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Original Article

Sleep in Mowat-Wilson Syndrome: a clinical and video-polysomnographic study

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ABSTRACT

Objective: Sleep disturbances are frequently reported in Mowat-Wilson Syndrome (MWS). The current study aimed to evaluate clinical and video-polysomnographic (VPSG) characteristics of the sleep architecture and abnormal electroencephalogram (EEG) patterns during sleep in MWS.
Methods: Sixteen individuals with MWS (range 16 months–25 years), attending the Department of Child Neurology and Psychiatry of the University of Bologna, were included. The "Sleep Disturbances Scale for Children (SDSC)" questionnaire was administered to all parents of MWS patients, and all patients underwent a VPSG recording.
Results: The analysis of the SDSC questionnaire revealed disturbances mainly at the sleep–wake transition and in initiating and maintaining sleep. Evaluation of sleep structure in MWS patients showed a significant reduction of total sleep time, an increase of wake after sleep onset and arousal index as compared to normal controls. An EEG pattern characterized by slowing of background activity and poverty of physiological sleep characterisitcs was observed in all patients. Moreover, in patients aged >7 years, anteriorly predominant spike and waves were observed, markedly activated by sleep configuring a sub-continuous or continuous activity.
Conclusion: Our data (both clinical and VPSG) documented the presence of significant and clinically relevant sleep disturbances in MWS patients. Moreover, we identified a characteristic age-dependent sleep EEG pattern that could provide a new element to assist in the management of MWS.

1. Introduction

Mowat-Wilson syndrome (MWS) is a genetic disease caused by heterozygous mutations or deletions of *ZEB2*, associated with typical facial gestalt, moderate to severe Intellectual Disability (ID), epilepsy (80% of the patients) and multiple congenital malformations, including brain anomalies, Hirschsprung disease,

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genital anomalies, congenital heart defects and eye anomalies [1–4].

In 2013, we delineated the electroclinical phenotype of epilepsy in MWS [5]. It is usually characterized by atypical absence and focal (frontal lobe) seizures, mainly occurring during sleep. An age-dependent electroencephalographic (EEG) pattern was also observed: presence of normal EEGs or only mild slowing background at epilepsy onset and, later in the course of disease, the appearance of frequent diffuse frontal dominant spike and wave discharges during the awake state and a near to continuous spike and wave activity during slow sleep [5]. Recently, other authors reported three children with MWS who presented electrical status epilepticus during sleep (ESES) [6].

Sleep disturbances are a common concern for families of children with MWS. Evans et al., investigated sleep problems with the "Sleep Disturbance Scale for Children" (SDSC) questionnaire [7]; the SDSC suggested a high rate of sleep–wake transition disorders.

However, no systematic polysomnographic studies have been carried out in MWS. Here we report the clinical and video polysomnographic (VPSG) characteristics of 16 patients with MWS and characterize the abnormal sleep architecture and EEG patterns during sleep in relationship with age changes.

2. Methods

2.1. Participants

Sixteen individuals with genetically confirmed MWS (eight females and eight males, mean age nine years and seven months, range 16 months–25 years), attending the Department of Child Neurology and Psychiatry of the University of Bologna, were included in this prospective study. Participants were referred to our hospital by several Italian centers. In Table 1, the clinical features of our population are described. All patients had moderate to severe ID. Epilepsy was present in 11/16 patients (69%); all of them were on antiepileptic drugs (AEDs). All epileptic patients presented focal seizures, mainly sleep-related. Eight out of 11 patients also presented atypical absences.

Neuroimaging studies showed the typical features of MWS [8].

We divided the participants into two subgroups, depending on age: subgroup A aged 16 months-four years and six months (patients 1–5; two females and three males) and subgroup B aged seven years and four months– 25 years (patients 6–16; six females and five males).

The local ethics committee approved the study (protocol MWS_EEG 326/2017/O/Oss). Informed consent was obtained from the parents of all patients included in the study.

2.2. Control children

The VPSG data of all MWS patients and the two subgroups were compared, respectively, with those of a control group of 15 subjects (1–18 years) and with the same controls matched for age (five subjects for subgroup A, range 1–5 years and ten subjects for subgroup B, range 8–18 years). All subjects in the control group had negative anamnesis for neurological disorders, ID and sleep problems.

2.3. Procedure

2.3.1. Questionnaire

The "Sleep Disturbances Scale for Children (SDSC)" questionnaire was administered to all parents of MWS patients. SDSC consisted of 26 items in a Likert-type scale with values 1–5 (1 = never; 2 = occasionally; 3 = sometimes; 4 = often; 5 = always), arranged so that higher numerical values reflected a greater clinical severity of symptoms [9]. The scale yields six factor scores (Disorders of initiating and maintaining sleep, Sleep breathing disorders, Disorders of arousal, Sleep-wake transition disorders, Disorders of excessive daytime somnolence and Sleep hyperhidrosis) and a total score.

For each factor, we calculated the percentage of patients with MWS falling into the normal (scores under 50), borderline (scores between 50 and 70) and clinical disorder (scores above 70) range.

2.3.2. Video-polysomnography

All patients underwent a full-night video-EEG-polysomnography in our sleep laboratory. Polysomnography included 19 EEG channels, left and right electrooculogram (EOG), the chin electromyography, electrocardiogram and the respiratory signals (airflow, movements of the chest wall and abdomen, O2 saturation of arterial blood).

Recording started at the patient's usual bedtime and continued until spontaneous awakening.

2.3.3. Sleep analysis

Sleep was subdivided into 30-s epochs and scored according to the standard criteria of the American Academy of Sleep Medicine [10].

We calculated the following polysomnographic variables: time in bed (TIB), sleep period time (SPT; time from sleep onset to sleep end), total sleep time (TST; SPT minus time spent in sleep after sleep onset), sleep efficiency index (TST/TIB*100), sleep onset latency (SOL; time from lights out to sleep onset, defined as the first any sleep stage epoch in minutes), first REM latency (FRL), minutes and percentage of wake after sleep onset (WASO), minutes spent in each stage and percentage relative to TST, number of arousals/hour, number of awakenings/hour, number of apneas-hypopneas/hour (AHI).

2.3.4. EEG pattern analysis

For each patient, we analyzed the EEG pattern, and we calculated the spike-and-wave during overnight sleep by using the spike-and-wave index (SWI). This index was obtained as the total number of minutes of all spike-and wave abnormalities divided by the total number of minutes of non-rapid eye movement (NREM) sleep and multiplied by 100 [11]. SWI was considered significant for ESES pattern when >85%.

2.3.5. Statistical analysis

For the VPSG and EEG studies, the comparisons between sleep parameters obtained in patients with MWS vs. normal controls were conducted using the nonparametric Mann–Whitney U test for independent data sets.

3. Results

3.1. Questionnaire

Parental reports showed that 62% of patients fell into the clinical disorder range in "sleep–wake transition disorders" sub-scale and 50% in "disorders of initiating and maintaining sleep" sub-scale while 12.5% fell into the borderline range in both sub-scales. Regarding the remaining sub-scales, only two patients reached pathological range in the "Sleep breathing disorders" sub-scale and one in "Disorders of arousal". No clinical disorder nor borderline range were observed in "Disorders of excessive daytime somnolence" and "Sleep hyperhidrosis" sub-scales.

Table 1
Clinical features and sleep EEG pattern of our population.

Patient	Age/sex	*ZEB2* Variant[a]	Seizure Type	NREM sleep EEG	REM sleep EEG	Spindles/K complexes	SW index
1	18 m/M	c.714_716delG p.E239Rfs*23 frameshift mutation	None	Slow high-voltage waves, no epileptiform abnormalities	Asymmetrical theta-delta waves in the occipital region, no epileptiform abnormalities	Present	<50%
2	2 ys/F	c.1052_1057delGTTCTTinsTCCTC p.G351Vfs*19 frameshift mutation	None	Slow high-voltage waves, sporadic central spike, more represented in the first cycle of sleep	Asymmetrical theta waves in the occipital region, no epileptiform abnormalities	Present, particularly in the second part of the night	<50%
3	2 ys 4 m/M	c.2718delT p.A907Lfs*24 frameshift mutation	None	Slow high-voltage waves, sporadic central-parietal SW, more represented in the first cycle of sleep	Asymmetrical theta waves in the occipital region, Sporadic SW in some epochs	Present, particularly in the second part of the night	<50%
4	4 ys 4 m/F	large deletion affecting all exons	None	Slow high-voltage waves, theta activity in the right temporoparietal region, frontal SW, more represented in the first cycle of sleep	Asymmetrical theta waves in the occipital region, no epileptiform abnormalities	Present	<50%
5	4 ys 6 m/M	c.2053C > 7 p.Q685* nonsense mutation	None	Slow high-voltage waves, sporadic fronto-central SW, more represented in the first cycle of sleep	Asymmetrical theta-delta waves in the occipital region Sporadic SW in some epochs	Present	<50%
6	7 ys 4 m/F	c.274G > T p.G92* nonsense mutation	FS, AA	Sub-continuous/ continuous diffuse frontal dominant discharges of high-voltage SW	Asymmetrical theta waves in the occipital region, Sporadic SW in some epochs	Sporadic	>85%
7	7 ys 10 m/F	c.274G > T p.G92* nonsense mutation	FS, AA	Sub-continuous fronto-central dominant discharges of high voltage SW, more represented in the first cycle of sleep	Persistence of recurrent SW in some epochs	Sporadic	50–85%
8	9 ys 4 m/M	c.2254dupA p.Y752Nfs*4 frameshift mutation	FS, AA	Sub-continuous frontal dominant discharges of high voltage SW, more represented in the first cycle of sleep	Persistence of recurrent SW in some epochs	Sporadic	50–85%
9	9 ys 6 m/F	c.477_484delTGCAGTCA p.H159Qfs*10 frameshift mutation	FS, AA	Sub-continuous/ continuous diffuse frontal dominant discharges of high-voltage SW	Persistence of sub-continuous SW in some epochs	Sporadic	>85%
10	10 ys 6 m/F	c.310C > T p.Q104* nonsense mutation	FS, AA	Sub-continuous frontal dominant discharges of high voltage SW, more represented in the first cycle of sleep	Asymmetrical theta waves in the occipital region Persistence of recurrent SW in some epochs	Present	50–85%
11	11 ys 5 m/M	c.2701C > T p.Q901* nonsense mutation	FS, AA	A recurrent spike in centro-parietal and diffuse frontal dominant discharges of high-voltage SW, more represented in the first cycle of sleep	Persistence of sub-continuous SW in some epochs	Sporadic	50–85%
12	11 ys 7 m/M	Large deletion affecting all exons	FS	Sub-continuous fronto-central dominant discharges of high voltage SW, more represented in the first cycle of sleep	Sporadic SW in some epochs	Present	50–85%
13	12 ys 3 m/M	c.625C > T p.Q209* nonsense mutation	FS, AA	Sub-continuous/ continuous diffuse frontal dominant discharges of high-voltage SW	Persistence of recurrent SW in some epochs	Sporadic	50–85%

Table 1 (*continued*)

Patient	Age/sex	*ZEB2* Variant[a]	Seizure Type	NREM sleep EEG	REM sleep EEG	Spindles/K complexes	SW index
14	13 ys 7 m/F	c.2083C > T p.R695* nonsense mutation	FS, Myoclonic	Sub-continuous fronto-central dominant discharges of high voltage SW + focal slow activity	No epileptiform abnormalities	Sporadic	50–85%
15	15 ys 9 m/F	large deletion affecting all exons	FS, AA	Diffuse frontal dominant discharges of high voltage spikes	Persistence of frequent SW in some epochs	Sporadic	50%
16	25 ys/M	c.2083C > T p.R695* nonsense mutation	FS	Diffuse temporo-parietal dominant discharges of high-voltage SW	No registration of REM	Rare	<50%

[a] All variants are heterozygous; positions refer to transcript NM_014795/protein NP_055610; FS: focal seizure; AA: atypical absence.

Table 2
Sleep parameters and statistical comparison between all MWS patients and normal controls.

	MWS (n = 15)		Controls (n = 15)		Mann–Whitney	
	Mean	SD	Mean	SD		p
TIB min	472.6	104.44	542.6	72.17	ns	0.053
SPT min	449.06	113.12	526.2	68.88	s	0.04*
TST min	365.46	124.2	503.2	64.35	s	0.001*
Sleep efficiency %	76.15	18.31	93.15	3.68	ns	0.44
SOL min	12.06	16.06	7.39	4.65	ns	0.43
FRL min	82.16	31.11	82.37	48.7	ns	0.88
WASO (%SPT)	19.72	17.4	4.18	4.06	s	0.009*
N1 (%TST)	5.98	3.49	4.7	2.94	ns	0.8
N2 (%TST)	31.81	8.56	50.29	7.72	ns	0.11
N3 (%TST)	42.81	13.81	16.64	3.73	s	0.01
REM (%TST)	19.39	10.65	28.39	5.87	ns	0.25
Arousal index (n/h TST)	9.69	5.23	5.45	2.77	s	0.04*
Awakenings index (n/h SPT)	2.5	1.68	1.01	0.77	ns	0.75
AHI	0.5	0.4	0.5	0.4	ns	1

* Significant p-value.

3.2. Video-polysomnography: sleep architecture

Table 2 shows the sleep parameters (mean and standard deviation) of MWS patients of all ages and controls. On average, MWS patients displayed a statistically significant reduction of TST with a significant increase of WASO. Compared to controls, the percentage of stage N3 and the arousal index were significantly increased. We did not observe any difference in AHI between patients and controls.

Tables 3 and 4 show the sleep parameters (mean and standard deviation) of MWS patients subgroup A and subgroup B in comparison to age-matched controls. In both groups, we observed a significant decrease of TST and increase of WASO (especially in subgroup B). In subgroup A, the arousal index was significantly higher than in controls; in subgroup B, the N3 stage was significantly increased.

3.3. Video-polysomnography: sleep EEG pattern

In all patients, the EEG background activity during NREM sleep was characterized by high voltage delta waves (predominantly in the frontal regions).

In younger patients (subgroup A), we observed only isolated focal spikes slightly activated by sleep. Spindles were generally present (Table 1).

In patients older than seven years (subgroup B), sleep EEGs showed very frequent diffuse frontal dominant discharges of high-voltage spike-waves (Table 1). During the first sleep cycle, we observed a continuous epileptiform activity in NREM stages in most

Table 3
Sleep parameters and statistical comparison between MWS subgroup A and normal controls.

	MWS (Subgroup A) 16 m –4 ys 6 m (n = 5)		Controls 1-5 ys (n = 5)		Mann–Whitney	
	Mean	SD	Mean	SD		p
TIB min	467	173.22	561	48.66	ns	0.4
SPT min	436.2	171.64	540.4	44.33	ns	0.29
TST min	354.6	142.84	515.8	50.85	s	0.03*
Sleep efficiency %	76.06	12.21	92.76	5.65	ns	0.54
SOL min	12.08	13.13	7.1	0.56	ns	0.35
FRL min	60	23.43	80.3	47.12	ns	1
WASO (%SPT)	17.44	12	4.32	6.6	ns	0.12
N1 (%TST)	7.36	4.59	4.92	3.31	ns	0.87
N2(%TST)	29.8	6.71	49.08	6.55	ns	0.49
N3 (%TST)	37.48	13.83	16.36	2.3	ns	0.15
REM (%TST)	25.38	13.32	29.68	3.37	ns	0.88
Arousal index (n/h TST)	13.96	3.83	4.87	1.43	s	0.04*
Awakenings index (n/h SPT)	2.8	1.9	0.54	0.45	ns	0.81
AHI	0.3	0.29	0.4	0.2	ns	0.97

* Significant p-value.

Table 4
Sleep parameters and statistical comparison between MWS subgroup B and normal controls.

	MWS (Subgroup B) 7 ys 4 m-15 ys 9 m (n = 10)		Controls 8-18 ys (n = 10)		Mann–Whitney	
	Mean	SD	Mean	SD		p
TIB min	475.4	60.05	533.4	82.3	ns	0.14
SPT min	455.5	81.7	519.1	79.6	ns	0.14
TST min	370.9	121.78	496.9	71.8	s	0.01*
Sleep efficiency %	76.2	21.33	93.3	2.6	ns	0.7
SOL min	12.05	18.02	7.4	5.1	ns	0.7
FRL min	93.25	29.2	83.4	51.9	ns	0.8
WASO (%SPT)	20.87	19.97	4.1	2.5	s	0.05
N1(%TST)	5.21	2.74	4.59	2.9	ns	0.81
N2 (%TST)	32.81	9.52	50.9	8.5	ns	0.13
N3 (%TST)	45.77	13.67	16.78	4.38	s	0.04*
REM (%TST)	16.39	8.23	27.75	6.86	ns	0.19
Arousal index (n/h TST)	7.98	4.82	4.4	1.56	ns	0.52
Awakenings index (n/h SPT)	2.35	1.65	1.2	0.8	ns	0.87
AHI	0.64	0.51	0.5	0.4	ns	1

* Significant p-value.

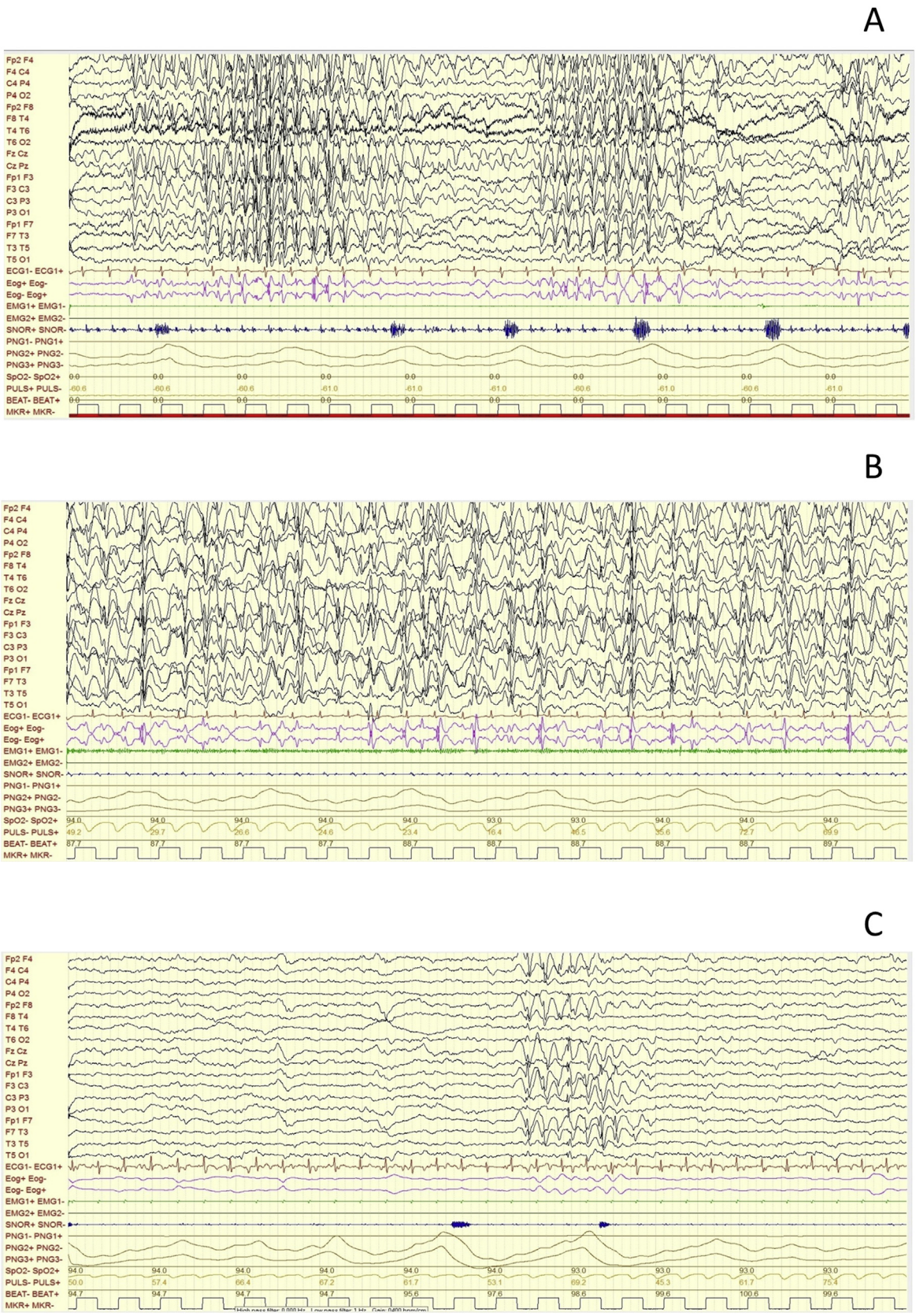

Fig. 1. EEG patterns during different sleep stages. Description: Patient 8, nine years old: during drowsiness frequent generalized discharges of high voltage SW are observed (A); during NREM sleep sub-continuous frontal dominant discharges of high voltage SW are recorded (B); during REM sleep persistence of asymmetrical recurrent SW discharges is observed (C).

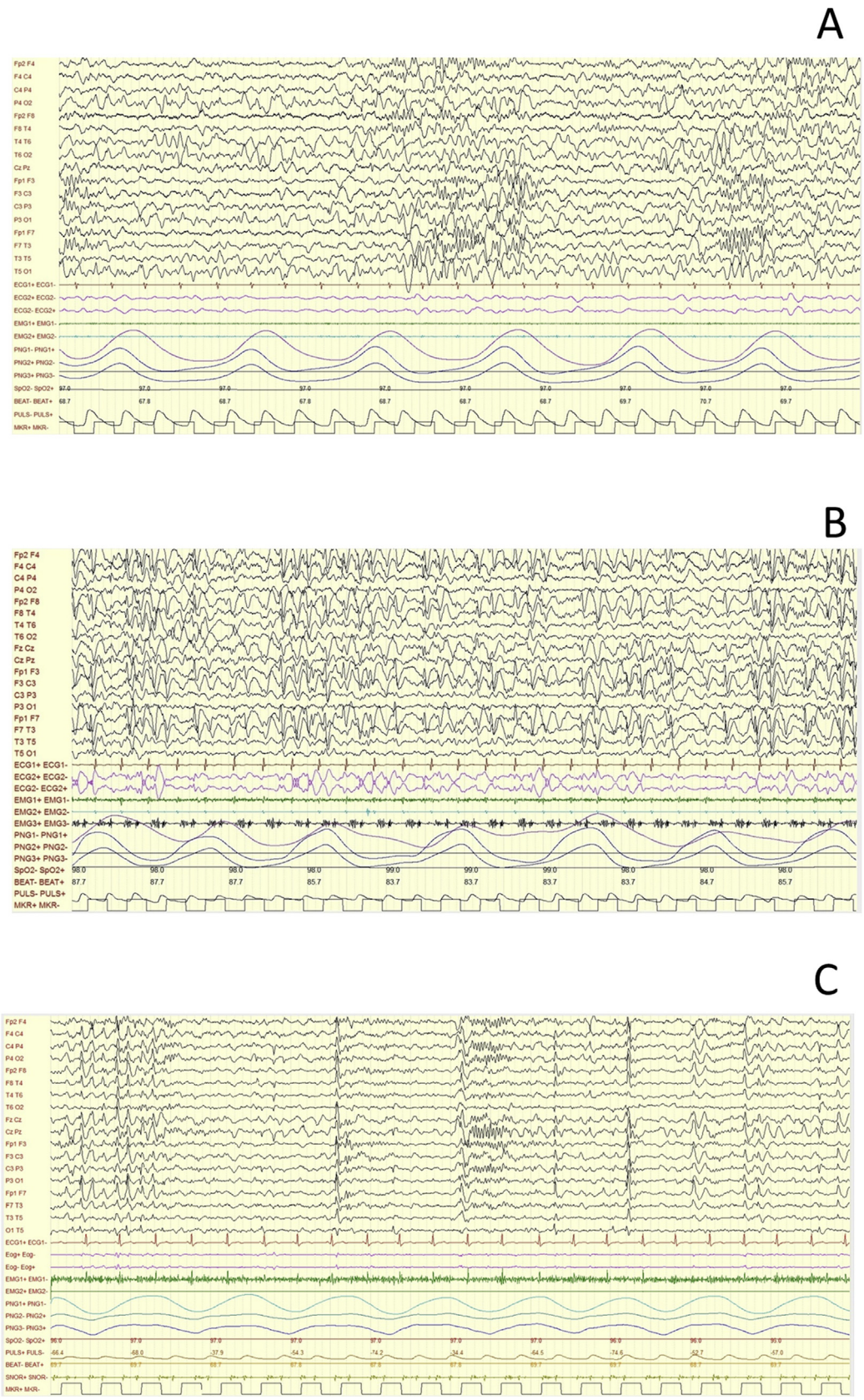

Fig. 2. NREM sleep EEG patterns at different ages. Description: (A) Patient 3, two years old, no epileptiform abnormalities, sleep spindles (asymmetric) are present; (B) Patient 9, nine years old, continuous frontal dominant discharges of high voltage SW are observed; (C) Patient 15, 15 years old, less frequent diffuse frontal dominant discharges of high voltage spikes and sporadic K complexes and sleep spindles are recorded.

patients. The frequency of spike-and-waves decreased during subsequent sleep cycles, and in only two patients the overnight SWI was >85%, configuring an ESES pattern. During REM sleep spike-and-waves frequency was <50% (Fig. 1).

In the two patients older than 14 years we observed the persistence of epileptiform activity in NREM sleep, although less frequent. Fig. 2 shows NREM sleep EEG patterns at different ages. We recorded only one focal seizure during sleep, characterized by sudden awakening and right head deviation. Ictal EEG showed rhythmic focal spikes in right temporal and parietal regions.

Physiological sleep characteristics such as sleep spindles and K-complexes are rare in this group of patients.

4. Discussion

This study represents the first attempt to objectively evaluate the sleep pattern of MWS patients by a clinical study with the administration of a sleep disturbance questionnaire and a video-polysomnographic study.

The analysis of the "Sleep Disturbances Scale for Children" questionnaire revealed disturbances mainly at the sleep–wake transition and in initiating and maintaining sleep. A previous questionnaire-based study on sleep in MWS patients showed similar results [7]. Moreover, difficulty in settling at night and nocturnal awakenings are observed in other genetic syndromes with a neurodevelopmental disability, such as Angelman syndrome [12–14].

The results of the polysomnography in our patients more precisely defined sleep disturbances in MWS and correlated well with the results of the questionnaire. Analyzing sleep structure, we found significant differences between the sleep parameters of MWS children and controls, and specifically a significant reduction of TST and an increase of WASO and arousal index, which could be interpreted as signs of disturbed sleep, confirming the data of the SDSC questionnaire. Also, we observed a significant increase in the N3 stage percentage in MWS children >7 years old, probably due to the slowing of EEG background activity typical of this syndrome, and as described for other genetic syndromes [13].

All these data suggest that sleep disturbances in MWS are not related to age but instead are an intrinsic feature of this syndrome: the same alterations were observed in both age subgroups, except for the increase in the arousal index which, in the older group, didn't reach statistical significance, possibly due to small sample size. In the same way, sleep does not seem to be influenced by the frequency of EEG or respiratory abnormalities, as shown by the AHI, or by the motor disturbances. Although we could not use tibial EMG due to insufficient collaboration by MWS children, the videos were analyzed and helped us to exclude the presence of motor disturbances.

Because of the sleep fragmentation confirmed by VPSG, we suggest the possible administration of medications such as melatonin, niaprazine or benzodiazepines, to improve sleep in MWS. In children with neurodevelopmental disabilities, poor sleep can result in additional learning and behavioral problems [14]. Based on our results, potential sleep problems should be investigated by physicians involved in the management of these children.

Also, given the good correlation between the questionnaire and the video-polysomnographic study, we would consider the SDSC questionnaire an effective instrument to monitor and evaluate sleep in MWS.

On the other hand, EEG pattern analysis revealed a clear age-dependent sleep EEG pattern in MWS patients, characterized in the first years of life by delta waves of background activity during sleep with a slight representation of spindles and K-complex, mainly in the first part of the night, and isolated focal spikes slightly activated by sleep. In older children, NREM EEG was characterized by sub-continuous or continuous diffuse frontally dominant discharges of high voltage spike-waves, particularly in the first cycle of sleep. Nevertheless, we observed an ESES pattern with SW index >85% in only 2/16 patients (12,5%). Other authors reported the presence of an anterior ESES pattern in MWS in a much higher percentage, although they had a smaller number of patients (3/5 patients) [6]. In our population, we did not find a direct correlation between EEG pattern and sleep disturbances, not even for patients with an SW index>85%. Further studies are needed to better understand the potential role of sleep EEG epileptiform abnormalities in cognitive performances of children with MWS. However, the data of the present study underline the presence of an electroclinical age-dependent phenotype typical of MWS, as we described in a previous study of epilepsy in MWS [5]. This pattern, in our opinion, could be ascribable to the intrinsic molecular defect rather than a structural cause, as well as for the presence of different neuroimaging findings [8]. This hypothesis is supported by studies on *ZEB2*'s role in the neurogenesis of GABAergic interneurons: in conditional mouse models, the lack of a *ZEB2* expression caused an incorrect migration of GABAergic interneurons in the striatal zone rather than in the cortical one, leading to a lack of adequate inhibition of cortical electrical activity [15,16]. A GABAergic mechanism for sleep-related EEG abnormalities was also proposed for other genetic syndromes with epilepsy and neurodevelopmental disability, such as Angelman syndrome [13]. Moreover, *Zeb2* is crucial for the formation of intracortical, intercortical and cortico-subcortical connections [17]. Alterations of brain connectivity could explain, at least in part, sleep disturbances observed in MWS individuals.

We should point out a limitation of the current study: the group we studied does not include individuals between age four and six months and age seven and four months. Therefore, our results do not extend to this unrepresented age group.

In conclusion, this is the first study which objectively reports sleep disorders in MWS using VPSG. Our data (both clinical and VPSG) document the presence of significant and clinically relevant sleep disturbances. Based on our results, we suggest the use of the SDSC questionnaire to monitor and evaluate sleep in individuals with MWS and to perform VPSG for a better definition of sleep disturbances. Physicians should always investigate sleep problems in these individuals and where indicated they should consider medication.

Moreover, the identification of a characteristic sleep EEG pattern, as already described in other genetic syndromes, could provide a new element to assist in the management of MWS.

Finally, all data revealed by our study could open new scientific research leads, to improve the management approaches and the sleep quality of individuals with MWS.

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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.2019.04.011.

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