MRE− patients						
25	13.5	F	Severe	Down syndrome	–	–
26	7.5	F	Borderline	Not spec.	–	–
27	10	M	Borderline	Not spec.	–	–
28	7.01	M	Mild	ADHD, autism	–	–
29	10	F	Borderline	ADHD	–	–
30	9.58	M	Borderline	LD	–	–
31	6.92	F	Borderline	CP	–	–
32	5.92	M	Moderate	Opitz syndrome	–	–
33	4.58	M	Moderate	Autism	–	–
34	5.02	M	Severe	Y trisomy	–	–
35	2.92	F	Not spec.	CP	–	–
36	6.92	M	Borderline	ADHD	–	–
37	7.17	F	Borderline	ADHD, LD	–	–
38	14	M	Moderate	Congenital myotonic distrophy	–	–
39	3.08	M	Not spec.	Ataxia teleangectasia	–	–

ADHD, attention deficit hyperactivity disorder; CP, cerebral palsy; LD, learning disability; MRE+, mental retardation and epilepsy; MRE−, mental retardation without epilepsy; CBZ, clobazam; CLN, clonazepam; DZP, diazepam; ETS, etosuccimide; LTG, lamotrigine; PHE, phenobarbital; RPD, risperidone; VPA, valproic acid; TP, topiramate; AE, absence epilepsy; FC, febrile convulsions; ME, myoclonic epilepsy; PE, partial epilepsy; TCGS, tonic–clonic generalized seizure.

which were used to score sleep and evaluate sleep respiratory parameters and leg movements.

Recordings started at the patients' usual bedtime and continued until spontaneous awakening.

2.2.1. Sleep variables

In all subjects, sleep was subdivided into 30 s epochs and sleep stages were scored according to the standard criteria by Rechtschaffen and Kales (1968); for AS subjects, these criteria were slightly modified in order to take into account their specific EEG patterns (Miano et al., 2004). In fact, the presence of the characteristic high-amplitude potentials of AS throughout the entire recording and the reduced occurrence of K complexes, sleep spindles and rapid eye movements, caused some difficulties in scoring sleep by means of criteria arranged for normal subjects; however, we were able to score the different stages based on the following points:

1. Sleep stage 1 was detected when, after wakefulness or movement, the EMG tone was clearly diminished, movement artifacts were absent, and the EEG did not show sleep-specific patterns (such as spindles or K-complexes).
2. Sleep stage 2 was recognized because of the presence of sleep spindles and K-complexes, mostly during

the pauses between the different runs of high-amplitude slow waves.
3. Slow wave sleep (SWS) was characterized by the presence of subcontinuous high-amplitude slow-wave activity.
4. REM sleep was characterized by decreased EMG tone and presence of runs of high-amplitude slow waves, which showed duration and amplitude clearly smaller than during NREM sleep. Eye movements were difficult to recognize in all stages because of the presence of high-activity amplitude artifacts in the EOG tracings due to the scalp high-amplitude runs of slow activity.

The following conventional sleep parameters were evaluated:

- Time in bed (TIB).
- Total sleep time (TST): the time from sleep onset to the end of the final sleep epoch minus time awake.
- Sleep period time (SPT): time from sleep onset to sleep end.
- Sleep efficiency (SE): the percentage ratio between total sleep time and time in bed (SEI; TST/TIB*100).
- Sleep onset latency (SOL): time from lights out to sleep onset, defined as the first of two consecutive epochs of stage 1 sleep or one epoch of any other stage, in minutes.
- Wakefulness after sleep onset (WASO): the time spent awake between sleep onset and end of sleep.
- Total duration of stage 1, stage 2, stage 3, stage 4 NREM sleep and REM sleep.
- First REM Latency (FRL): time from sleep onset to the first REM epoch.
- Number of stage shifts/hour.
- Number of awakenings/hour.
- Number of movement time/hour (MT/h).

2.2.2. Respiratory parameters

Central, obstructive and mixed apnea events were counted according to the criteria established by the American Thoracic Society (1996):

- An obstructive apnea was defined as the absence of airflow, with continued chest wall and abdominal movement, for a duration of at least two breaths.
- A central apnea was defined as the absence of airflow with the cessation of respiratory effort, lasting more than 20 s and associated with bradicardia and desaturation; central apnea occurring after gross body movements or after sighs, was not considered as a pathological finding.
- A mixed apnea was defined as an apnea that usually begins as central and ends in obstruction, according to changes in the chest, abdominal, and flow traces.
- Hypopneas were defined as a decrease in nasal flow of at least 50% with a corresponding decrease in SpO2 of at least 4% and/or an arousal.
- The apnea/hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of TST.

We considered as clinically significant an AHI >5, according to the American Academy of Pediatrics (2002).

2.2.3. PLM parameters

Leg movements (LMs) during sleep were defined as an activation of the tibialis anterior muscles lasting between 0.5 and 5 s, with an amplitude higher than 25% of the EMG amplitude at maximal flexion of the foot, recorded during pre-sleep test period. PLMs were identified as sequences of 4 or more LMs, separated by at least 5 s and no more than 90 s, according to the American Sleep Disorders Association criteria (ASDA, 1993).

A PLM index (PLMI = number of PLMS per hour of sleep) higher than five was considered as clinically significant (Crabtree et al., 2003).

Sleep variables were recorded on a computerized sleep system and analyzed by means of the Hypnolab 1.2 sleep software analysis (SWS Soft, Italy). All the recordings were visually scored by one of the Authors (SM) and the sleep parameters derived were tabulated for the statistical analysis.

2.3. Statistical analysis

The statistical comparison between the sleep structure parameters obtained from the AS and mentally retarded patient groups was carried out by means of the one-way ANOVA; when this was significant, the Fisher LSD post-hoc test was computed in order to find significant differences between individual groups.

The commercially available Statistica software package (StatSoft, Inc., 2001. STATISTICA data analysis software system, version 6, www.statsoft.com) was used for this statistical analysis.

3. Results

3.1. Sleep parameters

Table 2 shows the statistical comparison between sleep parameters obtained in the three groups. Time in bed resulted significantly different mostly because of its longer duration in AS patients. Sleep period time and total sleep time were not significantly different in the three groups; on the contrary the percentage of wakefulness after sleep onset was increased in patients with AS, as a consequence sleep efficiency was significantly reduced in the same patients. Also the rate of awakenings per hour was higher in AS than

Table 2
Comparison of the sleep parameters in the three groups

	AS		MRE+		MRE−		One-way ANOVA	Fisher LSD Post hoc		
	Mean	SD	Mean	SD	Mean	SD	*p*	1 vs. 2	1 vs. 3	2 vs. 3
Age	5.8	4.23	6.8	2.02	7.6	3.31	NS			
TIB,m	659.1	175.01	646.2	71.87	560.3	84.43	0.05	–	0.04	–
SPT,m	548.6	197.57	549.8	82.05	519.4	88.52	NS	–	–	–
TST,m	391.3	133.75	459.9	132.32	478.5	72.18	NS	–	–	–
SOL,m	90.4	88.51	66.3	63.15	33.2	36.84	0.1>*P*0.05	–	–	-
FRL,m	228.9	203.42	152.3	135.99	102.03	72.96	0.1>*P*0.05	–	–	–
SS/h	15.3	7.19	10.8	6.17	12.8	3.71	NS	–	–	–
AWN/h	3.2	1.89	1.5	1.25	2.2	1.09	0.025	0.007	–	–
MT/h	0.8	0.53	0.5	0.51	0.9	0.63	NS	–	–	–
SE (%)	61.0	23.36	71.5	19.86	85.7	8.35	0.005	NS	0.0015	0.04
WASO (%)	27.5	22.84	15.9	21.36	7.4	5.12	0.03	NS	0.009	NS
S1 (%)	1.6	2.08	0.7	0.93	1.1	0.78	NS	–	–	–
S2 (%)	19.9	17.72	24.1	21.42	35.3	11.42	NS	–	–	–
S3 (%)	8.4	7.06	6.6	4.80	9.9	5.67	NS	–	–	–
S4 (%)	32.2	17.88	39.5	24.79	24.2	9.88	NS	–	–	–
SWS (%)	40.5	21.35	46.2	22.85	34.0	13.94	NS	–	–	–
REM (%)	10.4	6.45	13.2	7.79	22.2	8.44	0.0015	NS	0.001	0.0045
PLMI	9.9	10.77	5.3	5.57	4.6	2.96	NS	–	–	–
AHI	5.5	6.22	3.8	2.87	3.0	2.58	NS	–	–	–

TIB, time in bed; SPT, sleep period total; TST, total sleep time; SOL, sleep onset latency; FRL, first REM latency; SS/H, stage shifts per hour; AWN/h, awakenings per hour; MT/h, movement time/hour; SE, sleep efficiency; WASO, wakefulness after sleep onset; S1, stage 1; S2, stage 2; S3, stage 3; S4, stage 4; SWS, slow-wave sleep (S1+S2+S3+S4); REM, REM sleep; PLMI, periodic leg movement index; AHI, apnea-hypopnea index.

in MRE+ patients. REM sleep percentage was higher in MRE− patients than in the other two groups.

Sleep onset latency and REM latency tended to be longer in the group of subjects with AS than in the other two groups.

3.2. Sleep respiratory and PLM parameters

Table 2 also shows the statistical comparison between sleep respiratory and PLM variables obtained in the three groups. There is a tendency for AS subjects to present a higher PLMI than the other two groups. AHI >5 was found in 30% of AS subjects, in 30.8% of MRE+, and only in 20% of MRE− patients ($\chi^2=2.359$, NS); on the other hand, we found that 70% of AS patients, 38.5% of MRE+, and 46.7% of MRE− subjects had PLMI >5 ($\chi^2=3.088$, NS). Although this statistical analysis did not disclose significant differences in frequency of AHI >5 or PLMI >5 between the three groups, a clear tendency for patients with AS to show PLMI>5 could be seen. Fig. 1 shows the individual values of PLMI and AHI in the three groups of subjects and confirms the tendency described above.

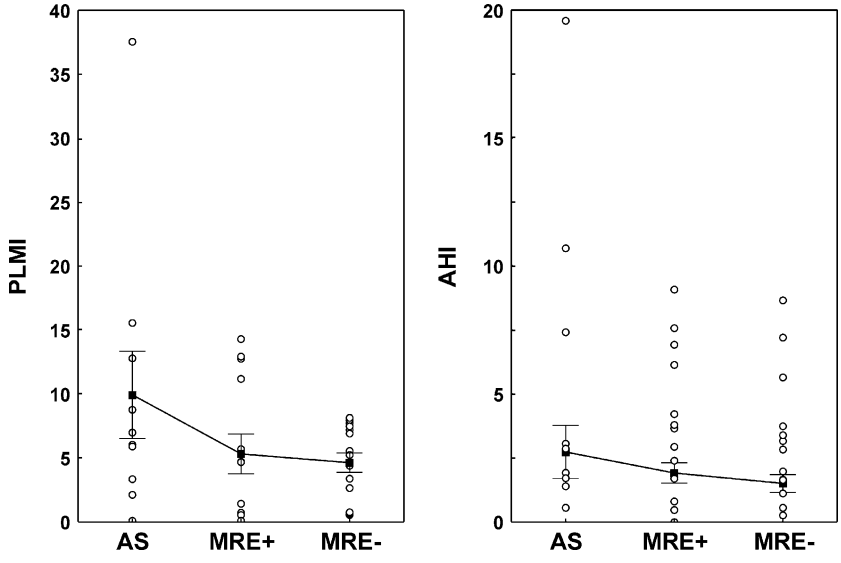

Fig. 1. Mean PLMI and AHI values for the three groups of subjects. Individual values are plotted together with the group mean (+SEM).

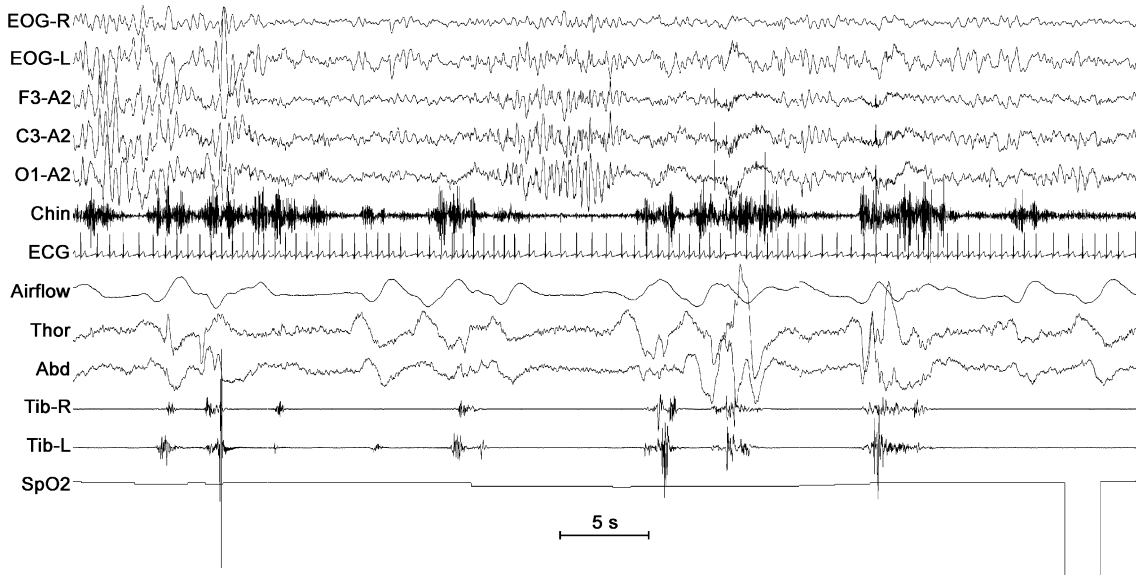

Fig. 2. PLM sequences in one patient with AS.

Fig. 2 shows an example of the relationship between the respiratory events and PLMs in a child with AS and Fig. 3 shows the hypnograms obtained in two patients with AS, one with PLMI >5 and another with PLMI <5.

Respiratory events were obstructive in most cases; central apneas were found only in one patient with MRE+ (non-specific mental retardation) and in one with MRE− who had both AHI >5 and cerebral palsy.

4. Discussion

The results of the analysis of the sleep macrostructure showed only few significant differences between children with AS and the other two groups of subjects: AS patients showed higher WASO% and sleep onset latency; this confirms our previous studies performed with sleep questionnaires and PSG (Bruni et al., 2004; Miano et al., 2004). The percentage of REM sleep was reduced in AS and in MRE+ subjects; this might suggest an important causative role for epileptiform discharges and antiepileptic drugs in the disruption of sleep continuity (Bruni et al., 1995; Lahorgue Nunes et al., 2003); however, we must admit that our MRE− subjects were affected by milder degrees of MR than the other two groups and this direct comparison needs to be performed with a group of subjects with comparable MR, for a confirmation of our results which should be considered with caution. It is also of interest that, recently, Kelly et al. (2004) have reported that antiepileptic drugs do not seem to induce deterioration of sleep after 18 months of therapy in a sample of mentally retarded people with epilepsy.

A recent review on the relationship between sleep and epilepsy suggested that symptoms of disturbed sleep, such as excessive daytime sleepiness, insomnia, or increased seizure frequency indicate an underlying sleep disorder rather than the effect of epilepsy or medication on sleep (Vaughn and D'Cruz, 2004). For this reason, sleep should be

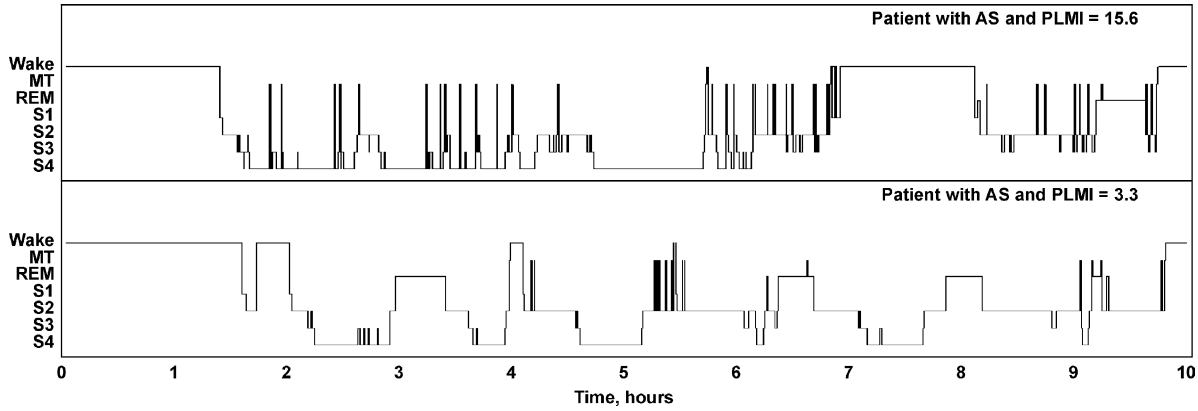

Fig. 3. Hypnograms obtained in two patients with AS, one with PLMI >5 (upper panel) and another with PLMI <5 (bottom panel).

carefully evaluated and sleep disturbances treated as an important part of the total care in most patients with epilepsy (Bazil, 2003).

In our study, we found a high frequency of sleep apneas and of PLMs during sleep, even if we did not compare our patients with normal age-matched controls. We found a high number of subjects with PLMI >5 in the AS group with a similar trend in the MR+E group, although not statistically significant. These results confirm our previous questionnaire-based findings of a high prevalence of SBD and PLMs in AS (Bruni et al., 2004) and allow us to hypothesize that epilepsy, rather than mental retardation by itself, might exacerbate these sleep disorders, even if statistical significance was not reached for the differences between the three groups. Also in this case, the differences between the groups should be considered with caution, because of the same reason introduced above.

The relationships between sleep breathing patterns, PLMs and epilepsy have been evaluated in different studies. Newell and Drake (1994) found that sleep apnea is infrequent in drug-free patients with complex partial seizures; but some patients may have exaggerated PLMs with arousals, possibly related to epileptiform discharges and perhaps exacerbated by medications. Malow et al. (1997) suggested that excessive sleepiness, a common complaint of epileptic patients frequently attributed to antiepileptic medication, might be linked to undiagnosed sleep disorders such as restless legs syndrome or sleep apnea. Manni et al. (2003) reported that older age at onset of seizures was significantly correlated with the presence of obstructive sleep apnea.

The treatment of sleep disorders such as breathing disorders or PLMs in epileptic subjects might reduce seizure frequency and improve daytime sleepiness (Bazil, 2003; Vaughn and D'Cruz, 2004) and we can expect the same in children with mental retardation and epilepsy.

The high number of subjects with PLMI >5 among our patients (70% of AS patients, 38.46% of MRE+, and 46.67% of MRE− subjects) suggests that mentally retarded people might be a population at risk to present important PLMs during sleep, higher than expected for their age; in fact, a PLMI >5 has been reported only in 11.9% of children recruited in a community survey (Crabtree et al., 2003).

The successful treatment with dopaminergic agents points to an impairment of the dopaminergic system in PLMs during sleep (Hening et al., 2004; Stiasny et al., 2002) and we can hypothesize the existence of a similar dysfunction in AS, in particular, where we found a very high incidence of PLMI >5.

Our results also show a relatively high prevalence of SBD in AS, similar to that reported in different genetic syndromes such as Down, Prader–Willi and craniofacial syndromes (Ferri et al., 1997, 1998; Harvey and Kennedy, 2002; Levanon et al., 1999; Manni et al., 2001; Pijpers et al., 2004; Richdale et al., 1999; Stores, 2001; Vgontzas et al., 1996; Zucconi and Bruni, 2001); on the contrary, the importance of PLMs during sleep in these syndromes is not known. The role of SBD associated to PLMs in sleep fragmentation and cognitive functioning involvement has been investigated only in children without mental retardation (Archbold et al., 2004; Chervin and Archbold, 2001; Chervin et al., 2003) in whom a disruption of executive functioning and impairment of attention has been found. Unfortunately, there is no data about the significance of SBD associated to PLMs in mentally retarded subjects and the impact on their cognitive functioning.

We have shown that SBD associated to PLMs represent an important issue in children affected by mental retardation, which might contribute to their cognitive impairment and to the worsening of life quality in this population. Therefore, our findings suggest the need to explore these sleep disorders in children affected by MR and to set up a correct treatment (i.e. evaluation of craniofacial characteristics, adentotonsillectomy, ventilatory therapy as Continuous Positive Airway Pressure, dopamine-agonist therapy of PLMs).

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