Sleep Problems in Individuals With Angelman Syndrome

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Abstract

Prevalence of severe sleep problems and its association with other variables were investigated with 109 individuals who have Angelman syndrome. Severe settling problems, frequent night waking, and early waking were found in 2%, 37%, and 10% of the individuals, respectively. Sleep problems were persistent in this sample. No statistically significant associations were found between presence of a severe sleep problem and other variables (e.g., epilepsy, age, living environment, cause of genetic disorder, parents' and caregivers' coping strategies). Most parents reported adverse effects of their child's sleep problems on their own well-being. Implications for analysis and treatment of sleep problems in individuals with Angelman syndrome are discussed.

Angelman syndrome is a multiple congenital anomaly mental retardation syndrome caused by absence or nonfunctioning of the normally active maternal allele at 15q11-q13. Genetic mechanisms underlying this disorder can be categorized into four main groups: (a) deletions of region 15q11-q13 of the maternally derived chromosome (70% to 75% of cases), (b) paternal uniparental disomy of chromosome 15 (2% to 5% of cases), (c) methylation imprinting mutations (2% to 5% of cases), and (d) UBE3A and other presumed single gene mutations (20% to 25% of cases) (Buiting et al., 1995; Clayton-Smith & Laan, 2003; Kishino, Lalande, & Wagstaff, 1997; Knoll et al., 1989; Matsuura et al., 1997; Otha et al., 1999). At present, Angelman syndrome is a clinical diagnosis that can be confirmed by either cytogenetic or DNA testing in about 80% to 85% of the cases. This syndrome is of specific importance because of the involved phenomenon of genetic imprinting, that is, the differential expression of genetic information whether inherited from the mother or from the father.

Angelman syndrome is characterized by neurological (e.g., ataxic movements) and craniofacial abnormalities (e.g., protruding tongue, microbrachycephaly). Most people with the syndrome have a seizure disorder. They typically function in the profound and severe range of mental retardation. Some of the features of Angelman syndrome may become more or less prominent as individuals grow older (e.g., Buntinx et al., 1995; Smith et al., 1996; Zori et al., 1992).

During the past decade, an increasing number of studies have been published suggesting that Angelman syndrome is associated with a behavioral phenotype. A *behavioral phenotype* is defined as an increased probability that a person with a given syndrome will exhibit certain behavioral characteristics compared to persons without the syndrome (see Dykens, 1995). Results of within-syndrome as well as between-syndrome studies

have shown that many people with Angelman syndrome exhibit excessive laughter or laughter-like facial grimacing, hyperactivity, noncompliance, stereotypic behaviors, incontinence, eating difficulties, communication deficits, and sleep problems (e.g., Clarke & Marston, 2000; Clayton-Smith, 1993; Didden, Korzilius, Duker, & Curfs, 2004; Didden, Sikkema, Bosman, Duker, & Curfs, 2001; Oliver, Demetriades, & Hall, 2002; Summers, Allison, Lynch, & Sandler, 1995; Summers & Feldman, 1999).

Sleep problems are relatively common in people with Angelman syndrome. In one of the first studies that assessed its prevalence in individuals with Angelman syndrome, Zori et al. (1992) compared sleep problems in a sample of children who were living with their families in the United Kingdom ($n = 39$) and in the United States ($n = 27$). Using a questionnaire, they found sleep problems in 74% and 33% of the samples, respectively. Clayton-Smith (1993) observed 82 children and adolescents who were between 1.5 and 26 years old, most of whom lived at home. Interviews with parents and analysis of medical records yielded sleep problems in 90% of this sample, and it appeared that sleep problems were worse between 2 and 6 years. She also found a reduced sleep need, with children sleeping 5 to 6 hours per night on average. A similar high rate of sleep problems have been found by Smith et al. (1996) among 27 persons who were between 3 and 34 years old. Sleep problems were defined in terms of frequent night waking, and such problems were found in 86% of the sample. In some cases, sleep seemed to have spontaneously improved when the children were 6 to 8 years old. Among a small sample of children with Angelman syndrome ($n = 11$), Summers et al. (1995) found settling problems and frequent night waking in 91% and 100% of the children, respectively. Finally, Clarke and Marston (2000) used the Reiss Screen for Maladaptive Behavior (Reiss, 1988) with 73 persons, most of whom were living at home (90%) and found that sleep problems were present in 42% of the cases.

Sleep problems may have detrimental effects on both the individual involved and his or her parents and other caregivers. In reviewing prevalence studies on sleep problems in individuals with mental retardation, Didden and Sigafoos (2001) concluded that many parents and other caregivers report fatigue, adverse effects on their social life, increased levels of distress, and irritability towards the individual with sleep problems. Presence of sleep problems may also be associated with daytime fatigue and/or decreased cognitive functioning in the individual involved. For example, Espie et al. (1999) found that individuals with sleep problems (i.e., sleep deprivation) showed poor daytime vigilance as assessed by a two-choice reaction time test compared to individuals without sleep problems. Finally, several researchers have found significant associations between the presence of sleep problems and daytime behavior problems in individuals with mental retardation. Sleep problems may be conceptualized as setting events for the occurrence of daytime behavior problems; that is, the presence of sleep problems may increase the likelihood of behavior problems, such as hyperactive or aggressive behavior, in the daytime (see, e.g., O'Reilly & Lancioni, 2000).

Despite the growing database on sleep problems in people with Angelman syndrome, there are several limitations of the above studies. In each study, only a gross and general measure of sleep (i.e., yes/no format) had been employed, and data on sleep behaviors and sleep problems were rarely collected using a standardized instrument (i.e., Clarke & Marston, 2000) or questionnaire. Also, in several studies the number of participants with Angelman syndrome on which conclusions were drawn was rather small. Furthermore, no analyses had been conducted to explore associations between presence of sleep problems and other relevant variables, such as presence or absence of epilepsy, age, and living environment. Such correlational analyses may reveal significant associations that provide hypotheses about the cause(s) of sleep problems in individuals with Angelman syndrome. Causes of sleep problems in people with mental retardation may be environmentally based (e.g., daytime naps or inadvertent parental attention reinforcing disruptive behavior during nighttimes). Other causes relate to health issues, such as epilepsy, use of medication, or nighttime incontinence. (For a review, see Didden and Sigafoos, 2001.) Finally, in the studies on Angelman syndrome cited above, investigators did not collect data on consequences of the person's sleep problems for parents and other caregivers nor on their coping strategies.

The present study, therefore, extends the literature on sleep problems in individuals with Angelman syndrome in several ways. First, we used a relatively large sample ($n = 109$). This sample

constitutes a large part of the population of individuals with Angelman syndrome who live in the Netherlands and the Dutch-speaking part of Belgium (i.e., Flanders). Second, we used a standardized questionnaire to provide a detailed description of types of sleep behaviors and sleep problems in this sample. Third, associations between the presence of a *severe* sleep problem and individual- as well as parent- and caregiver-related variables were explored. Furthermore, information about the coping strategies of parents and other caregivers concerning the individual's sleep problem was gathered as well as consequences these problems have for the caregivers' and parents' well-being.

Method

Participants and Procedure

A sleep questionnaire (see *Materials*) was sent to parents who were members of the Dutch Angelman Parent Association and who had a child with Angelman syndrome ($N = 133$). In a letter accompanying the questionnaire, parents were asked to complete it jointly. If the participant was living in a residential facility, parents were asked to complete the questionnaire together with a staff member who had known the participant at least 3 months. Staff members working on daytime shift gathered information from sleep logs and shift reports completed by staff members working on overnight shift.

If a questionnaire was not returned within 3 weeks, a reminder was sent to those parents. The sleep questionnaire was completed for 109 individuals, constituting a response rate of 82%. Sixty-seven percent of the participants lived at home with their parents, and 33% lived in a residential facility. Of the participants, 49% were male, and their mean age was 15.2 years (standard deviation [*SD*] = 9.3, range = 2 to 44).

Materials

Sleep questionnaire. A sleep questionnaire was used to investigate participant's sleep behaviors and problems. This questionnaire was adapted from Wiggs and Stores (1996a) and Didden, Korzilius, van Aperlo, van Overloop, and de Vries (2002) and consisted of three parts. Part One addresses demographic information about the individual (e.g., presence of seizure disorder, genetic cause of Angelman syndrome). The second half of Part One contains items about the family's sleep (e.g., "Do you feel that you get enough sleep yourself?") as well as treatment for their child's sleep problems (e.g., "Have you ever received any advice or help about your child's sleep problems?"). Part Two covers settling, nighttime waking, and early waking behaviors. With some items, parents are asked to rate its frequency on a 5-point scale: 1, never; 2, less than once per month; 3, 2 to 4 times per month; 4, several times per week; and 5, nightly (e.g., "How often does your child wake in the night?") or length of time: 1, few minutes; 2, up to half an hour; 3, up to 1 hour; 4, 1 to 2 hours; and 5, more than 2 hours (e.g., "How long does it usually take to settle him/her?"). Some items require yes/no answers (e.g., "Once asleep, does s/he sleep soundly?"). Other questions elicit information related to parents' reactions (e.g., "If your child will not go to bed or settle to sleep what do you do about it?"). This part also contains items that require either a yes/no answer (e.g., "Does s/he usually wake up in a good mood?") or a reply in hours (e.g., "What time does your child usually go to bed?"). Part Three is comprised of items that address several sleep behaviors (e.g., "Grinds teeth in sleep"), and parents are asked to rate frequency of occurrence on a 5-point scale: 1, never; 2, less than once per month; 3, 2 to 4 times per month; 4, 3 nights per week; and 5, nightly.

Definition of a Severe Sleep Problem

In order to define a *severe* sleep problem, we used the criteria established by Wiggs and Stores (1996a) and Didden et al. (2002). Three types of sleep problems were distinguished. *Early waking* was defined as severe if the individual woke before 5 a.m. and stayed awake during 3 or more nights per week. *Night waking* was defined as severe if it occurred 3 or more nights per week, if the individual woke for more than a few minutes, and if the parent(s) or caregiver(s) were disturbed during that time (e.g., individual sleeps with the parent in one bed). Finally, *severe settling problems* occurred 3 or more nights per week, whereby the individual took more than 1 hour to fall asleep and if the caregiver was disturbed. A *severe sleep problem* was diagnosed if an individual had at least one of the above three types of sleep problems.

Results

Demographic Information

The diagnosis of Angelman syndrome was made by chromosomal and/or DNA assessment

in 85% of the individuals. Within this group, a deletion was the most common cause of Angelman syndrome (i.e., 78%). A disomy and translocation inversion were diagnosed in 11% and 3% of the individuals, respectively. In 8% of the cases, parents failed to mention the diagnosis or genetic testing had not been completed at the time of our study. In 15% of the cases, diagnosis was based on clinical history and features. Mean age at which the diagnosis of Angelman syndrome was made was 7 years (SD = 7.9, range = 0 to 36).

Of the participants, 78% had a seizure disorder, of whom 48% suffered from absences only and 12% from grand mal attacks only. A combination of both types of seizures was found in 17% of the participants. Other types of epilepsy were found in 23% of the individuals. Seventy-three percent of the participants took anticonvulsive medication, and most of them (65%) showed no epileptic activity as a result of this medication. Medication failed to control epilepsy in 7% of the individuals, and in 27%, epileptic seizures were only partially controlled. The seizure disorder was present from birth for 9%, whereas for 68%, seizures had begun between 1 and 3 years of age and at a later age for 22%. Twenty-four percent showed predominantly nighttime seizures and 58%, predominantly daytime epileptic activity.

Through parental reports, level of mental retardation was assessed by previously administered cognitive tests or the Vineland Adaptive Behavior Scales (Sparrow, Balla, & Cicchetti, 1984). Percentages of individuals with profound, severe, and moderate mental retardation were 38, 53, and 9, respectively. Most individuals were able to walk independently (66%), whereas 26% were able to walk with help; others crawled (6%) or used a wheelchair (3%).

Descriptive Analysis

Individual-related variables. Types and percentages of sleep behaviors that occurred 3 nights per week or more are shown in Table 1. For example, most children (93%) had nighttime enuresis and encopresis, 22% took medication intended for improving sleep (of whom 42% took Dipiperon®, 32% took melatonin [range = 3 to 5mg], and 26% took other types of medication), and 51% appeared to be more active than other individuals during daytime.

According to our research criteria, severe types of settling problems, frequent night waking, and early waking were found in 2%, 37%, and 10% of the cases, respectively. The percentage of children with a severe sleep problem was 40%. Of participants with severe frequent night waking, 46% took up to 30 minutes before going back to sleep, 23% stayed awake for a maximum of 1 hour, and 31% took more than 1 hour to resettle.

Table 1. Percentage of Individuals Exhibiting Sleep Behaviors During 3 to 7 Nights Per Week

Sleep behavior	Endorsement (%)
Particular bedtime routine	94
Wakes up in a good mood	94
Nighttime incontinence	93
Wakes up rested	83
Insists on bedtime rituals before going to sleep	63
Needs security object	63
Breathes through mouth rather than nose	60
Appears more active than other children[a]	51
Snores	26
Restless sleep	25
Takes sleep medication	22
Daytime napping[b]	22
Reluctant to go to sleep	12
Seems drowsy can't stop from sleeping[a]	12
Wakes in morning before 5 a.m. and stays awake	10
Sweats a lot during sleep	10
Grinds teeth	10
Sleeps with head tipped right back	9
Quick movements of arms and legs	9
Has urges to fall asleep[a]	8
Rocks body	7
Falls to the ground due to muscle weakness[a]	7
Gags and chokes	6
Repeatedly stops breathing for 15 to 30 seconds	4
Afraid of the dark	3
Bangs head	2
Afraid of going to bed	0
Nightmare[c]	0
Nighttime screaming in terror[d]	0
Sleep walks	0
Bites tongue	0

[a]During daytime. [b]Children older than 5 years. [c]Last half of night. [d]First half of night.

In case they woke up, 24% usually started to cry, 43% called out for their parent or caregiver, 20% got out of bed, 7% banged their head, 29% played with toys, and 44% exhibited other behaviors (e.g., laughing).

Parent and caregiver-related variables. Parents and caregivers were asked whether they thought that the child had a current severe sleep problem (no criteria or definition of a severe sleep problem were provided to them). This question was answered in an affirmative way in 54% of the cases. Of the total sample, frequent night waking was mentioned most often (40%), whereas settling problems and early waking were mentioned in 23% and 27% of the cases, respectively. We also found that few parents and caregivers (7%) rated daytime sleepiness as problematic.

According to parents and staff members, reported sleep problems were highly persistent. In most individuals (90%), such problems existed for at least 1 year. Mean duration of sleep problems was 9.7 years (SD = 8.0, range = 0.5 to 34). For those individuals who did not currently have sleep problems, 53% had had a sleep problem in the past; night waking was rated most often (84%) as problematic.

A minority of parents and caregivers (33%) reported that they had received any advice or help about the treatment of the individual's (current as well as past) sleep problems. Table 2 contains type and effectiveness of help and advice received. Sleep medication was used most often (in 23% of the cases); only 24% of the parents and other caregivers of the individuals who used sleep medication reported this type of treatment as effective. Although only 6% of parents and caregivers received advice about behavioral treatment, 43% of them reported this type of treatment as effective. (We defined *effectiveness of treatment* as a substantial reduction or elimination of the target behaviors as a result of this treatment.)

Table 2. Type of Help and Advice Received by Parents and Their Effectiveness for Sleep Problems (in %)

Type of help/advice	Received	Effective[a]
Psychological[b]	6	43
Education	11	33
Sleep medication[c]	23	24
Operation	3	0
Other[d]	3	0

[a]Treatment was effective in cases where a substantial reduction or elimination of target behaviors was established as a result of that treatment. [b]For example, behavioral treatment. [c]For example, melatonin. [d]For example, homoeopathic treatment.

Percentages of parents and caregivers showing different types of behaviors and emotional reactions towards participant's severe sleep problems are depicted in Table 3. It may be concluded that in many cases participant's sleep problem is associated with adverse effects on the well-being of parents and other caregivers.

Inferential Analysis

Upon being asked whether the individual had a severe type of sleep problem, parents and caregivers mentioned a severe type of frequent night waking in 40% of the cases. According to our criteria, prevalence rate of severe night waking was 37%, which was consistent with parents' and caregivers' opinion, $\chi^2(1, N = 53) = 22.54$, $p < .001$. Also, they mentioned severe settling problems and early waking for 23% and 27% of the total sample, whereas according to our criteria, these problems were present in 2% and 10% of the sample, respectively. (Due to low cell frequencies, differences in prevalence rates of settling problems and early waking between parent's and caregivers' opinion and our research criteria could not be subjected to statistical analysis.)

Mean age of participants with a *severe* sleep problem was 167 months (SD = 108.82). Participants without a severe sleep problem had a mean age of 179 months (SD = 100.63). However, the difference in age between both groups failed to attain statistical significance. Also, the point biserial correlation between age in years and presence of a severe sleep problem was not statistically significant, $r_{pb} = -.08$.

Percentages of participants with a severe sleep problem associated with several individual-related variables are shown in Table 4. Chi-square analyses revealed no individual-related variables associated with the presence of a severe sleep problem, although some associations (i.e., use of medication—anticonvulsives, medication to treat physical discomfort such as constipation, medication intended to improve sleep; daytime napping; breathing through mouth; only one type of epilepsy) approached statistical significance. Relatively high percentages of a severe sleep problem were found in individuals who used medication, showed daytime napping, breathed though their

Table 3. Parental/Caregiver Behaviors and Reactions to Participant's Sleep Problem (in %)

Behaviors and reactions	Endorsement
Refrain from responding to participant in case of waking up	30
Respond to participant's sleep problem	70
In case parents and other caregivers respond, they	
Provide play activities	16
Provide food and drinks	20
Put participant back into bed	15
Allow participant to sleep in parent's bed	13
Provide other type of comfort (e.g., change diaper)	36
Participant's sleep problem negatively affects own sleep	65
Report fatigue due to participant's sleep problem	100
Feelings of irritation toward participant because of sleep problem	75
Report feeling depressed	29
Arguments with partner about how to deal with sleep problem	29
Feel powerless in coping with participant's sleep problem	64
Take special measures to ensure participant's safety at night	80

mouth when asleep, and had more than one type of epilepsy.

Finally, we analyzed whether parents' and caregivers' coping strategies were associated with the presence of a severe sleep problem. There were no statistically significant associations with the presence of a severe sleep problem and parental and other caregivers' coping strategies (see also Table 3).

Discussion

In our large sample (n = 109) of individuals with Angelman syndrome who lived in the Netherlands and Flanders, 40% had a severe sleep problem. Severe types of frequent night waking occurred most often (37%), followed by early waking (10%). Only 2% showed severe settling problems.

Differences in both definition and measurement of sleep problems in individuals with Angelman syndrome renders direct comparison between our results and those found by others difficult (e.g., Clarke & Marston, 2000; Clayton-Smith, 1993; Summers et al., 1995). Using the same questionnaire as we did, Wiggs and Stores (1996a) and Didden et al. (2002) found severe sleep problems in individuals with profound and severe mental retardation in 43% and 33% of the samples, respectively. Future studies should be conducted to compare types of sleep problems and sleep behaviors in individuals with Angelman syndrome with those exhibited by individuals with other genetic disorders or nonspecific mental retardation in order to assess whether certain types of sleep problems or sleep behaviors are part of a behavioral phenotype of Angelman syndrome. Furthermore, future investigation of sleep architecture by polysomnography may increase our understanding of the nature and cause(s) of sleep problems in individuals with Angelman syndrome. Sleep architecture derived from polysomnography in these individuals and comparing that sleep architecture to that of other individuals may lead to identification of a polysomnographic phenotype in individuals with Angelman syndrome (see Harvey & Kennedy, 2002).

In our sample, no statistically significant associations were found between the presence of a severe sleep problem and individual-related variables (e.g., cause of Angelman syndrome; presence, onset, and type of epilepsy; level of mental retardation; living environment; age; and hyperactive behavior) nor were parents' and caregivers' coping strategies significantly related to severe sleep problems. In some cases, however, such as in the case of use of medication (i.e., anticonvulsives), presence of one versus more types of epilepsy, daytime napping, and one type of parents' and caregivers' coping strategies (i.e., entering the individual's bedroom and providing comfort), chi-square values approach significance. In epi-

Table 4. Participants With a Severe Sleep Problem Related to Individual Variables

Variable (*n*)	Sleep problem (%)	$\chi^2(1)$
Level of mental retardation		.36
Profound (27)	44	
Severe (30)	37	
Moderate[a] (4)	25	
Use of medication (77)	46	3.36
No medication (15)	20	
Deletion (51)	39	1.44
Other causes of AS[b] (14)	11	
Epilepsy (69)	45	1.49
No epilepsy (23)	30	
Only one type of epilepsy (46)		
More than one type of epilepsy (17)	39	3.27
Daytime epilepsy (42)	52	2.72
Epilepsy at other times (33)	33	
Nighttime epilepsy (18)	42	
Epilepsy at other times (53)	47	0.01
Seizure-free (45)	47	0.01
Not free from seizures (22)	46	
Lives at home (66)	44	0.67
Lives in facility (26)	35	
Daytime naps (17)	59	2.91
No daytime naps (64)	36	
Incontinence (84)	42	0.05
Continent (5)	40	
Breathes through mouth (50)	52	3.02
Breathes through nose (31)	32	
Insists on bedtime rituals (54)	48	1.67
No bedtime rituals (35)	34	
Needs security object (54)	43	0.12
No object (31)	39	
Daytime hyperactivity (47)	47	0.54
No hyperactivity (41)	39	

[a]Not included in the analysis due to low cell frequency. [b]Angelman syndrome.

demiological studies among individuals with nonspecific mental retardation, researchers have found a relationship between presence of a seizure disorder and sleep problems in that individuals with a seizure disorder more often show severe sleep problems than those without a seizure disorder (see, e.g., Didden et al., 2002). There may be a reciprocal relationship between epilepsy and severe sleep problems. Seizures may induce sleep disturbance, whereas sleep deprivation may facilitate the occurrence of epileptic activity (see, e.g., Mendez & Radtke, 2001). Furthermore, anticonvulsive medication may modify both sleep architecture and sleep–wake cycle (see, e.g., Placidi, Diomedi, Scalise, Marciani, Romigi, & Gigli, 2000). Both factors may be responsible for the relatively high percentage of individuals with Angelman syndrome who show severe types of frequent night waking. Future researchers should investigate the relationship between sleep problems, epilepsy, and use of anticonvulsive medication in individuals with Angelman syndrome.

Another possible explanation for sleep problems in individuals with Angelman syndrome is that such problems are the symptoms of a circadian rhythm disorder. As melatonin is a strong chronobiotic drug, with negligible hypnotic effect, results of the present study suggest that sleep problems in this group may be caused by a circadian rhythm disorder. In our study, many individuals showed sleep onset problems, which is a main feature of the delayed sleep phase syndrome. Recently, a length polymorphism of the circadian clock gene Per3 was shown to be linked to the delayed sleep phase syndrome (see Archer et al., 2003). Future researchers should investigate whether a clock gene defect is closely related to the chromosomal defect that is involved in Angelman syndrome.

It is a well-established fact that sleep problems are related to family functioning as well as the well-being of other caregivers. For example, Richdale, Francis, Gavidia-Payne, and Cotton (2000) showed that the presence of sleep problems in children with mental retardation was associated with increased scores of indices of parental stress. In the present study, most parents reported that their child's sleep problem adversely affected their own sleep and well-being. We also found that only a minority of parents and other caregivers had been offered any help or advice in managing the sleep problem of the individual. This is consistent with other studies in this area. For example, Wiggs and Stores (1996b) found that 47% of parents who had a child with a severe sleep problem had received any type of treatment advice. More recently, Didden et al. (2002) found a much lower percentage (19%) of parents who had received any type of advice. In the present study as well as in

the Wiggs and Stores study, medication was used most often as treatment option, followed by behavioral intervention and education. In both studies, medication was considered less effective than behavioral intervention. It should be noted, however, that only 6% of the parents and caregivers in the present study had used behavioral treatment.

These results suggest that the service provision to parents and caregivers is inadequate and highlights the importance of good clinical alertness for sleep problems and assuring optimal care through providing guidelines for treatment strategies. However, until present, few studies have been published that describe results of effective treatment of sleep problems in children and adults with Angelman syndrome. Results of studies by Summers et al. (1992) and Zhdanova, Wurtman, and Wagstaff (1999) suggest that such problems are amenable to pharmacological and/or behavioral treatment. In a study with 10 children with Angelman syndrome who were between 2 to 10 years old, Zhdanova et al. found that low doses of melatonin resulted in decreased motor activity during sleep and increased total sleep. Psychological treatment may also be effective in the treatment of sleep problems in individuals with this syndrome. Summers et al. (1992) implemented a treatment package, consisting of pharmacotherapy and scheduling, to treat the severe sleep problem in a 9-year-old boy with Angelman syndrome. This package resulted in an immediate increase of the total hours of sleep. Results were maintained after medication was withdrawn. However, follow-up data were collected as early as 45 days, and it is not known whether the reported positive results were maintained long-term.

Further, extinction (i.e., ignoring disturbing nighttime behaviors) may be indicated in cases where such behaviors are reinforced by parental attention. In many cases, parents' and caregivers' coping strategy (e.g., entering the individuals bedroom and providing comfort) was to react to the child contingent on sleep problems, thereby inadvertently maintaining the disturbing nighttime behaviors (for a description of the extinction procedure, see Didden & Sigafoos, 2001). Functional analysis/assessment of the sleep behavior(s) and an assessment of potential medical factors (e.g., epilepsy, reflux disease, cerebral palsy) underlying a severe sleep problem in a given individual should precede any treatment.

A limitation of our questionnaire study is that data on sleep behaviors in individuals with Angelman syndrome were not collected using direct measures of observation. It is still unknown whether our data reflect actual sleep behavior in these individuals. This may have threatened the validity of our conclusions.

In future studies investigators should assess whether circadian rhythms are disturbed in individuals with Angelman syndrome who show sleep problems and whether behavioral treatment and/or exogenous melatonin are effective in decreasing and eliminating sleep problems in this group. Effective treatment of severe sleep problems in individuals with Angelman syndrome may not only lead to a normalized sleep pattern in the individual involved, but also to an improvement in the well-being of his or her parents and other family members and caregivers. In addition to parental or staff members' logs and diaries, direct measures of sleep behaviors should be employed, such as actigraphy.

References

Archer, S., Robilliard, D., Skene, D., Smits, M., Williams, A., Ahrendt, J., & Von Schantz, M. (2003). A length polymorphism in the circadian clock gene Per3 is linked to the delayed sleep phase syndrome and extreme diurnal preference. *Sleep, 26,* 413–415.

Buiting, K., Saitoh, S., Gross, S., Dittrich, B., Schwartz, S., Nicholls, R., & Horsthemke, B. (1995). Inherited microdeletions in the Angelman and Prader-Willi syndromes define an imprinting center on human chromosome 15. *Nature Genetics, 9,* 395–400.

Buntinx, I., Hennekam, R., Brouwer, O., Stroink, H., Beuten, J., Mangelschots, K., & Fryns, J. (1995). Clinical profile of Angelman syndrome at different ages. *American Journal of Medical Genetics, 56,* 176–183.

Clarke, D., & Marston, G. (2000). Problem behaviors associated with 15q- Angelman syndrome. *American Journal on Mental Retardation, 105,* 25–31.

Clayton-Smith, J. (1993). Clinical research on Angelman syndrome in the United Kingdom: Observations on 82 affected individuals. *American Journal on Medical Genetics, 46,* 12–15.

Clayton-Smith, L., & Laan, L. (2003). Angelman syndrome: A review of the clinical and genet-

ic aspects. *Journal of Medical Genetics, 40,* 87–95.

Didden, R., Korzilius, H., van Aperlo, B., van Overloop, C., & de Vries, M. (2002). Sleep problems and daytime problem behaviours in children with intellectual disability. *Journal of Intellectual Disability Research, 46,* 537–547.

Didden, R., Korzilius, H., Duker, P., & Curfs, L. (2004). *Communicative functioning of individuals with Angelman syndrome: A comparative study.* Manuscript submitted for publication.

Didden, R., & Sigafoos, J. (2001). A review of the nature and treatment of sleep disorders in individuals with developmental disabilities. *Research in Developmental Disabilities, 22,* 255–272.

Didden, R., Sikkema, S., Bosman, I., Duker, P., & Curfs, L. (2001). Use of a modified Azrin-Foxx toilet training procedure with individuals with Angelman syndrome. *Journal of Applied Research in Intellectual Disabilities, 14,* 64–70.

Dykens, E. (1995). Measuring behavioral phenotypes: Provocations from the "New Genetics." *American Journal on Mental Retardation, 99,* 522–532.

Espie, C., Paul, A., McColl, J., McFie, J., Amos, P., Gray, J., Hamilton, D., & Jamal, G. (1999). Cognitive functioning in people with epilepsy plus severe learning disabilities: A systematic analysis of predictors of daytime arousal and attention. *Seizure, 8,* 73–80.

Harvey, M., & Kennedy, C. (2002). Polysomnographic phenotypes in developmental disabilities. *International Journal of Developmental Neuroscience, 20,* 443–448.

Kishino, T., Lalande, M., & Wagstaff, J. (1997). UBE-3A/E6-AP mutations cause Angelman syndrome. *Natural Genetics, 15,* 70–73.

Knoll, J., Nicholls, R., Magenis, R., Graham, J., Lalande, M., & Latt, S. (1989). Angelman and Prader–Willi syndromes share a common chromosome 15 deletion but differ in parental origin of the deletion. *American Journal of Medical Genetics, 32,* 285–290.

Matsuura, T., Sutcliffe, J., Fang, P., Galjaard, R., Jiang, Y., Benton, C., Rommens, J., & Beaudet, A. (1997). De novo truncating mutations in E6-AP ubiquitin-protein ligase gene (UBE3A) in Angelman syndrome. *Natural Genetics, 15,* 74–77.

Mendez, M., & Radtke, R. (2001). Interactions between sleep and epilepsy. *Journal of Clinical Neurophysiology, 18,* 106–127.

Oliver, C., Demetriades, L., & Hall, S. (2002). Effects of environmental events on smiling and laughing behavior in Angelman syndrome. *American Journal on Mental Retardation, 107,* 194–200.

O'Reilly, M., & Lancioni, G. (2000). Response covariation of escape-maintained aberrant behavior correlated with sleep deprivation. *Research in Developmental Disabilities, 21,* 125–136.

Otha, T., Buiting, K., Kokkonen, H., McCandless, S., Heeger, S., Driscoll, D., Cassidy, S., Horsthemke, B., & Nicholls, R. (1999). Molecular mechanisms of Angelman syndrome in two large families involves an imprinting mutation. *American Journal of Human Genetics, 64,* 385–386.

Placidi, F., Diomedi, M., Scalise, A., Marciani, M., Romigi, A., & Gigli, G. (2000). Effect of anticonvulsants on nocturnal sleep in epilepsy. *Neurology, 54,* S25–S32.

Reiss, S. (1988). *Reiss Screen for Maladaptive Behavior test manual.* Worthington, OH: IDS.

Richdale, A., Frances, A., Gavidia-Payne, S., & Cotton, S. (2000). Stress, behaviour, and sleep problems in children with an intellectual disability. *Journal of Intellectual and Developmental Disability, 25,* 147–161.

Smith, A., Wiles, C., Haan, E., McGill, J., Wallace, G., Dixon, J., Selby, R., Colley, A., Marks, R., & Trent, R. (1996). Clinical features in 27 patients with Angelman syndrome resulting from DNA deletion. *Journal of Medical Genetics, 33,* 107–112.

Sparrow, S., Balla, D., & Cicchetti, D. (1984). *Vineland Adaptive Behavior Scales.* Circle Pines, MN: American Guidance Service.

Summers, J., Allison, D., Lynch, P., & Sandler, L. (1995). Behavior problems in Angelman syndrome. *Journal of Intellectual Disability Research, 39,* 97–106.

Summers, J., & Feldman, M. (1999). Distinctive pattern of behavioral functioning in Angelman syndrome. *American Journal on Mental Retardation, 104,* 376–384.

Summers, J., Lynch, P., Harris, J., Burke, J., Allison, D., & Sandler, L. (1992). A combined behavioral pharmacological treatment of sleep-wake schedule disorder in Angelman syndrome. *Journal of Developmental and Behavioral Pediatrics, 13,* 284.

Wiggs, L., & Stores, G. (1996a). Severe sleep disturbance and daytime challenging behaviour in children with severe learning disabilities. *Journal of Intellectual Disability Research, 40,* 518–528.

Wiggs, L., & Stores, G. (1996b). Sleep problems in children with severe intellectual disabilities: What help is being provided? *Journal of Applied Research in Intellectual Disabilities, 9,* 159–164.

Zhdanova, I., Wurtman, R., & Wagstaff, J. (1999). Effects of a low dose of melatonin on sleep in children with Angelman syndrome. *Journal of Pediatric Endocrinology and Metabolism, 12,* 57–67.

Zori, R., Hendrickson, J., Woolven, S., Whidden, E., Gray, B., & Williams, C. (1992). Angelman syndrome: Clinical profile. *Journal of Child Neurology, 7,* 270–280.

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