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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),