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ORIGINAL ARTICLE

Polysomnographic findings in Rett syndrome: a case–control study

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Abstract
Purpose Rett syndrome is a severe neurodevelopmental disorder mainly affecting females and usually linked to mutations in the methyl-CpG-binding protein 2 gene, with an estimated prevalence of 1 in 10,000 live female births. Clinical features which usually become more apparent over time include breathing dysfunction, seizures, spasticity, peripheral vasomotor disturbance, scoliosis, growth retardation, and hypotrophic feet, with a great variety of presentations. The clear immaturity in brainstem mechanisms is expressed by the presence of early sleep disorders such as nocturnal awakenings, bruxism, and difficulty falling asleep, and no conclusive findings were derived from the few polysomnographic studies about the sleep macrostructural aspects. The aim of this study is to analyze the sleep macrostructural parameters, the nocturnal respiratory characteristic, and the presence of periodic limb movements in a sample of children affected by Rett syndrome.
Materials Thirteen Rett subjects underwent a polysomnographic study, and the findings were compared with those obtained by a group of 40 healthy children.
Results The Rett group shows a great impairment in sleep macrostructural and respiratory parameters, with a higher percentage of pathological periodic limb movements than the controls.
Conclusions This study may be considered a report about the ventilatory impairment during sleep in Rett syndrome and the first approach to the macrostructural aspects of sleep supported by the PSG data that could be considered mandatory for a better comprehension of this very complex syndrome.

Keywords Rett syndrome · Polysomnography · Central sleep apnoea · Obstructive sleep apnoea · Periodic limb movements

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Introduction

In 1966, Andreas Rett first described 22 young girls relentlessly wringing their hands as they sat in the laps of their respective mothers, reporting for the first time a unique clinical entity that now bears his name [1]. Rett syndrome (RTT) is a severe neurodevelopmental disorder mainly affecting females and usually linked to mutations in the methyl-CpG-binding protein 2 gene (MeCP2) [2], with an estimated prevalence of 1 in 10,000 live female births.

Clinically, the RTT is characterized by loss of hand and communication skills between 6 and 30 months; psychomotor retardation, acquisition of stereotypical hand movements, gait or truncal apraxia between 1 and 4 years, and deceleration in head growth. The first 6 months often seem to be asymptomatic, although there is evidence that there may be subtle abnormalities of movements, hand postures, and body behaviors [3–5].

Clinical features which usually become more apparent over time include breathing dysfunction, seizures, spasticity, peripheral vasomotor disturbance, scoliosis, growth retardation,

and hypotrophic feet, with a great variety of presentations [5], and rarely, males have been reported with the Rett-like phenotype [2].

The RTT subjects tend to present many abnormalities in the electroencephalogram (EEG) (i.e., multifocal and generalized epileptiform discharges) and the occurrence of rhythmic slow theta activity, all effects of an altered cortical excitability. However, the EEG patterns cannot be diagnostic of RTT, particularly because they vary between patients and at different stages of the disorder [6].

Moreover, the usual report of abnormalities in cardiac and respiratory patterns and the low level of cardiovascular parasympathetic activity indicate an intrinsic brainstem immaturity [7]. A recent study has also shown that the expression of the MeCP2 protein is severely deficient in the brainstem of Rett patients indicating immaturity of the brainstem as expression of MeCP2 protein normally increases as neurons mature [8]. The maturity of the brainstem in Rett indicated by tritiated lysergic acid diethylamide-binding studies [9] is very similar to the maturity age given by the level of cardiovascular parasympathetic activity [7].

This clear immaturity in brainstem mechanisms is expressed by the presence of early sleep disorders such as nocturnal awakenings, bruxism, and difficulty falling asleep [10–13], and no conclusive findings were derived from the few polysomnographic studies about the sleep macrostructural aspects [14, 15]. The aim of this study is to analyze the sleep macrostructural parameters, the nocturnal respiratory characteristic, and the presence of periodic limb movements in a sample of children affected by Rett syndrome.

Materials and methods

For this study, 13 Rett subjects (mean age, 8.08; SD±1.41) and 40 healthy children (mean age, 8.15; SD±1.03; p= 0.847) underwent an overnight polysomnography (PSG) recording in the Sleep Laboratory of the Clinic of Child and Adolescent Neuropsychiatry of the Second University of Naples and in the Sleep Laboratory of the Oasi Institute of Troina, after one adaptation night, in order to avoid the first-night effect. All RTT subjects involved in this study present the classical phenotype at III or IV clinical stage.

The Departmental Ethical Committee of the Second University of Naples approved the study. Informed consent was obtained by parents. The reported investigation has been carried out in accordance with the principles of The Declaration of Helsinki, as revised in 2000.

Polysomnographic evaluation

The EEG recordings and electrode placement were performed according to the 10–20 system [16], and the PSG montage included at least eight EEG channels (F3, F4, C3, C4, T3, T4, O1, and O2) referenced to the contralateral mastoid, left and right electrooculogram, chin electromyogram (EMG), left and right tibialis EMG, electrocardiogram (one derivation), nasal cannula, thorax and abdominal effort, peripheral oxygen saturation, pulse and position sensors [17].

Recordings were carried out using a Brain Quick Micromed System 98 recording machine, and signals were sampled at 256 Hz and stored on hard disk for further analysis. EEG signals were digitally band-pass filtered at 0.1–120 Hz, 12-bit A/D precision.

The presence of the high-amplitude potentials composed by complexes of sharp waves or spikes and slow waves' activity and the eventual 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, then according to Miano et al. [18]; similarly, we scored 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 artefacts 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, even during the pauses between the different runs of epileptiform discharges.
3. SWS was also defined when composed mostly by subcontinuous sharp wave or spike–slow-wave complexes.
4. REM sleep was characterized by decreased EMG tone with shorter epileptiform discharge duration and lower frequency than during NREM sleep.

Then, the following conventional sleep parameters were evaluated:

- Time in bed (TIB).
- Sleep period time (SPT): time from sleep onset to sleep end.
- Total sleep time (TST): the time from sleep onset to the end of the final sleep epoch minus time awake.
- Sleep latency: time from lights out to sleep onset, defined as the first of two consecutive epochs of sleep stage 1 or one epoch of any other stage, in minutes.
- REM latency: time from sleep onset to the first REM sleep epoch.
- Number of stage shifts/hour (SS/h).
- Number of awakenings/hour.
- Sleep efficiency (SE%): the percentage ratio between total sleep time and time in bed (TST/TIB×100).
- Percentage of SPT spent in wakefulness after sleep onset (WASO%), i.e., the time spent awake between sleep onset and end of sleep.
- Percentage of SPT spent in sleep stages 1, 2, slow-wave sleep (SWS%), and REM sleep (REM%).

All recordings started at the subject's usual bedtime and continued until spontaneous morning awakening. Sleep was subdivided into 30-s epochs, and sleep stages were scored according to the standard criteria [17] and analyzed by means of Hypnolab 1.2 sleep software analysis (SWS Soft, Italy). All the recordings were visually scored by one of the investigators (MC), and the sleep parameters derived were tabulated for statistical analysis.

Respiratory events

Central, obstructive, and mixed apneic events were counted according to the criteria established by the American Thoracic Society [19]:

- 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 at least two respiratory cycles.
- 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.
- The apnea index was defined as the number of apneas per hour of TST.
- Hypopneas were defined as a decrease in nasal flow of at least 50% with a corresponding decrease in SpO_2 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.
- The mean oxygen saturation, as measured by pulse oximetry (SpO_2), together with SpO_2 nadir, was determined.
- Desaturation events were considered if there was more than a 4% decrease in the oxygen saturation level, according to the American Thoracic Society [19], and the oxygen desaturation index (ODI) was computed (number of desaturation events per hour of sleep).
- Central apneas were taken into account if lasting more than 20 s and associated with bradycardia and desaturation. Central apnea, which occurred after gross body movements or after sighs, was not considered as a pathological finding.

According to Miano et al. [18] we take into account as pathologic an AHI>5.

Analysis of LM activity

The periodic limb movement (PLM) index was calculated as the number of LMs included in a series of four of more, separated by more than five and less than 90 s, per hour of sleep [20, 21]. A PLM index (number of PLMS per hour of sleep) higher than five was considered as clinically significant [22, 23].

Statistical analysis

The comparisons between sleep, respiratory (CAI, OAI, HI, AHI, ODI, and mean oxygen saturation percentage) and PLM % between Rett subjects and normal controls were carried out by means of the nonparametric Mann–Whitney *U* test. Differences were considered as statistically significant at $p<0.05$.

The statistical power was calculated with the online software http://www.dssresearch.com/toolkit/spcalc/power_a2.asp. The alpha error level of confidence interval was 5%.

Bonferroni correction was applied. *P* values <0.05 were considered statistically significant. The commercially available software STATISTICA (data analysis software system), version 6, StatSoft, Inc. (2001) was used for all statistical tests.

Results

The study population and the control group did not differ for age ($p=0.160$). Table 1 shows the comparisons of macrostructural sleep parameters between children with Rett syndrome and normal controls. No differences between the two groups were found among the TIB, SPT, and TST.

Children with Rett syndrome have an increased rate of SS/h ($p=0.0013$) and of awakenings per hour ($p=0.000$), and WASO% ($p=0.000998$). No differences among the stage percentage distribution were found, except for SWS % and REM% ($p=0.003273$ and $p=0.000149$) that was higher and lower than control, respectively.

About the respiratory parameters, Rett subjects present a slight increase in all the parameters with respect to the control group as shown in Table 1, for the mean oxygen saturation (93.6608±2.16734 vs. 96.67±1.01; $p<0.001$) and for PLM (9.5185±1.89454 vs. 2.81±1.0982; $p<0.001$). The statistical power showed the following values: 99.9% for SS/h, 85% for awakenings per hour, 87% for SE%, 85.8% for WASO%, and 100% for REM%. Among the respiratory parameters, the statistical power was: 100% for obstructive apnea index per hour (OAI), 100% for central apnea index per hour (CAI), 90.8% for hypopnea index per hour (HI), 100% for apnea/hypopnea index per hour (AHI), 95.1% for the oxygen desaturation index hour (ODI/h), and 99.3% for the mean oxygen saturation percentage. For the PLM%, the statistical power showed a value of 100%.

Discussion

RTT can be considered as unique among genetic, chromosomal, and other developmental disorders because of its usually

Table 1 Comparison between sleep scoring parameters found in children with Rett syndrome and in control subjects

	Rett, *N=3*		Control, *N=40*		Mann–Whitney	
	Mean	SD	Mean	SD	*U*	*p*
TIB (min)	591.5231	63.10771	585.7750	83.61189	220.5000	NS
SPT (min)	562.1154	64.63778	558.0750	85.45036	216.5000	NS
TST (min)	502.1692	83.12539	531.0625	79.97076	215.0000	NS
SOL (min)	15.4154	12.13005	19.7625	14.29721	215.5000	NS
FRL (min)	147.9000	60.04176	120.3625	45.75968	184.0000	NS
SS/h	12.9385	2.99125	8.2200	3.51161	83.5000	0.0013
AWN/h	6.3308	2.97220	1.8700	1.75969	49.5000	0.000000
SE (%)	84.7245	8.69177	90.7300	5.14548	139.0000	NS
WASO (%)	13.2226	9.53861	4.6900	4.42550	98.0000	0.000998
S1 (%)	0.8796	1.38641	3.1175	3.82776	82.0000	NS
S2 (%)	30.1054	8.39295	45.4325	27.70823	97.0000	NS
SWS (%)	43.2735	13.69332	28.9800	10.02699	108.0000	0.003273
REM (%)	12.3989	7.71837	22.1650	5.55539	83.0000	0.000149
OAI/h	5.6685	4.42456	0.3480	0.26705	0.0000	0.000
CAI/h	7.7815	3.80737	0.3085	0.28396	0.0000	0.000
HI/h	7.7685	5.37938	0.3598	0.29043	0.0000	0.000
AHI	16.7362	3.51547	0.9940	0.20460	0.0000	0.000
ODI	13.0923	4.92341	0.4125	0.30650	0.0000	0.000
Mean oxygen saturation (%)	93.6608	2.16734	96.6700	1.01000	53.5000	0.000
PLM%	9.5185	1.89454	2.8100	1.09820	0.0000	0.000

TIB time in bed, *SPT* sleep period time, *TST* total sleep time, *SOL* sleep onset latency, *FRL* first REM sleep latency, *SS* stage shifts, *AWN* awakenings, *SE* sleep efficiency, *WASO* wake time after sleep onset, *S1* sleep stage 1, *S2* sleep stage 2, *SWS* slow-wave sleep, *REM* rapid eye movement sleep percentage, *OAI* obstructive apnea index per hour, *CAI* central apnea index per hour, *HI* hypopnea index per hour, *AHI* apnea/hypopnea index (normal value, ≤1/h), and *ODI* oxygen desaturation index (normal value, ≤1/h), *PLM%* periodic limb movement percentage (normal value, ≤5%), *NS* not significant

[a]Bonferroni-corrected value

sporadic occurrence, extreme female gender bias, early quite normal development and subsequent developmental regression, autonomic dysfunction, stagnation in brain growth, and distinctive neuropathology [24]. Clinical disorders involving ventilatory control during infancy and childhood range from rare genetic syndromes such as congenital central hypoventilation syndrome [25] and Prader-Willi Syndrome [26] to common problems such as apnea of prematurity [27], bronchopulmonary dysplasia, apparent life-threatening events, and SIDS. Perhaps surprisingly, given its relevance to a wide variety of disorders in infancy and childhood, ventilatory control tends to be a somewhat neglected topic in pediatric medicine. In general, the ventilatory control may be depressed or overstimulated by a variety of external factors (i.e., drugs, toxins, respiratory viral infections, and sepsis) and others that can induce hyperpnea, tachypnea, hyperventilation, hypoventilation, bradypnea, respiratory dysrhythmias, apnea, and even death due to respiratory failure. In this perspective, Rett syndrome could be considered as a disorder due to immature or abnormal ventilatory control [28].

In fact in RTT, the autonomic nervous system is abnormal at various levels, from the central to the peripheral nervous system as shown by a lower heart rate variability, associated with an increase of adrenergic tone with a possible relationship with serotoninergic dysfunction [29–31], or with leptin levels [32] that have a crucial role in the ventilatory regulation at the level of the solitary tract nucleus [33].

In this perspective, our results can be interpreted as a ventilatory impairment of RTT subjects shown by the presence of a pathological index in all respiratory parameters and in a lower mean oxygen desaturation percentage with respect to the control. Moreover, the central apneas may strengthen the evidences that were secondary to RTT, such as in patients with other cerebral neurological disease [34, 35].

On the other hand, the report of Kerr et al. [36] that 26% of the deaths attributed to Rett syndrome are sudden and unexpected suggests that respiratory dysrhythmia could be an important contributory factor. Moreover, an increased percentage of PLM has been found in children with mental retardation [37], suggesting that the PLMs might contribute to the cognitive impairment and to the worsening of life quality of subjects with MR.

About the macrostructural parameters, we have also found a higher percentage of SWS that can be considered as the effect of abnormal activity in the thalamocortical connections, as suggested by Miano [18] in a sample of children with mental retardation with or without epilepsy. The same explanation could be suggested also for the decrease in REM% in RTT that can be considered as the direct effect of an imbalance in stage shifting or as the cause of the abnormal synaptogenesis of the cerebral cortex modulated by a region or layer specifically from an early stage of the development [38] that in RTT subjects is strongly compromised as the neuronal circuitry [39].

Furthermore, abnormality of REM/NREM rhythm suggests an abnormality in reciprocal activation of the monoaminergic and the cholinergic system, and the leakage of REM components to NREM stages implies hypofunction of the 5HT neurons of the dorsal raphe and the NA neurons of the locus coeruleus [11].

In addition, each sleep parameter takes a specific maturational course reflecting the function of specific neurons in the brainstem and midbrain. The spatial and temporal relations of these parameters reflect the regulation of these neurons by a higher neuronal system. Ultradian rhythm or REM-related components mature earlier than circadian or deep sleep-related parameters and are controlled by the pons, as the respiration [11].

In fact, morphometric and volumetric studies in RTT have identified a specific reduction in frontal and temporal lobes, caudate nucleus, thalamus, and midbrain [40–42] that could be considered the explanation of these alterations in sleep cycling.

Herein, we should take into account some limitations of this study: our data were derived from a group affected by Rett syndrome exclusively at advanced clinical stage, and no follow-up evaluation was performed. Notwithstanding these limitations, this could be considered a report about the ventilatory impairment during sleep in RTT syndrome and the first approach to the macrostructural aspects of RTT sleep supported by the PSG data that could be considered mandatory for a better comprehension of this very complex syndrome.

Conflict of interest The authors have no conflict of interest.

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