

Original 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].

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