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Original article

Sleep disturbances in Angelman syndrome: a questionnaire study

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Abstract

Only few studies are available on sleep disorders in Angelman syndrome (AS), a neurodevelopmental disorder with several behavior disturbances. The aim of this study was to determine the prevalence of sleep disorders in a relatively large group of AS subjects, compared to that of age-matched controls. Fourty-nine consecutive parents of patients with AS (26 males and 23 females aged 2.3–26.2 years) were interviewed and filled out a comprehensive sleep questionnaire. Based on their genetic etiology, four groups were defined: deletion of chromosome 15q11–13 (25 subjects); methylation imprinting mutation (six subjects), UBE3A mutations (seven subjects) and paternal uniparental disomy (five subjects). In the remaining cases genetic testings were negative. A significantly high frequency of disorders of initiating and maintaining sleep, prolonged sleep latency, prolonged wakefulness after sleep onset, high number of night awakenings and reduced total sleep time were found in our AS patients, as compared to age-matched controls. We also found other types of sleep disorders, never reported before, such as enuresis, bruxism, sleep terrors, somnambulism, nocturnal hyperkinesia, and snoring. No differences were found between the four genetic aetiology groups. Moreover, we did not find important improvement of sleep disturbances from pre-pubertal to post-pubertal ages. Our data confirm the significant presence of sleep/wake rhythms fragmentation, peculiar of AS, and also demonstrate the presence of several other types of sleep disturbances in this syndrome.

Keywords: Angelman syndrome; Questionnaire study; Sleep disorders

1. Introduction

Angelman syndrome (AS) is a neurodevelopmental disorder characterized by mental retardation, severe speech impairment, ataxia of gait and/or tremulous movement of limbs, specific behavioral traits – such as frequent laughter, jerky (puppet-like) movements – microcephaly, abnormal EEG features, epilepsy and dysmorphic cranio-facial features. A consensus for diagnostic criteria was established in 1995, the symptoms and/or signs listed above are present in approximately 80–100% of cases [1]. The prevalence of AS is estimated to be around 1:10,000–1:20,000 and the clinical diagnosis can be confirmed by cytogenetic or DNA testing in 80–85% of cases while in 15–20% of subjects the etiology is still unknown [2].

Sleep problems such as sleep/wake rhythm disorders, multiple nocturnal awakenings, or difficulties in falling asleep are known to be frequent in AS [1] but have not been assessed by means of specific tools for their detection. Instead, they have been found using questionnaires built for the assessment of other behavioral features [3–7].

There are also indications that sleep might show an age-related improvement in AS because Smith [4] studied an Australian sample of 21 patients and found that their previous sleep problems had disappeared in a large percentage (75%) at follow up, 10 years later. Moreover, a recent report has shown an increase in total sleep time and improvement in sleep quality in adolescents and adults with AS [7]; the same authors suggested that some developmental factors, probably linked to cerebral plasticity, might be responsible for both the early sleep-wake disruption and for its improvement with age.

The main scope of our study was to determine the prevalence of sleep disorders in a relatively large group of subjects with AS, in comparison with that found in

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age-matched healthy controls, by means of a questionnaire specifically arranged for the study of sleep characteristics of children and adolescents and already validated [8]; moreover, our aim was also to assess the eventual presence of specific sleep disorders in AS and to confirm or not their age-related improvement already reported in the literature [4,7].

2. Material and methods

2.1. Subjects

A group of 49 patients with AS was included in this study which was composed of 26 males (53%) and 23 females (47%); their age ranged between 2.3 and 26.2 years (mean age of 10.10 SD 6.1). Because of their wide age range, the patients were subdivided into two subgroups: Group A formed by 37 subjects aged 2.3–14.8 years (20 males and 17 females) and Group B formed by 12 subjects aged between 15.8 and 26.2 years (six males and six females). The parents of our 49 AS subjects were interviewed during a meeting of the Italian Association for AS (OrSA) and represented 21.4% of their membership at the time of the present study. Twenty-five out of the 49 AS patients presented deletion of chromosome 15q11–13, six had methylation imprinting mutation, seven had UBE3A mutations, and five paternal uniparental disomy; in six cases all the genetic testings were negative.

The control group (Group C) was formed by a large cohort of normal healthy children and adolescents, composed of Caucasian subjects mostly from families with a working and middle class background, randomly selected in three public schools of Rome. This group was comprised of 442 males and 451 females aged 6.5–14.10 years (mean age 9.9 years). Family factors were similar for both groups (patients and controls) and the education level of mothers and fathers did not differ significantly for the two groups.

2.2. Materials and procedure

The questionnaire on clinical-historical data and on sleep habits and disorders [8] was prepared to be completed by the parents. Background information was obtained for each subject and their family. Subject information included gender, height, weight, birth order, existing medical condition and medication history.

The sleep questionnaire (see Appendix 1) was made up of 45 items in a Likert-type scale with values 1–5 (1 = never; 2 = occasionally; 3 = often; 4 = very often; 5 = always) to measure individual differences in several areas of sleep disorders (disorders of initiating and maintaining sleep, sleep-wake transition disorders, other parasomnias, night waking, movement disorders during sleep, sleep breathing problems, excessive daytime somnolence, narcolepsy and morning symptoms).

The items 1 and 2 pertained respectively to sleep duration (categorized as follows: 1 = 9–11 h; 2 = 8–9 h; 3 = 7–8 h; 4 = 5–7 h; 5 = less than 5 h) and sleep latency (categorized as follows: 1 = less than 15 min; 2 = 15–30 min; 3 = 30–45 min; 4 = 45–60 min; 5 = more than 60 min).

Some items were removed from the original questionnaire because the clinical features of AS children, language capabilities in particular, did not allow their parents to evaluate some disorders (waking up complaining of headache, waking up with leg cramps, report of frightening dream, hypnagogic hallucinations and hallucinations on waking up in the morning).

Instructions for completing the scale were always given to the parents by the same person (G.D.). The entire questionnaire took the parents 10–15 min to complete. The questionnaire assessed sleep behaviors and disorders observed during the last 6 months of the subject's life.

An introduction letter explaining the scope of the study was given to the parents and confidentiality was assured.

2.3. Statistical analysis

First, the comparison between patient Group A and age-matched normal controls (Group C) was carried out by means of the non-parametric Chi-square test. For this comparison the number of subjects with score 1 or 2 and that of subjects with score 3 or higher was used, for each questionnaire item, in each group. The comparison between patient groups A and B was carried out in the same way in order to evaluate the eventual presence of age-related changes. Finally, the same test was applied in order to detect differences between AS patients with different genetic asset. The commercially available software STATISTICA (data analysis software system), version 6, StatSoft, Inc. (2001) was used for all statistical tests.

3. Results

3.1. Comparison between AS patients aged less than 15 and age-matched normal controls

No statistically significant difference for age and sex was found between Groups A and C and Table 1 displays the statistical analysis of differences between these two groups for each questionnaire item. This table shows that AS patients aged less than 15 years are affected by several types of sleep disturbances which can be identified not only as dyssomnias, but also as parasomnias, sleep-disordered breathing, excessive daytime sleepiness and sleep movements disorders, with frequency significantly higher than normals.

3.1.1. Sleep duration and sleep latency

AS Group A showed sleep duration shorter than 8 h in 70.27% of cases versus 9.63% of the control group (Chi-square 117.68; $P < 0.00001$). Also sleep latency was prolonged with 32.43% of subjects belonging to AS Group A who took more than 30 min to fall asleep versus 6.61% in group C (Chi-square 30.04; $P < 0.0001$).

Table 1
Comparison between AS patients aged less than 15 (group A) and age-matched normal controls (group C)

	Group C (%)	Group A (%)	Chi-square	$P <$
Bedtime problems				
1. Sleep less than 8 h	9.63	70.27	117.68	0.00001
2. Latency to sleep >30 min	6.61	32.43	30.04	0.00001
3. Reluctant to go to bed	29.68	59.46	13.41	0.003
4. Bedtime variations	38.63	48.65	1.11	NS
5. Difficulty getting to sleep at night	8.96	56.76	78.98	0.00001
6. Anxiety/fear when falling asleep	8.17	43.24	46.52	0.00001
7. Drink stimulant beverages in the evening	27.32	27.03	0.02	NS
8. Need for light or TV in the bedroom	27.21	32.43	0.26	NS
9. Need for a transitional object	18.25	48.65	19.05	0.00001
10. Fluids or drugs to facilitate sleep	0.67	32.43	172.46	0.00001
Sleep-wake transition disorders				
11. Hypnic jerks	5.04	59.46	149.35	0.00001
12. Rhythmic movements while falling asleep	2.69	27.03	53.04	0.00001
13. Falling asleep sweating	10.30	13.51	0.12	NS
Sleep quality				
14. Poor sleep quality	13.89	70.27	79.38	0.00001
Night awakenings				
15. More than two awakenings per night	6.83	62.16	125.73	0.00001
16. Waking up screaming in the night	5.49	18.92	9.08	0.003
17. Waking up to drink or eat in the night	13.55	24.32	2.59	NS
18. Getting up to use to the bathroom	10.64	2.70	1.64	NS
19. Difficulty to fall asleep after awakenings	4.82	56.76	141.58	0.00001
Abnormal movements during sleep				
20. Nocturnal hyperkinesias	29.00	67.57	23.12	0.00001
21. Unusual movements during sleep	5.94	48.65	85.96	0.00001
22. Pains of unknown origin during sleep	0.56	10.81	28.99	0.00001
23. Convulsions during sleep	0.67	5.41	4.61	0.035
Sleep breathing problems				
24. Sleep breathing difficulties	6.83	18.92	5.98	0.015
25. Sleep apnea	1.01	2.70	0.03	NS
26. Snoring	14.67	32.43	7.30	0.007
Parasomnias				
27. Night sweating	15.90	18.92	0.07	NS
28. Sleepwalking	3.14	5.41	0.08	NS
29. Sleep talking	14.45	2.70	3.16	NS
30. Bed-wetting	2.35	35.14	99.30	0.00001
31. Bruxism	7.39	21.62	7.98	0.005
32. Sleep terrors	1.34	5.41	1.69	NS
33. Nightmares	10.64	0.00	3.30	NS
Morning symptoms				
34. Difficulty in waking up in the morning	35.95	35.14	0.01	NS
35. Variation of waking time	25.87	37.84	2.04	NS
36. Sleep paralysis	4.14	13.51	5.22	0.025
Daytime sleepiness				
37. Daytime somnolence	4.48	24.32	24.20	0.00001
38. Falling asleep at school	0.34	8.11	22.45	0.00001
39. Sleep attacks	1.46	2.70	0.01	NS

3.1.2. Bedtime problems

AS Group A showed bedtime problems, mainly bedtime resistance, difficulty to fall asleep and fear or anxiety when falling asleep more frequently than Group C. Also more than one third of AS subjects (Group A) needed to take fluids or drugs in order to fall asleep (32.43%) versus 0.67% in Group C ($P < 0.00001$).

3.1.3. Sleep-wake transition disorders

Two sleep-wake transition disorders (hypnic startles and rhythmic movement disorders) were more prevalent in AS subjects belonging to Group A, while no differences with Group C were found for falling asleep sweating.

3.1.4. Sleep quality

Parents reported poor sleep quality in 70.27% of AS subjects (Group A) versus 13.89% of Group C ($P < 0.0001$).

3.1.5. Night awakenings

AS Group A showed a frequently interrupted sleep since more than two awakenings per night were reported in 62.16

versus 6.83% of the Group C, waking up screaming during the night was found in 18.92% of patients (versus 5.49% in Group C) and difficulty in falling asleep again after awakenings was more frequent in the same patients than in normal controls (56.76 versus 4.82%).

3.1.6. Abnormal movements during sleep

Three out of four items related to movements during sleep were significantly different between the two groups in Table 1. The parents of AS Group A referred as an important trouble the presence of nocturnal hyperkinesia in 67.57% of cases (versus 29.00% Group C), of unusual movements during sleep in 48.65% (versus 5.94% Group C), of pain of unknown origin during sleep in 10.81% (versus 0.56% Group C) and of nocturnal seizures in 6.12% of cases (versus 0.67% Group C).

3.1.7. Sleep-disordered breathing

We found a high prevalence of sleep breathing disorders in AS patients belonging to Group A which has not been reported previously in this type of mental retardation syndrome: snoring was reported in 32.43% (versus 14.67% of controls), sleep breathing difficulties in 18.92% (versus 6.83%).

3.1.8. Parasomnias

Other sleep disorders such as parasomnias were also reported frequently: enuresis in 35.14%, bruxism in 21.62%, sleep terrors in 5.14% (N.S.), sleepwalking in 5.41% (N.S.). Obviously, sleep talking was less represented in AS Group A (2.70%) than in controls (14.45%).

3.1.9. Morning symptoms and daytime sleepiness

Of the morning symptoms, only sleep paralysis was more frequent in AS Group A (13.51%) than in Group C (4.14%) and no differences were found for difficulty getting up in the morning.

Diurnal somnolence seemed to be an important issue for AS Group A subjects, affecting 24.32% of cases (versus 4.48% Group C). This somnolence might also be responsible for falling asleep at school time (8.11 versus 1.46% Group C).

3.2. Comparison between AS patients aged less than 15 and those aged more than 15 years

Table 2 shows the results of the statistical comparison between AS Groups A and B which was carried out in order to detect eventual age-related differences in these two subgroups. Only for one item, in this table, a statistically significant difference was found between the two patient subgroups because subjects aged more than 15 years were reported to present seizures during sleep more often than those belonging to Group A (5.41 versus 0.67%; Chi-square 4.61; $P < 0.035$). Moreover, important although not significant differences were found for the following two items.

- The subject feels anxious or afraid when falling asleep: Group A 43.24% versus Group B 8.33%; Chi-square 3.45 ($0.1 > P > 0.05$).
- The subject startles or jerks parts of the body while falling asleep: Group A 59.46% versus Group B 25.00%; Chi-square 3.04 ($0.1 > P > 0.05$).

3.3. Comparison between AS patients with different genetic asset

Finally, four genetically different subgroups were present in our group of AS subjects which did not show significant differences between them for all the items analyzed. However, the UBE3A mutation group seemed to show sleep disorders less frequently than the other genetic subgroups, mainly for the items related to sleep duration and bedtime difficulties.

4. Discussion

Even if our study was based on retrospective data and on parental reports as sources of information, we were able to confirm the already reported high prevalence of sleep problems in children with AS, in form of disturbances in initiating and maintaining sleep [3,4,6] and to find additional disorders such as parasomnias, movement disorders, sleep breathing disorders and excessive daytime somnolence which were not reported in the previous literature.

Further, we can suggest that some sleep problems, such as movement disorders and excessive somnolence, are specifically associated to AS and probably linked to the pathophysiology of the syndrome (i.e. GABA-A receptor dysfunction).

Some limitations of this study should be underlined: a number of items in the questionnaire are based on subjective judgment of caretakers (such as sleep quality, unusual movements or sleep breathing difficulties) and we cannot exclude that the high prevalence of sleep disorders in our group of patients might be partially explained by a selection bias because, often, caretakers of the severely affected members usually attend association meetings.

It is known that sleep problems are common and long lasting in children with mental retardation and are considered to be causative factors of distress in caregivers [9]. During the past 10 years, many studies have evaluated the prevalence of sleep disorders in individual with developmental disabilities. The majority of the studies investigating sleep in mental retardation included groups of patients heterogeneous for their clinical features and did not attempt to find significant differences between the various types of mental retardation.

Questionnaire and interview based studies among mentally retarded subjects show that approximately 15–50% of adults [10,11] and 30–67% of children [9,12] do have sleep problems.

Table 2
Comparison between AS patients aged less than 15 (group A) and those aged more than 15 years (group B)

	Group A (%)	Group B (%)	Chi-square	$P <$
Bedtime problems				
1. Sleep less than 8 h	70.27	50.00	0.87	NS
2. Latency to sleep >30 min	32.43	25.00	0.02	NS
3. Reluctant to go to bed	59.46	50.00	0.06	NS
4. Bedtime variations	48.65	25.00	1.22	NS
5. Difficulty getting to sleep at night	56.76	58.33	0.06	NS
6. Anxiety/fear when falling asleep	43.24	8.33	3.45	$0.1 > P > 0.05$
7. Drink stimulant beverages in the evening	27.03	0.00	2.58	NS
8. Need for light or TV in the bedroom	32.43	33.33	0.57	NS
9. Need for a transitional object	48.65	8.33	4.62	NS
10. Fluids or drugs to facilitate sleep	32.43	50.00	0.09	NS
Sleep-wake transition disorders				
11. Hypnic jerks	59.46	25.00	3.04	$0.1 > P > 0.05$
12. Rhythmic movements while falling asleep	27.03	25.00	0.06	NS
13. Falling asleep sweating	13.51	16.67	0.04	NS
Sleep quality				
14. Poor sleep quality	70.27	66.67	0.02	NS
Night awakenings				
15. More than two awakenings per night	62.16	58.33	0.01	NS
16. Waking up screaming in the night	18.92	25.00	0.00	NS
17. Waking up to drink or eat in the night	24.32	0.00	2.14	NS
18. Getting up to use to the bathroom	2.70	8.33	0.00	NS
19. Difficulty to fall asleep after awakenings	56.76	41.67	0.33	NS
Abnormal movements during sleep				
20. Nocturnal hyperkinesias	67.57	75.00	0.02	NS
21. Unusual movements during sleep	48.65	25.00	1.22	NS
22. Pains of unknown origin during sleep	10.81	0.00	0.34	NS
23. Convulsions during sleep	0.67	5.41	4.61	0.035
Sleep breathing problems				
24. Sleep breathing difficulties	18.92	16.67	0.06	NS
25. Sleep apnea	2.70	16.67	1.12	NS
26. Snoring	32.43	50.00	0.57	NS
Parasomnias				
27. Night sweating	18.92	0.00	1.33	NS
28. Sleepwalking	5.41	16.67	0.40	NS
29. Sleep talking	2.70	0.00	0.36	NS
30. Bed-wetting	35.14	50.00	0.33	NS
31. Bruxism	21.62	8.33	0.36	NS
32. Sleep terrors	5.41	8.33	0.11	NS
33. Nightmares	0.00	0.00		
Morning symptoms				
34. Difficulty in waking up in the morning	35.14	41.67	0.00	NS
35. Variation of waking time	37.84	25.00	0.21	NS
36. Sleep paralysis	13.51	8.33	0.00	NS
Daytime sleepiness				
37. Daytime somnolence	24.32	16.67	0.02	NS
38. Falling asleep at school	8.11	8.33	0.34	NS
39. Sleep attacks	2.70	0.00	0.36	NS

The sleep disturbances more commonly reported in children with mental retardation are: night-time settling difficulties, night waking and short duration of night-time sleep [9,11,12]; moreover, there seems to be a relationship between the severity of sleep disorders and the severity of mental retardation, both in syndromic and non-specific forms. Further, severe sleep disorders in mentally retarded subjects are common and persist well beyond the age at which they usually stop in normal children [13].

It has been reported that sleep disruption, represented mostly by interrupted sleep and bedtime difficulties, is directly correlated with the degree of mental retardation [9]. Our results demonstrating a high prevalence of difficulties in initiating and maintaining sleep in AS confirm this report. However, different and specific sleep disorders are present in various types of neuro-developmental syndromes such as Prader-Willi syndrome [14], Tuberous Sclerosis [15], Sanfilippo syndrome [16], Smith-Magenis syndrome [17],

Down syndrome [18], Fragile-X syndrome [19], etc. Therefore, distinctive factors can be thought to play a role in the pathogenesis of sleep disturbances of different syndromes. For this reason, it seems more important to evaluate sleep in specific subgroups and types of mental retardation than attempting generalizations that risk being limited in meaning and clinical usefulness [13].

In our AS patients we found disturbances in initiating and maintaining sleep together with parasomnias, movement disorders, sleep breathing disorders and excessive daytime somnolence.

Difficulties in falling asleep and night awakenings have been reported in all the previous sleep studies in AS with a prevalence ranging from 42 to 100% [3,6]. In our patients, we found more than two awakenings per night in 61.22% of cases and, also, bedtime resistance, difficulty to fall asleep and fear or anxiety when falling asleep, with a prevalence ranging from 35 to 57%.

We can hypothesize that the higher percentage of such disorders reported by other authors [3,7] might have been influenced by different factors such as age range, small patient group size and lack of specificity of the questionnaire (i.e. a modified version of the Child Behavior Checklist).

Regarding the other categories of sleep problems which have been scarcely investigated in AS, and in other mental retardation syndromes, we found a high frequency of abnormal movements (nocturnal hyperkinesias, restless sleep and unusual movements during sleep). Periodic limb movements have already been reported in Williams syndrome and in mentally retarded children with ADHD comorbidity [20]. Our findings clearly indicate the presence of nocturnal movements which might be part of the extrapyramidal symptoms of AS in addition to other movement disorders such as dyskinesia, myoclonus and tremors [21]. However, we should take into account that both presence of unusual movements and enuresis might be related also to the occurrence of nocturnal seizures.

As expected, hypnic startles and rhythmic movement disorders were frequent in AS; this is in agreement with some reports showing that these kinds of parasomnias are frequent in mentally retarded subjects [22].

Only few studies have investigated the prevalence of other parasomnias in mentally retarded subjects and have shown that bruxism and sleep terrors are most common [23]. In AS we found a high frequency of enuresis, bruxism, sleep terrors and sleepwalking. Recent studies on parasomnias in autism have shown that nightmares, sleep terrors, sleep-walking, confusional arousals, bruxism, and snoring were present in a significant number of subjects [24,25].

Sleep breathing difficulties were also frequent in our AS patients and we can not exclude that snoring and apneas might be in some relation with craniofacial dysmorphic features. Sleep breathing disorders are commonly reported in some specific syndromes such as Down syndrome, Prader-Willi syndrome and different craniofacial syndromes (craniosynostosis, micrognathia, Arnold-Chiari malformation) [20]. In Down syndrome, both obstructive and central sleep apnea have been reported and the latter has been interpreted in terms of hyperexcitability at the level of the brainstem [18].

In the Prader-Willi syndrome sleep apnea can be an important factor contributing to hypersomnia which, in turn, might be part of a series of narcoleptic-like symptoms [26–28]. Daytime sleepiness is a common complaint in several neuro-developmental disorders, it might be in relation with central nervous system dysfunction influencing circadian rhythms and also with irregular sleep schedule [23].

We have found that excessive daytime somnolence, hypersomnia and sleep paralysis are also frequent in AS. AS and Prader-Willi syndrome genes map to the same chromosome region but are two clinically different conditions; however, it is possible that some common clinical traits can be detected and sleep abnormalities might be some of them.

The exact nature of excessive daytime sleepiness in AS children is difficult to be interpreted because of the presence of several confounding variables such as sleep breathing disorders, sedation induced antiepileptic drugs, irregular schedule and genetic factors.

We found no particular age-effect on sleep problems in AS and were able to confirm the finding that sleep disorders in children with severe or profound mental retardation rarely improve with age. Clements et al. [12], in a large sample of subjects with severe mental retardation, found sleep problems in 56% of children under 5 years of age, which did not improve spontaneously as in normal children. In a longitudinal survey on 200 children with severe mental retardation, sleep disorders were represented by difficulties of initiating and maintaining sleep, with a frequency of 51 and 67%, respectively; these sleep problems still persisted after 3 years follow-up [9]. These findings were also confirmed by Wiggs and Stores [29] who found an average duration of sleep problems in children with severe intellectual disability of approximately 7 years and, more recently, by Richdale et al. [30] who reported, in a sample of 52 children with mental retardation, a prevalence of sleep disorders that remained stable over time.

Based on our findings, we suggest that the pathogenesis of sleep disorders in AS might be linked to different factors (degree of mental retardation, seizures, speech delay, locomotor dysfunction, etc.). However, we also hypothesize that sleep disturbances might be related to the pathophysiology of AS (i.e. GABA receptor dysfunction). Located within the AS-deletion region 15q11–13, there is a cluster of GABA-A receptor subunit genes, which encode the GABA-A receptor protein subunits. GABA is the most abundant inhibitory neurotransmitter in the brain and is implicated in decreasing cortical activation, induces non-REM sleep and influences the initiation and maintenance of sleep. Thus, a disruption of the GABA-A receptor genes might contribute to the clinical severity of AS with gene deletion, and especially to sleep disorders

and epilepsy [31]. Therefore, GABAergic dysregulation might influence sleep homeostasis and determine dyssomnias (insomnia, hypersomnia, narcolepsy) and parasomnias. Finally, the decrease of GABA-A receptors might also determine loss of inhibitory influence on motor cortical function and be responsible of motor disorders during sleep [32]. However, the role of GABA dysfunction and its relationships with sleep disruption is not currently fully understood and these issues require further investigations, by means of more refined tools such as polysomnographic recordings.

Appendix 1. Sleep questionnaire*

Please answer the questions by circling or striking the number 1 to 5. (consider each question as pertaining to the **past 6 months** of the child's life)

How many hours of sleep does your child get on most nights **1.** *9-11* **2.** *8-9* **3.** *7-8* **4.** *5-7* **5.** *<5h*

How long after going to bed does your child usually fall asleep **1.** *< 15'* **2.** *15-30'* **3.** *30-45'* **4.** *45-60'* **5.** *> 60'*

1 **Never**	2 **Occasionally (once or twice per month or less)**	3 **Sometimes (once or twice per week)**	4 **Often (3 or 5 times per week)**	5 **Always (daily)**

3. The child goes to bed reluctantly	1	2	3	4	5
4. The child's bedtime varies by more than an hour on school days	1	2	3	4	5
5. The child has difficulty getting to sleep at night	1	2	3	4	5
6. The child feels anxious or afraid when falling asleep	1	2	3	4	5
7. The child drinks coke, tea, coffee, chocolate or similar substances late in the afternoon or in the evening	1	2	3	4	5
8. The child needs a little light on or TV on to fall asleep in the bedroom	1	2	3	4	5
9. The child needs a special toy, doll or stuffed animal before bedtime, without which he/she cannot sleep	1	2	3	4	5
10. The child has to drink fluids or drugs to facilitate sleep	1	2	3	4	5
11. The child startles or jerks parts of the body while falling asleep	1	2	3	4	5
12. The child shows repetitive actions such as rocking or head banging while falling asleep	1	2	3	4	5
13. The child experiences vivid dreams-like scenes while falling asleep	1	2	3	4	5
14. The child sweats excessively while falling asleep	1	2	3	4	5
15. The child's quality of sleep is good	1	2	3	4	5
16. The child wakes up more than two times per night	1	2	3	4	5
17. The child wakes up screaming in the night without knowing why	1	2	3	4	5
18. The child wakes up to drink or eat in the night	1	2	3	4	5
19. The child gets up to use to the bathroom	1	2	3	4	5
20. The child wakes up complaining of headache	1	2	3	4	5
21. The child wakes up with leg cramps	1	2	3	4	5
22. After waking up in the night, the child has difficulty to fall asleep again	1	2	3	4	5
23 The child has frequent twitching or jerking of legs while asleep or changes often position during the night or kicks the covers off the bed.	1	2	3	4	5
24 The child has unusual movements during sleep	1	2	3	4	5
25 .Child's sleep is disturbed by (undefined) pains of unknown origin	1	2	3	4	5
26. The child has difficulties in breathing during the night	1	2	3	4	5
27. The child gasps for breath or is unable to breathe during sleep	1	2	3	4	5
28. The child snores	1	2	3	4	5
29 The child sweats excessively during the night	1	2	3	4	5
30. You have observed the child sleepwalking	1	2	3	4	5
31. You have observed the child talking in his/her sleep	1	2	3	4	5
32. The child has problems with bed-wetting	1	2	3	4	5
33. The child grinds teeth during sleep	1	2	3	4	5
34. The child wake from sleep screaming or confused so that you can't seem to get trough to him/her, but has no memory of these events the next morning	1	2	3	4	5
35. The child has nightmares which he/she doesn't remember the next day	1	2	3	4	5
36. Your child tell you about having a frightening dream	1	2	3	4	5
37. The child has convulsions during sleep	1	2	3	4	5
38. The child is unusually difficult to wake up in the morning	1	2	3	4	5
39. The child's waking up time varies by more than one hour on school days	1	2	3	4	5
40. The child awakes in the morning feeling tired	1	2	3	4	5
41. The child feels unable to move when waking up in the morning	1	2	3	4	5
42. The child experiences vivid dream-like scenes when waking up in the morning	1	2	3	4	5
43. The child experiences daytime somnolence	1	2	3	4	5
44. The child falls asleep during school hours	1	2	3	4	5
45. The child falls asleep suddenly in inappropriate situations	1	2	3	4	5

The questionnaire is filled in by: O mother O father O others

* Please note that questions 13, 20, 21, 36 and 42 were removed because the clinical features of AS children, language capabilities in particular, did not allow their parents to evaluate some disorders.

References

[1] Williams CA, Angelman H, Clayton-Smith J, Driscoll DJ, Hendrickson JE, Knoll JHM, et al. Angelman syndrome consensus for diagnostic criteria. Am J Med Genet 1995;56:237–8.

[2] Laan LA, Haeringen A, Brouwer OF. Angelman syndrome: a review of clinical and genetic aspects. Clin Neurol Neurosurg 1999;101:161–70.

[3] Summers JA, Allison DB, Lynch PS, Sandler L. Behavior problems in Angelman syndrome. J Intellect Disabil Res 1995;39:97–106.

[4] Smith A, Wiles C, Haan E, McGill J, Wallace G, Dixon J, et al. Clinical features in 27 patients with Angelman syndrome resulting from DNA deletion. Am J Med Genet 1996;33:107–12.

[5] Zhdanova IV, Wurtman RJ, Wagstaff J. Effects of a low dose of melatonin on sleep in children with Angelman syndrome. J Pediatr Endocrinol Metab 1999;12:57–67.

[6] Clarke JD, Marston G. Problem behaviors associated with 15q-Angelman Syndrome. Am J Ment Retard 2000;105:25–31.

[7] Clayton-Smith J. Angelman syndrome: evolution of the phenotype in adolescents and adults. Dev Med Child Neur 2001;43:476–80.

[8] Bruni O, Fabrizi P, Ottaviano S, Cortesi F, Giannotti F, Guidetti V. Prevalence of sleep disorders in childhood and adolescence with headache: a case-control study. Cephalalgia 1997;17:492–8.

[9] Quine L. Sleep problems in children with mental handicap. J Ment Defic Res 1991;35:269–90.

[10] Espie CA, Tweedie FM. Sleep patterns and sleep problems amongst people with mental handicap. J Ment Defic Res 1991;35: 25–36.

[11] Brylewski JE, Wiggs L. Questionnaire survey of sleep and nighttime behaviour in a community-based sample of adults with intellectual disabilities. J Intellect Dis Res 1998;42:154–62.

[12] Clements J, Wing L, Dunn G. Sleep problems in handicapped children: a preliminary study. J Child Psychol Psychiatry 1986;27: 399–407.

[13] Stores G. Practitioner review: assessment and treatment of sleep disorders in children and adolescents. J Child Psychol Psychiatry 1996;37:907–25.

[14] Sarimski K. Specific eating and sleeping problems in Prader-Willi and Williams-Beuren syndrome. Child Care Health Dev 1996;22:143–50.

[15] Bruni O, Cortesi F, Giannotti F, Curatolo P. Sleep disorders in tuberous sclerosis: a polysomnographic study. Brain Dev 1995;17: 52–6.

[16] Colville GA, Watters JP, Yule W, Bax M. Sleep problems in children with Sanfilippo syndrome. Dev Med Child Neurol 1996;38:538–44.

[17] Smith AC, Dykens E, Greenberg F. Sleep disturbance in Smith-Magenis syndrome (del 17 p11.2). Am J Med Genet 1998;81:186–91.

[18] Ferri R, Curzi-Dascalova L, Del Gracco S, Elia M, Musumeci SA, Stefanini MC. Respiratory patterns during sleep in Down's syndrome: importance of central apnoeas. J Sleep Res 1997;6:134–41.

[19] Musumeci SA, Colognola RM, Ferri R, Gigli GL, Petrella MA, Sanfilippo S, et al. Fragile-X syndrome: a particular epileptogenic EEG pattern. Epilepsia 1988;29:41–7.

[20] Stores G. Sleep-wake function in children with neurodevelopmental psychiatric disorders. Semin Pediatr Neurol 2001;8:188–97.

[21] Viani F, Romeo A, Viri M, Mastrangelo M, Lalatta F, Selicorni A, et al. Seizure and EEG patterns in Angelman's syndrome. J Child Neurol 1995;10:467–71.

[22] Schwartz SS, Gallagher RJ, Berkson G. Normal repetitive and abnormal stereotyped behaviour of non-retarded infants and young mentally retarded children. Am J Ment Defic 1986;90:625–30.

[23] Stores G. Annotation: sleep studies in children with a mental handicap. J Child Psychol Psychiatry 1992;33:1303–17.

[24] Bruni O, Canitano R, Miano S, Nobile MS, Ottaviano S. Sleep problems in autistic spectrum disorders. Sleep 2000;23(S2):A362.

[25] Schreck KA, Mulick JA. Parental report of sleep problems in children with autism. J Autism Dev Disord 2000;30:127–35.

[26] Vgontzas AN, Kales A, Seip J, Mascari MJ, Bixler EO, Myers DC, et al. Relationship of sleep abnormalities to patients genotypes in Prader-Willi syndrome. Am J Med Genet 1996;67:478–82.

[27] Richdale AL, Cotton S, Hibbit K. Sleep and behaviour disturbance in Prader-Willi syndrome: a questionnaire study. J Intellect Disabil Res 1999;43:380–92.

[28] Manni R, Politini L, Nobili L, Ferrillo F, Livieri C, Veneselli E, et al. Hypersomnia in the Prader Willi syndrome: clinical-electrophysiological features and underlying factors. Clin Neurophysiol 2001;112: 800–5.

[29] Wiggs L, Stores G. Severe sleep disturbance and daytime challenging behaviour in children with severe learning disabilities. J Intellect Disabil Res 1996;40:518–28.

[30] Richdale A, Gavidia-Payne S, Francis A, Cotton S. Stress, behavior and sleep problems in children with an intellectual disability. J Int Dev Disability 2000;25:147–61.

[31] DeLorey TM, Olsen RW. GABA and epileptogenesis: comparing gabrb3 gene-deficient mice with Angelman syndrome in man. Epilepsy Res 1999;36:123–32.

[32] Marsden CD, Hallett M, Fahan S. The nosology and pathophysiology of myoclonus. In: Marsden CD, Hallett M, Fahan S, editors. Movements disorders. London: Butterworth; 1982. p. 196–249.