



Review article

Are there distinctive sleep problems in Angelman syndrome?

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Abstract

Angelman syndrome is a neurogenetic condition characterized by developmental delay, absence of speech, motor impairment, epilepsy and a peculiar behavioral phenotype that includes sleep problems. It is caused by lack of expression of the *UBE3A* gene on the maternal chromosome 15q11-q13. Although part of the diagnostic description, ‘sleep problems’ are not well characterized. A pattern emerges from the available reports. It includes reduced total sleep time, increased sleep onset latency, disrupted sleep architecture with frequent nocturnal awakenings, reduced rapid eye movement (REM) sleep and periodic leg movements. Poor sleep does not significantly interfere with daytime alertness and sleep problems commonly diminish by late childhood, with continuing improvement through adolescence and adulthood. Sleep problems in Angelman syndrome reflect abnormal neurodevelopmental functioning presumably involving dysregulation of GABA-mediated inhibitory influences in thalamocortical interactions. Management may be difficult, particularly in young children; it primarily involves behavioral approaches, though pharmacological treatment may be required. The relationship between sleep and seizure disorder, and between sleep and learning raises critical questions, but more studies are needed to address these relationships adequately.

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1. Introduction

Sleep patterns are often altered in individuals with neurodevelopmental conditions, particularly those with intellectual impairment. With the genetic characterization of a number of these conditions, there has been increasing interest in the insights that specific gene expression might give into the pathophysiology of the sleep disturbances. However, such insights should be based on sound description of sleep patterns. A high

prevalence (>80%) of sleep disorders was found in a questionnaire study in Rett syndrome [1], a common developmental disorder affecting girls, with cognitive impairment and epilepsy, mostly due to a mutation/deletion in the *MECP2* gene located on the Xq28 chromosome. The authors found a positive relationship between age, size and position of the deletion and the likelihood of sleep disorder. By contrast, abnormalities of the paternally inherited chromosome 15q11-q13 result in Prader–Willi syndrome, a condition characterized by hypotonia, learning difficulties, obesity and hypogonadism. A characteristic profile of reported sleep disorders in Prader–Willi syndrome includes hypersomnia, sleep-onset REM periods and breathing abnormalities. The latter are often ascribed to obesity, which can cause obstructive sleep apnea (e.g., [2]). In contrast,

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hypersomnia has been associated with alteration in the ‘cyclic alternating pattern’ (CAP) with altered growth hormone secretion and central dysfunction [3]. This process of describing sleep alterations in neurogenetic conditions has also been underway for Angelman syndrome [4,5], but the available findings are still limited. Here, we review the commonly reported sleep problems in Angelman syndrome.

Angelman syndrome is a neurogenetic disorder caused by the lack of expression of the *UBE3A* gene, which can result from various abnormalities of maternally inherited chromosome 15q11–q13. The product of the *UBE3A* gene, an E3A ubiquitin-protein ligase, plays a role in ubiquitin-mediated specific protein labeling, for example, in targeting for proteolysis. Molecular abnormalities giving rise to Angelman syndrome include submicroscopic deletions on the maternally inherited chromosome (70% of cases), paternal uniparental disomy of chromosome 15 (2–3% of cases), imprinting defect resulting in lack of the typical maternal pattern of DNA methylation in the 15q11–q13 region (3–5% of cases) and mutations of the maternal *UBE3A* allele (5–10% of cases) [6]. In contrast, abnormalities of the paternally inherited chromosome 15q11–q13 result in Prader–Willi syndrome (see above).

Overall prevalence of Angelman syndrome is around 1:12000; it affects males and females equally. It is characterized clinically by severe developmental delay, absence of speech, motor impairment (due to a combination of corticospinal and cerebellar signs [7], epilepsy and a peculiar behavioral phenotype. Patients consistently exhibit happy demeanor with prominent laughter, a peculiar communication pattern with virtually absent speech contrasting with relatively preserved receptive and non-verbal communication skills, excitability, hyperactivity and stereotypies including mouthing behaviors [8]. Sleep problems are listed as ‘associated features’ in the clinical diagnostic criteria. Most reports addressing these problems present the results of questionnaire surveys, and only limited polysomnographic data is currently available. Here, we review the reported findings according to the type of study.

2. Observational studies

The prevalence of sleep disorders ranges from 20% to 80% of affected individuals [8]. Higher prevalence figures of sleep problems have been reported (up to 90% in a study of 82 children and young adults aged between 18 months and 26 years [9]). The wide variation in reported prevalence may be related to discrepancies in what is considered a sleep problem. Despite the clinical importance of sleep disturbances, few systematic studies of sleep have been conducted in Angelman syndrome. The results from questionnaires administered to parents or caregivers [10–17] are summarized in Table 1. Not all

of these studies included a control group. Moreover, the size of study populations was variable and age and associated parameters (including severity of epilepsy, medication and environmental factors) were heterogeneous or inconsistently recorded.

As in other neurodevelopmental conditions [1,2,18], sleep problems appear to be more severe in early childhood. Overall, sleep problems are maximal between the ages of 2 and 6 years [9]. Some authors have suggested that they commonly diminish or disappear altogether by late childhood [12,14,15,19], the improvement of sleep quality being consolidated through adolescence and adulthood [19]. This improvement may seem unexpected, as adolescence is often a difficult period for sleep–wake scheduling in the general population because of a phase delay in the sleep period. It might be related to other aspects of neurophysiological maturation [20] or could suggest the existence of protective factors, such as a greater sensitivity to external *zeitgebers*. In some individuals with Angelman syndrome, however, sleep problems may persist [14,15].

2.1. Sleep onset

Increased latency of sleep onset and time spent awake between sleep onset and the end of the considered period of sleep have been documented [15,21,22]. A high proportion of children are reported to experience great difficulties in settling and falling asleep [11,13,15,17]. Unstable, very variable circadian cycles in young children with Angelman syndrome may impede physiological readiness to sleep following a regular schedule. It has been hypothesized but not confirmed that this might be due to decreased production of melatonin, decreased expression of its receptors or other factors determining sensitivity to this hormone [23].

2.2. Associated movements

Sleep onset may be accompanied by hypnic myoclonias (sleep starts), which can be generalized or predominate in the lower limbs, the upper limbs or the axial muscles, and occasionally contribute to difficulties in initiating sleep. They are bilateral but sometimes asymmetric. They may occur in a repetitive fashion, raising the question of differential diagnosis with myoclonic seizures, depending on the clinical context. Hypnic myoclonias have been hypothesized to represent intensification of otherwise normal events, due to decreased inhibition from descending pathways [24]. They are not specific to Angelman syndrome but are common at any age, depending on individual predisposition, and are probably not more prevalent in this condition than in the general population. In one questionnaire study, they were reported in about 60% of patients aged less than 15 years and 25% of patients aged 15–26 years [15].

Table 1
Subjective data

Ref. No.	No. of patients	Age range	Assessment tool	Sleep specific (Y/N)	Compared with group found (%age)	Prevalence	Sleep time reduced	Settling problems	Findings night waking disrupted sleep	Early waking	Rhythmic movements	Bed-wetting	Parasomnias other	Sleep-related breathing disorder	Daytime somnolence	Associations Phenotype
7 Zori et al. (1992)	66 USA 27 UK 39		Behavioral questionnaire	N		33% 74%										
6 Clayton-Smith et al. (1993)	82	1.5–26 y	Behavioral questionnaire	N		90%	90%									
8 Summers et al. (1995)	11	not available	Behavioral questionnaire	N		100%		91%	100%							
9 Smith et al. (1996)	27	3–34 y	Clinical?	N		86% (21 patients)			86%							
10 Clark and Marston (2002)	73	5–51y	Aberrant behavior Checklist + Reiss screen	N	PWS/5p-/ Smith-M/ other MR	42%	Reduced									
11 Didden et al. (2004)	109	2–44 y	Standardized	Y		40%		2%	37%	10%		93%		4% ^a	22%	N
12 Bruni et al. (2004)	49	2–26 y	Adapted for study	Y	Normal	70%	70%	32%	62%		67%	35%	21%	26% ^b 19% ^a	24%	N
13 Walz et al. (2005)	339	3–32 y	BEDS	Y		<40%	42%	48%		10%		40%	22%	32% ^b 4% ^a	14%	
14 Artigas y Pallarés et al. (2005)	49	1–22 y	Adapted for study	N		25%		36%	49%	60%						

BEDS, behavioural evaluation of disorders of sleep.

MR, mental retardation.

PWS, Prader-Willi syndrome.

Smith-M, Smith-Magenis syndrome.

^a Apnea.

^b Snoring.

Night rhythmiias ('rhythmic movement disorder') [25], such as body-rocking or rolling or head-banging, can also be seen at the onset of sleep. Occasionally, the movements are dramatic in intensity or noisy (e.g., in head-banging). However, they rarely result in more serious injury than eventual bruising or abrasion, which can be prevented by simple protective measures. Night rhythmiias have been reported in about two-thirds of typically developing children. They are probably not more prevalent in Angelman syndrome, though they might persist later than the commonly expected age of 3–4 years.

2.3. Sleep time and night awakening

Total sleep time is decreased in children with Angelman syndrome [15,16] to an average of 5–6 h per 24 h [9]. This type of sleeplessness does not usually correspond to common 'insomnia', in which daytime problems such as excessive fatigue, impairment of performance or emotional changes appear as obvious consequences of shortened night sleep [26]. However, one questionnaire study suggested that diurnal somnolence is an important issue in about 25% of children [15]. Total sleep time increases in adolescents and adults, even reaching values above normal in some individuals [19].

Reduced sleep time may relate to frequent nocturnal awakening. Although not uncommon in typically developing infants and young children, it is more frequent in children with Angelman syndrome. Frequent nocturnal awakenings were the mostly reported sleep problem (60%) in a sample of 68 individuals with Angelman syndrome aged 1–22 years (mean 9.6) [15]. More than two awakenings per night were reported in 62% of 37 patients aged 2–14 years [15]. Severe nighttime awakenings (qualified as such when lasting several minutes, occurring at least three nights per week and actually disturbing the parent or caregiver) correlated with the 'severe sleep problems' reported by parents or caregivers of patients with Angelman syndrome [14]. Severe night awakenings were reported for 37% of 109 patients aged between 2 and 44 years (mean 15.2 ± 9.3 years). Frequent night waking concerned 86% of a sample of 27 patients aged 3–34 years in another study [12] and all 11 children studied by Summers et al. [11]. The frequency of such awakenings decreases with age. This might explain the parallel increase in total sleep time.

2.4. Parasomnias

A variety of episodic sleep phenomena, referred to as 'parasomnias', have been reported in Angelman syndrome, none of them specific to the condition. The most common of these are bruxism, night terrors and somnambulism. These phenomena do not require treatment

when symptoms are mild and non-threatening. Bruxism has been reported by parents in 22% of patients [15,16]. It is not uncommon in the general population but is more prevalent in people with intellectual disability, with a possible relationship with the severity of the disability [27] and variability between syndromes (e.g., it seems to be more prominent in Rett syndrome than in Angelman syndrome). Bruxism also commonly occurs during wakefulness, along with other stereotyped behaviors, and may result in tooth enamel abrasion. Night terrors have been reported in 5–6% of individuals with Angelman syndrome [15,16], which was not significantly different from normal controls [15]. It is important to recognize them correctly, to distinguish them from paroxysmal events that have medical implications, such as seizures. Somnambulism occurs in the same proportion of patients as night terrors [16], which is similar to its occurrence in the general population [28]. Management of this parasomnia chiefly focuses on prevention of injury that might be associated with sleepwalking. Sleep talking, or somniloquy, is much rarer in individuals with Angelman syndrome than in the general population, due to the severe impairment of speech.

3. Polysomnographic studies

Polysomnography is technically difficult to obtain in children with intellectual disability, behavioral problems and marked sleep disruption, which are prevalent in Angelman syndrome. To date, there have been only two such studies.

3.1. Sleep stages

The characteristic electroencephalographic (EEG) features [20] show few changes in the transition between wakefulness and stage 1 sleep. Occurrence of sleep spindles and K complexes in stage 2 was reduced and more easily recognized when the runs of slow rhythmic activity [20] were not present [22]. However, the proportion of non-REM sleep stage 2 was not reduced and it was not different from children with non-specific intellectual disability, whether with or without associated epilepsy [22]. The percentage of REM sleep was reduced in a similar proportion to children with non-syndromic intellectual disability and epilepsy. This finding persisted in children older than 8 years of age. By contrast the same study found that slow-wave sleep was increased compared with normal children but not with other children with intellectual disability and epilepsy.

3.2. Relationship with epilepsy

The relationship with epilepsy poses special questions. Sleep fragmentation due to nocturnal seizures could be expected in Angelman syndrome as the

majority of patients have epilepsy. Overt seizures disrupt sleep architecture and in particular alters REM sleep [29,30]. Studies of sleep microstructure in different epileptic syndromes have demonstrated changes in the CAP [3,31,32]. In the studied developmental epileptic syndromes, both the rate of the CAP and the likelihood of seizures were found to be increased. In addition, there is a relationship between some sleep stages (particularly light sleep) or transition in sleep cycles (typically falling asleep and awakening) and the occurrence of seizures. Although it would be important to examine eventual alterations in CAP in Angelman syndrome, the nature of the characteristic EEG changes makes this particularly difficult. Moreover, effects of antiepileptic medication on sleep are varied and complex [33]. Finally, sleep deprivation classically enhances epileptic activity and may promote the occurrence of seizures. However, in a survey of more than 300 individuals with Angelman syndrome aged 3–22 years, no correlation was found between the presence of seizure disorder and total sleep time [16]. In clinical practice, the diagnosis of sleep-associated seizures may be difficult because of some degree of clinical similarity with non-epileptic paroxysmal phenomena that are not pathological (and, therefore, require no treatment), such as hypnic myoclonias, night rhythmicias or night terrors.

3.3. Periodic leg movements

The occurrence of stereotyped limb movements, in particular periodic leg movements, has recently been studied in 10 children with Angelman syndrome aged 2–16 years [22]. The movements were recorded in seven of these children, being more frequent (but not significantly) than in other groups of children with non-syndromic intellectual disability. No comparison was done with normal age-matched controls. There have been reports of increased prevalence of periodic leg movements in children with hyperactivity [34], a common feature in Angelman syndrome, though in a context which is markedly different from attention-deficit/hyperactivity disorder (ADHD) [8,35].

4. Pathophysiology

Angelman syndrome is caused by lack of *UBE3A* expression. In physiological conditions, this gene is imprinted, resulting in exclusive expression of the maternal allele in the brain [36]. Lack of *UBE3A* expression may result from several mechanisms outlined above [6]. The most common mechanism, accounting for about 70% of cases, is a submicroscopic deletion of the 15q11-q13 region of the maternally inherited chromosome 15. This deletion typically disrupts *UBE3A* as well as other genes, such as *GABRB3*, which encodes the $\beta 3$ subunit of the GABA_A receptor. An integrative hypothesis for

the molecular pathophysiology of this syndrome suggests dysregulation of synaptic neurotransmission through *UBE3A*-related recruitment of functional GABA_A receptors and the *GABRB3*-related amount of $\beta 3$ subunit in these receptors [20]. Abnormal sleep patterns in Angelman syndrome may involve thalamocortical dysfunction [20] through alterations in GABA_A receptor-mediated synaptic inhibition that might result from changes in subunit composition [6]. In homozygous *Gabrb3*-knockout mice, one of the engineered mouse models for Angelman syndrome [37,38], studies of reciprocal inhibitory connections demonstrated virtual abolition of GABA-mediated inhibition specifically in the thalamic reticular nucleus as well as a dramatic increase in oscillatory synchrony [39]. Secondary functional changes might also affect forebrain cholinergic systems [40]. However, much research is still needed to establish the role of such mechanisms in the patients' sleep problems. The electrophysiological fast rhythmic activities recorded from the cerebellar cortex of a mouse model with inactivation of maternally inherited *Ube3a* [41] may also point to abnormal cerebro-cerebellar cooperation in (slow-wave) sleep, possibly through deficient thalamic gating [42]. The relationships between sleep and hippocampal long-term potentiation [43] is likely to be of interest considering recent findings of alterations of these mechanisms in another mouse model of Angelman with inactivation of maternally inherited *Ube3a* [44,45]. Another research avenue has been the role of hypocretins (orexins) in the regulation of sleep and some food-related behaviors [46], which are abnormal in Angelman syndrome [8,35]. These neurohormones are produced by neurons in the lateral hypothalamus neurons in response to circadian light variations and nutritional influences. However, the levels of hypocretin-1 recently measured in the cerebrospinal fluid of two patients with Angelman syndrome were in the normal range [47].

5. Management

As a rule in sleep medicine, sleep problems need to be identified carefully for adequate management. This may include ruling out epileptic activity that may disrupt sleep. Usually, history-taking is sufficient to document features of the sleep–wake cycle sleep onset and sleep maintenance provided it is systematic, but a wake or sleep EEG or polysomnography may be indicated. The sleep problems of patients with Angelman syndrome are often difficult to stabilize through intervention, especially at a young age. The objective is, therefore, more often to reach a clinically acceptable compromise than to solve the problems completely. Anecdotally, difficult nights may occur in (possibly long) clusters alternating with periods of better sleep. Sometimes, factors that may precipitate these clusters can be identified and

prevented. Some parents have noted quasi-periodic cycles, offering the promise of relief after each bad period. However, no consistent correlations have been established with cyclic physiological phenomena.

Behavioral management is currently the most widely applied approach in pediatric sleep medicine. This probably holds true also for Angelman syndrome, though there is a lack of reported results. A single-case study describes successful combination of behavioral therapy and use of an antihistamine drug (diphenhydramine) [11]. Behavioral management is primarily based on characterization of factors underlying the individual's sleep problems. In some cases, reviewing these factors, including bedtime rituals, may lead to simple changes or establishment of routines that can affect sleep dramatically. Severe delays in initiating sleep may be addressed by chronotherapy programs. Children who stay awake for prolonged periods while the rest of the family would like to sleep can be taught to play in their bedroom without doing any damage or putting themselves in danger.

Sedative and hypnotic drugs are sometimes required, either for short periods (1–14 days) or long-term. In a questionnaire study including 339 patients aged 3–22 years, medicines to promote sleep were used in 98 (29%) patients [16]. There is clinical experience with a number of different drugs in several pharmacological families, but no study results are available. These drugs often have a combination of sedative, hypnotic and anxiolytic effects. The main limitation is the risk of side effects, which is increased with high doses or long-term administration. In clinical practice, neuroleptics, benzodiazepines or antidepressants are more commonly used, mostly depending on comorbidity and the clinician's experience.

For the last 10 years or so, use of melatonin has been considered in the management of sleep disorders in children in general and those with developmental disorders in particular [48–50]. In this context, there has been much debate on the effectiveness of melatonin on the sleep problems encountered in Angelman syndrome, mostly based on anecdotal reports of effectiveness. The full range of effects of melatonin is yet to be clarified. In one open, uncontrolled study, 13 children with Angelman syndrome aged 2–10 years were given 0.3 mg of melatonin daily for 6 days (regardless of their weight) before their usual bedtime [23]. The authors noted a decrease in recorded motor activity (on home-based actimetry) and an increase in total sleep time. One other child with Angelman syndrome was included in a randomized controlled study of 32 children, adolescents and young adults with sleep problems in the context of intellectual disability [50]. In this study, melatonin administration was accompanied by a decrease in sleep onset latency, but it did not modify the number of nocturnal awakenings nor total sleep duration. The patient with Angelman syndrome required high doses of mela-

tonin (about 9 mg/day). Wake–sleep cycle worsened in this child soon after discontinuing melatonin treatment and it promptly recovered when melatonin was restored in the open-label phase. More recently, a randomized double-blind placebo-controlled study of the effect of a daily dose of 5 mg was conducted in eight individuals with Angelman syndrome. Melatonin was found to significantly decrease sleep latency, increase total sleep time and reduce night awakenings, but levels of salivary melatonin became very high after a few weeks [51]. However, the claim that chronic administration of melatonin can effectively alleviate sleep problems in individuals with Angelman syndrome [23,52] currently lacks scientific evidence. If confirmed, it might suggest that at least some of the sleep problems reported in Angelman syndrome are due to dysfunction of circadian rhythms, though administered melatonin may either act by shifting sleep phases or through non-specific hypnotic effect [53]. More studies are required in order to know if melatonin can be safely recommended, what types of sleep problems it might help, in which patients it might be considered (e.g., according to age, basal melatonin production levels, etc.) and what dosage would be optimal.

6. Conclusion

Sleep problems are frequently encountered in Angelman syndrome. Until recently, emphasis has been exclusively placed on parental report of clinically apparent sleep disturbances rather than on polysomnographic documentation. The observed abnormalities are multiple, none being distinctively characteristic of Angelman syndrome. The emerging pattern involves a combination of difficulties in initiating or maintaining sleep (i.e., dys-somnias), irregular sleep-wake cycles, sometimes aggravated by inappropriate nocturnal behaviors (e.g., episodes of screaming or laughing), sleep-related seizure disorder or sleep-related movement disorder. They reflect abnormal neurodevelopment functioning presumably involving thalamocortical interaction. However severe the sleep problems may be, they do not usually affect the patients' alertness or activity level when awake or even their personal quality of life to such an extent that it has been suggested that children with Angelman syndrome have a 'diminished need for sleep' as compared with other children [8,9]. This would imply that they would not have higher 'sleep requirements' in order to function optimally, but this concept can hardly be verified. Although mild impairments of learning and other cognitive functions have been demonstrated in normal children following acute sleep deprivation [54], no similar studies have been conducted in children with Angelman syndrome, who are known to have severe to profound intellectual disability. Similarly, the relationship between acute or chronic sleep problems and behavioral problems or deterioration of epilepsy has

not been established in Angelman syndrome. There has been a lack of systematic evaluation of management. Stabilization of these sleep problems is often difficult to achieve. Behavioral management is recommended, following general principles of sleep hygiene. Pharmacological treatment may be required. Sleep problems often improve or disappear from late childhood, which is another remarkable aspect of their pattern of sleep problems. Nevertheless, the sleep problems of the individual with Angelman syndrome commonly affect the entire family. Parents in particular may experience more marked effects of sleep deprivation than the child who shows the primary problem. In addition to the anxiety, anger and feelings of helplessness that family members may experience in relation to the child's sleeplessness, they may suffer from fatigue, irritability, limitation of activities and other disturbances as a result of their own lack of sleep. More robust studies, including polygraphic recordings and neuropsychological testing, are needed to address the interrelationship between sleep and epilepsy, and between sleep and learning, as well as possible differences in the function of the molecular classes underlying Angelman syndrome.

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