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Sleep problems in children with Angelman Syndrome: The effect of a behavioral intervention program

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ABSTRACT

Background & aims: The aim of this study was to investigate the effect of a behavioral intervention on sleep problems, which are significant and an unmet clinical need in children with Angelman Syndrome (AS).

Methods & procedures: Children (2–18 years) with AS and sleep problems were randomized to a behavioral intervention program or a control group. Intervention consisted of a standardized program including home visits, psycho-education, feedback based on direct observation of bedtime routine and video footage of the night and behavioral treatment techniques by a behavioral therapist. Change in sleep duration (primary) and parental sleep, nighttime visits, sleep hygiene, daytime behavior, parental stress and quality of life (secondary) were assessed post-intervention and at follow-up using questionnaires, diary, actigraphy and videosomnography.

Outcomes & results: The groups, 9 children in each, did not differ at baseline. We found a significant effect of intervention on wake after sleep onset with classical statistical analysis (videosomnography). With single case analysis we found a positive effect on total sleep time (diary and actigraphy) and wake after sleep onset (diary) with a persistent effect on total sleep time (actigraphy) and wake after sleep onset (diary). On secondary outcome there was a significant and persistent effect on sleep hygiene and several quality of life domains.

Conclusions & implications: Behavioral intervention has a positive and persistent effect on sleep problems in children with AS. We advise psycho-education for all parents and use of videosomnography for both evaluation of and feedback on sleep behavior patterns, individual behavioral advice and specific behavioral techniques for children with sleep problems.

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1. Introduction

Angelman Syndrome (AS) is a rare neurodevelopmental disorder characterized by typical facial features, severe developmental delay with lack of speech, movement disorders, characteristic behavioral features, a high prevalence of epilepsy and sleep problems (Bindels-de Heus et al., 2020; Williams et al., 2006). AS is caused by a lack of a functional maternally inherited UBE3A gene, mostly due to a deletion of the chromosome 15q11.2-q13 region, followed by a paternal uniparental disomy (UPD), an imprinting center defect (IC) or a pathogenic variant of the maternal copy of the UBE3A gene (Beygo et al., 2019; Williams et al., 2006).

Sleep problems are reported by 50–90% of parents of patients with AS and can have a large impact on the quality of life of the family. Parents report difficulties with settling, sleep onset latency, frequent awakening at night, early awakening in the morning and/or a diminished total sleep time, and this is prevalent in all genotypes (Bindels-de Heus et al., 2020; Bruni et al., 2004; Clayton-Smith, 1993; Didden et al., 2004; Goldman et al., 2012; Khan et al., 2019; Pelc et al., 2008; Pereira et al., 2020; Spruyt et al., 2018; Trickett et al., 2017, 2018, 2019). In a study with 339 children and adolescents with AS with a mean age of 11 years (SD 4.9), parents indicated an average of about 8 h of sleep per night by diary. Problems are more frequently reported in infancy and early childhood, but may persist into adulthood (Didden et al., 2004; Thibert et al., 2013; Walz et al., 2005). Sleep problems in children usually result in sleep problems for parents; parents rate sleep problems of their children with AS one of their most serious concerns (Willgoss et al., 2021). Intervention options are reported by them as an unmet need (Goldman et al., 2012; Grieco et al., 2019; Pelc et al., 2008; Trickett et al., 2019; Wheeler et al., 2017).

To set a perspective: neurotypical children have a daily need of sleep of 14–16 h (0–1 year), 12–14 h (2–4 year), 10–12 h (5–12 years) and 8 h from puberty (Boer, 2011; Iglowstein et al., 2003). All children wake up several times briefly during the night at the end of the 60–90 min sleep cycle, but usually fall asleep again without rituals or parental assistance. This ability to fall asleep improves during the first year of life (Boer, 2011; Burnham et al., 2002; Iglowstein et al., 2003). Ten to thirty percent of neurotypical children in cross-sectional studies have significant bedtime problems and/or night waking, and in most cases, the causes are behavioral (Burnham et al., 2002; Owens & Mindell, 2011; Thorpy, 2012). In children with a developmental delay with or without a known underlying genetic condition, high rates of sleep problems (> 90%) are reported with often a bidirectional link between behavioral and sleep problems (Didden & Sigafoos, 2001; Gadoth & Oksenberg, 2014; Owens & Mindell, 2011; Tietze et al., 2012).

There seems to be a role for both physical as well as behavioral factors in sleep problems in AS. In AS some evidence suggest that the natural melatonin peak is delayed, and that some AS individuals are slow metabolizers for exogenous melatonin (Braam et al., 2008). Polysomnography has shown abnormal sleep architecture, irregular sleep-wake type and delayed sleep phase type (Miano et al., 2004; Takaesu et al., 2012). Epilepsy, gastro-esophageal reflux and constipation are well known co-morbidities and may also play a negative role in sleep (Bindels-de Heus et al., 2020; Conant et al., 2009). Besides these physical factors, behavioral factors also seem to play a role in sleep problems in AS. Behavioral problems during the day can extend into the evening and night (Wiggs & Stores, 1996). AS children often show pervasive behavior problems, sensory processing issues and impaired emotional regulation (Heald et al., 2020; Peters et al., 2004). They tend to have limited selfsoothing skills, becoming used to sleep facilitators easily, developing extensive rituals and need for co-sleeping (Allen et al., 2013; Trickett et al., 2019). The sleep problems can affect daytime functioning and behavior of the child and can also cause parental sleepiness and stress, creating a negative feedback loop (Allen et al., 2013; Goldman et al., 2012; Pelc et al., 2008; Trickett et al., 2019; Wiggs & Stores, 1996; Willgoss et al., 2021).

A variety of behavioral interventions to address sleep problems in children with developmental delay has been developed. Previous research has shown that parental education on sleep hygiene, sleep-wake schedules and bedtime routines, supplemented with intensive guidance by a behavioral therapist when necessary, can diminish sleep problems in children with developmental delay (Didden & Sigafoos, 2001; Grigg-Damberger & Ralls, 2013; Jan et al., 2008; Malow et al., 2012; Spruyt & Curfs, 2015; Wiggs & Stores, 1998). A systematic review on non-pharmacological management of problematic sleep in children with developmental disabilities identified 90 mainly single-case and case studies and showed reasonable evidence for a positive effect of behavioral interventions, however also concluded that there is a need for RCT's including objective measures that quantify improved sleep (Spruyt & Curfs, 2015). A recent systematic review on pharmacological and behavioral interventions to improve sleep in individuals with AS reported on ten studies in 54 children and concluded that there is provisional, but weak evidence for the effectiveness of behavioral interventions because of lack of treatment fidelity and interobserver agreement (Egan et al., 2020). In the single previous behavioral intervention study, five children with AS received behavioral intervention for sleep problems in a multiple baseline design (Allen et al., 2013). They slept longer and with less disruptive behavior after the intervention and parents were highly satisfied. However, the group was small, there was no control group and outcomes for effectiveness and statistical analysis were not predefined. Therefore, we decided to further investigate the effect of behavioral intervention on sleep problems in children with AS.

2. Material and methods

2.1. Design

We performed a randomized controlled single-blinded trial at the ENCORE Expertisecenter for AS. Parents of children with genetically confirmed AS, aged between 2 and 18 years and having sleep problems, were invited for a baseline assessment of their child.

The inclusion criteria for sleep problems at baseline assessment were:

- o Two hours less sleep than normal for the age (defined as a minimum of 12 h for children of 2–4 year, 10 h of 4–12 years and 8 h of 12–18 years (Boer, 2011; Iglowstein et al., 2003), and/or
- o Composite Sleep Index > 4 (based on the Sleep Questionnaire by Simonds and Parraga (SP-SQ) (Maas et al., 2011; Simonds & Parraga, 1982), and/or
- o The child sleeping in another location than his/her own bed or the need of more than normal rituals to fall asleep (e.g. bottle in bed, holding and/or rocking by parents, parent staying in the room or bed).

Exclusion criteria were:

- o Unstable physical causes of sleep problems, including uncontrolled seizures.
- o Change in antiseizure or psychoactive medication during last 3 months.
- o Not living at home with their parent(s).
- o Insufficient oral and written understanding of the Dutch language by parents.

Children whose sleep problems were confirmed at baseline assessment were randomized to either a behavioral intervention program for 6 weeks with a booster session at 8 and 10 weeks, or to a control group. We used computerized blocklist randomization and stratified for age (2–4; 5–12, 13–18 years). The control group was offered personal sleep advice at the end of the study based on parental preferences.

We aimed to include 36 children for sufficient statistical power to show a 1 SD improvement in actual hours of sleep in the night, based on the available literature suggesting a mean hours of sleep of 8 H with SD 1.8 [Waltz 2005].

This study was approved by our Medical Ethical Board (MEC 2016–010). The children were included from May 2016 to September 2018.

2.2. Outcome measures

We measured the following parameters at baseline and at 12 and 26 weeks from baseline (respectively T12 and T26, T12 being post-intervention and T26 at follow-up for the intervention group) as visualized in Fig. 1:

Primary outcomes:

1) The actual hours of sleep of the child during the night, defined as duration of total sleep time (TST), wake after sleep onset (WASO), sleep onset latency (SOL) and number of awakenings, as reported in a sleep diary and registered using actigraphy and video-somnography during 7 nights. Diary data reflect the parental perception of sleep duration (subjective measure), actigraphy is often used in previous studies, and we added videosomnography, because this both reflects actual sleep (objective measure) and adds information about the behavioral sleep patterns of the child and child-parent dyads. The primary outcome measure is therefore a combination of three ways of assessment of sleep duration, each focused on a specific aspect of sleep duration.
2) The CSI as reported in the Simonds & Parraga Sleep Questionnaire (SP-SQ) (Simonds & Parraga, 1982). The CSI has a range of 0–12 with a pathological cut-off of ≥ 4 points and is composed of items about both frequency and duration of problems with settling, nighttime awaking, early waking and co-sleeping.

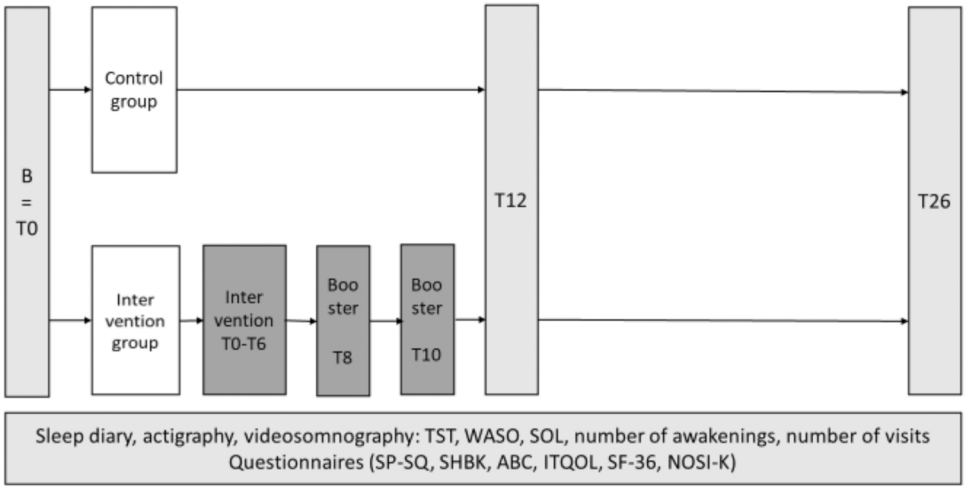

Fig. 1. Flowchart study measurements. B = baseline, TST= total sleep time, WASO = wake after sleep onset, SOL = sleep onset latency, SP-SQ = Simonds & Parraga Sleep Questionnaire, SHBK = Children's Sleep Hygiene Scale, ABC = Aberrant Behavior Chekclist, ITQOL = Infant Toddler Quality of Life Questionnaire, SF-36 = 36-item Short Form Health Survey, NOSI-K = Parenting Stress Index.

Secondary outcomes:

1) The actual hours of sleep of the parent during the night, defined as duration of total sleep time, wake after sleep onset and number of awakenings as reported in a sleep diary and number of nighttime parental visits to the child registered with videosomnography during 7 nights.
2) Total raw scores of (domains of) questionnaires on the following themes: sleep hygiene using the Children's Sleep Hygiene Scale (SHBK) (LeBourgeois, 2001), behavior problems during daytime using the Aberrant Behavior Checklist (ABC) (Aman et al., 1985), quality of life of child and parent using the Infant Toddler Quality of Life Questionnaire (ITQOL) (Landgraf, 2007) and 36-Item Short Form Health Survey (SF-36) (McHorney et al., 1993; Ware & Sherbourne, 1992) and parental stress using the Parenting Stress Index (NOSI-K) (de Brock et al., 1992). Both ITQOL and SF-36 consist of several subscales, covering both physical and psychosocial domains of quality of life (Landgraf, 2007; McHorney et al., 1993; Ware & Sherbourne, 1992).

For actigraphy we used a MotionWatch from CamNTech Ltd. We used the medium sensitivity, as this has shown to give valid results for TST and SOL, compared to polysomnography, WASO and number of awakenings showed no clear agreements (Elbaz et al., 2012; Quante et al., 2018; Sitnick et al., 2008). Sleep onset was defined as a period of at least 10 min of consecutively recorded immobile data, following the moment the child was put to bed, with no more than one epoch of movement within that time. Sleep end was found by looking backwards from the time child was taken out of bed, by determining a period of activity below the sleep-threshold and, allowing up to two intervals above this threshold (CamNtech Ltd). SOL was defined as the latency before sleep onset following bedtime. An epoch was counted as "awake" when the algorithm, based on the epoch and surrounding epochs, exceeded the threshold of 40 (an indication of movement). WASO was defined as the total epochs defined as "awake". Total sleep time was the time between sleep start and sleep end, diminished with the WASO (CamNtech).

For videosomnography we used a Alhua K35S videocamera. All baseline videos were analyzed by the behavioral therapist. Definitions, based on earlier consensus, were as follows (Ipsiroglu et al., 2015; Sitnick et al., 2008):

1. Lights out: Parent leaves the room after putting child to bed
2. Fell asleep: First minute of five consecutive minutes of sleep, defined as no intentional movement or vocalization and eyes closed, after child is put to bed.
3. Awake Child: One or more of the following: opens eyes for longer than 1 s, sits upright, lifts head, makes a series of intentional movements, plays with toys or vocalizes.
4. Number of awakenings: awakenings between fell asleep and woke up.
5. Morning wake time: First minute of being awake and not falling asleep again.

When footage was unclear, a blind observer (first author), decided upon the chosen code (sleep/awake). Data from T12 and T26 were analyzed by blind observers, who were unaware to group allocation or timing and trained by the behavioral therapist. The video footage was fast forwarded with two minutes. When movement was seen, the video was played backwards to see where movement began. We assessed the video footage parallel with the actigraphy output, and used actigraph registered movements to closely check on the videography footage for possible awakenings. Sleep onset latency was defined as the time between lights out and sleep and wake after sleep onset as the sum of "Awake" duration. Total sleep time was defined as the period between "fell asleep" and "woke up", minus WASO time (Ipsiroglu et al., 2015; Sitnick et al., 2008). Interobserver agreement for the videosomnography data was analyzed by randomly selecting 6.5% of the nights to be reanalyzed. Interobserver agreement for the diary data was analyzed in randomly selecting 9% of the nights. Missing data in videosomnography because the child was taken out of bed for a prolonged period of time and/ or did not return were left out in the analysis.

All questionnaires were scored according to their respective manuals. Two questions were left out in the SHBK scoring, because they were not applicable for children with AS ("complains about hunger, goes to bed with worries").

2.3. Behavioral intervention program

The intervention program was specifically developed for this study, based on a standardized behavior protocol used at the department of Child- and Adolescent Psychiatry and Psychology for children with developmental delay, enriched with specific information concerning AS (Allen et al., 2013; Didden & Sigafoos, 2001; Jan et al., 2008; Spruyt & Curfs, 2015). Parents in the intervention group received an information package with general information about sleep, sleep hygiene, types of sleep problems, their possible causes and potential behavioral interventions. The behavioral therapist visited the parents at home twice. During the first visit, the results of the baseline assessment were discussed with the parents, illustrated with relevant video fragments and followed by individually tailored advice. Also, psycho-education was given on sleep hygiene and the bedtime routine was observed by the therapist. Both parents were instructed, but one of the parents was appointed to perform the intervention to guarantee continuity and consistency. After a week, sleep hygiene, bedtime routine and sleep schedule were discussed during a phone call with the parents. In the third week, behavioral intervention was discussed during a second visit, taking into account the capabilities of the particular family and child, as well as the observed function of the problem behavior (e.g. related to anxiety, separation anxiety, attention seeking). The specific behavioral treatment techniques that were advised were bed time fading, gradual extinction and gradual distancing (Didden & Sigafoos, 2001; Jan et al., 2008; Spruyt & Curfs, 2015). During the intervention, parents filled out a sleep diary for therapy purpose only to evaluate and further tailor the intervention during the weekly phone calls. Parents were reinforced and supported with

difficulties, to enable them to continue. After this six week program, a booster session was held two and four weeks after intervention with focus on relapse prevention.

Parents of the control group received a written report of the baseline assessment with some general advices on sleep hygiene. The control group was offered personal sleep advice at the end of the study based on parental preferences.

2.4. Statistical analyses

All statistical analyses were performed using IBM SPSS version 25 (IBM SPSS Statistics for Windows, 2017). Non-parametric tests were used due to small participant numbers and non-normally distributed data. We analyzed:

1. Baseline differences between the intervention and control group of the baseline demographic and the mean sleep parameters data and mean raw scores of the questionnaires with a Mann-Whitney test and Fisher Exact test.
2. Baseline versus T12 and baseline versus T26 changes on three levels for the sleep parameters and questionnaires:
   - o between the intervention and control group: differences in change of median sleep parameters and differences in change of mean raw scores of the questionnaire with a Mann Whitney test
   - o within the intervention and within control group: changes of median sleep parameters and changes of mean raw scores of the questionnaires with a Wilcoxon Signed rank test.
   - o individual changes: changes of mean sleep parameters using Non-Overlap of All Pairs (NAP) (Parker & Vannest, 2009) with a ROC curve operation,
     - the stability of the effect (Parker & Vannest, 2009):.00-0.09 strong negative,0.09-0.34 negative,0.35-0.64 no effect, 0.65-91 positive;0.92-1.00 strong positive and
     - thresholds for clinically relevant change defined as (Sateia et al., 2017):
       - change in TST, WASO and SOL of 30 min, due to possible measurement error, we chose 25 min as a cut off.
       - change in number of awakenings and parental visits: diminished with 1 or more.

The medians for sleep parameters were chosen as not all children had seven data points per week and the number of data points per assessment could vary within children.

With NAP analysis, every measurement of the baseline assessment is compared with all measurements at T12 and T26 respectively and each postintervention point is assessed as above, equal or below the baseline point, in this way avoiding the influence of outliers and differences in number of data and analyzing effects in each case on its own (Kazdin, 2010; Parker & Vannest, 2009). The stability of the effect was calculated by the non-overlap of all pairs (NAP), which was executed by the ROC curve in SPSS. Thereby it is a measure for how well the intervention discriminates between baseline and postintervention and can be seen as effect size. This method is explained by Parker & Vannest (Parker & Vannest, 2009). We defined improvement as both clinically relevant and stable effect in $\geq$ 50% of the children. The NAP method is developed for analyzing the stability of positive effect. We also analyzed a potential negative effect by subtracting the proportion of the positive effect from 1 (f.i. 1.00–0.65 =0.35 for a medium negative effect), in that way using the exact same logic applied on both positive and negative effect.

We further analyzed interobserver agreement for sleep parameter assessment and reported on qualitative observations of videosomnography.

3. Results

3.1. Recruitment

Twenty of the 79 eligible children with AS between 2 and 18 years of age from the ENCORE Expertisecenter for AS were included for the baseline assessment. Reasons for not responding or not participating are displayed in Fig. 2. All children with reported sleep problems met the inclusion criteria for randomization after the baseline assessment. Parents of two children withdraw after baseline assessment. The effect of the intervention was analyzed in 18 children, 9 in the intervention and 9 in the control group.

3.2. Interobserver agreement analyses

Interobserver agreement for the videosomnography data was very strong for total sleep time (ICC =0.99), sleep onset latency (ICC =0.98) and wake after sleep onset (ICC =0.98), very strong for parental visit (Kendall's Tau =0.835) and moderate for number of awakenings (Kendall's Tau =0.583). Interobserver agreement for the diary data was strong to very strong, with an ICC range of.79 – 0.99.

3.3. Baseline assessment analyses

The children in the intervention and control group did not significantly differ on demographics, genotype, physical problems (tube feeding, GER, constipation, airway medication, snoring and independent walking) and in scores on the questionnaires (Table 1). Sleep parameters at baseline were also similar in the intervention and control group, except for diary data of total sleep time of parents with significant shorter duration in the intervention group. The number of awakenings as registered by the actigraph was not representative

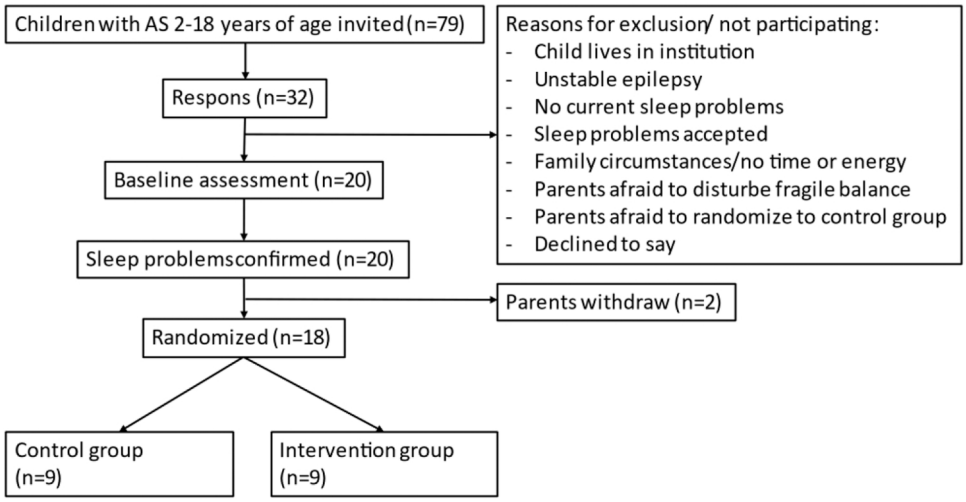

Fig. 2. Flowchart participants.

of actual awakenings as registered with videosomnography. We therefore did not use the actigraph awakenings data for analysis of the effect of intervention at T12 and T26. Videosomnography showed 35–60 min less total sleep time in children than their parents reported in the diary.

3.4. Pre- to post-intervention and pre-intervention to follow-up changes

3.4.1. Primary outcomes

The change from baseline to T12 in sleep parameters on both diary, actigraphy and videosomnography data was not significantly different between the intervention and control group. Significant difference in effect between the intervention and control group from baseline to T26 was seen in sleep onset latency on diary and actigraphy data in favor of the intervention group (Table 2, Fig. 3A). The analysis of the composite sleep index (CSI) showed no difference in change between and within intervention and control group from baseline to T12 and T26 (Table 2, Fig. 3B).

Within the intervention group, videosomnography showed a significant improvement of wake after sleep onset from baseline to T12 and of number of awakenings from baseline to T26 (Table 2, Fig. 3A).

NAP analysis showed a clinically relevant and stable improvement within the intervention group on total sleep time at diary and actigraphy data from baseline to T12, total sleep time at actigraphy data from baseline to T26, wake after sleep onset at diary data at T12 and at diary and actigraphy data at T26 and number of awakenings on videosomnography data at T26.

No significant effects on sleep parameters were seen within the control group from baseline to T12 and T26 (Tables 2, 4 A, 4B and 4 C, Figs. 3A and 3B).

3.4.2. Secondary outcomes

No difference of effect was seen on parental sleep parameters between the intervention and control groups from baseline to T12 and T26 (Table 2, Figs. 3A and 3B). Significant improvement of number of nighttime visits to their child of parents on videosomnography was seen within the intervention group at T26 (Table 2). No significant improvement on sleep parameters was seen within the control group at T12 and T26.

Analysis showed no significant difference of effect of the intervention on sleep hygiene (SHBK) between the intervention and control group, but within the intervention group significant improvement on sleep hygiene (SHBK) was found at T12 and T26 from baseline versus no improvement within the control group at T12 and T26 (Table 3, Fig. 4).

No differences were found between or within the intervention and control group on daily behavior of the child (ABC) and parental stress (NOSI-K) at T12 and T26 from baseline (Table 3, Fig. 4).

The ITQOL showed significantly more positive change on “Parental Impact” in the intervention group compared to the change in the control group at both T12 and T26 from baseline. “Parental Impact” items concern the amount of worry and time limitations experienced by the parent due to his or her child’s problems (Landgraf, 2007). Furthermore, a positive effect on “Combined Behavior” within the intervention group was shown at T12 and T26. A positive effect on “Temperament & Mood” was found in both groups at T12. “Combined behavior” items concern behavioral problems, such as not following directions, hitting, biting, throwing tantrums, being easily distracted and disability to cooperate. “Temperament & Mood” items concern certain moods and temperaments, such as sleeping/eating difficulties, crankiness, fussiness, unresponsiveness and lack of playfulness and alertness (Landgraf, 2007).

The SF36 showed no significant difference of change between the groups, but did show a significant effect on Vitality, Mental health and Social functioning within the intervention group at T12 from baseline with a persistent significant effect for Vitality at T26. No effect was seen within the control group at T12 and T26 (Table 3, Fig. 4).

Table 1
Characteristics at baseline.

		Intervention group (N = 10)	Control group (N = 10)
Age (mean (SD) in years)		8.3 (4.6)	6.6 (2.8)
Male-female (n)		Boys: 4	Boys 6
		Girls: 6	Girls: 4
Genetic subtype (n)		5 del	2 del
		5 non-del (2 mut, 2 UPD, 1 ICD)	8 non-del (5 mut, 2 UPD, 1 ICD)
AED (n)		5	4
Sleep or behavioral medication (n)		Melatonin (3), Alimemazin (1)	Melatonin (4), Clonidine (1), Pipamperon (1), Methylphenidate (1)
CSI (mean (SD))		5 (1.6)	4.3 (3.2)
TST	DIARY	581.1 (91.9)	585.9 (50.6)
(mean (SD) in minutes)		6.4 (5–7)	7(6–8)
mean nights	ACT	579.8 (95.2)	545.2 (57.8)
(n, range)		6.1(5–7)	6.4(4–8)
	VIDEO	512.4 (48.4)	550.8 (57.4)
		5.9(4–7)	6.2(3–7)
WASO	DIARY	48.6 (40.9)	44.4 (57.7)
(mean (SD) in minutes)		6.4(5–7)	7(6–8)
mean nights	ACT	92.1 (9.4)	99.2 (49.0)
(n, range)		6.1(5–7)	6.4(4–8)
	VIDEO	95.4 (52.6)	85.2 (34.3)
		5.9(4–7)	6.2(3–7)
SOL	DIARY	32.7 (35.7)	44.0 (44.6)6.6(3–8)
(mean (SD) in minutes)		6.4(5–7)	
mean nights	ACT	10.4 (9.4)	39.0 (43.7)
(n, range)		6.1(5–7)	6.9(5–8)
	VIDEO	28.6 (23.8)	46.0 (39.7)6.4(4–8)
		5.7(2–7)	
awakenings	DIARY	1.1 (1.1)	0.97 (0.9)
(n (SD)),		6.4(5–7)	7(6–8)
mean nights	ACT	43.6 (20.9)	46.0 (4.7)
(n, range)		6.1(5–7)	6.4(4–8)
	VIDEO	6.9 (3.6)	7.2 (3.5)
		5.9(4–7)	6.2(3–7)
visits parents	VIDEO	1.7 (1.5)	1.6 (1.5)
(n (SD))		6.1(5–7)	6.1(3–7)
mean nights			
(n, range)			
TST parent[#]	DIARY	389.2 (79.8)	504.8 (126.8)
(mean (SD) in minutes)		6.3(5–7)	6.6(3–7)
mean nights			
(n, range)			
WASO parent		49.8 (39.9)	26.7 (24.1)
(mean (SD) in minutes)		6.2(5–7)	6.6(3–7)
mean nights			
(n, range)			
awakenings parent		1,1 (0.8)	1.1 (1.0)
(n (SD))		6.2(5–7)	6.6(3–7)
mean nights			
(n, range)			

AED = antiepileptic drugs, ACT = actigraphy, TST = Total Sleep Time, WASO = wake after sleep onset, SOL = sleep onset latency
[#]$p < 0.05$ Mann-Whitney test

3.5. Qualitative observations

At videosomnography, we also observed some specific, more subjective sleep details. The children moved a lot, also when they were asleep. Specific sleep phases seemed shorter. The longest periods of being awake were seen in the second half of the night. They often removed their duvets and some were able to pull them back up again. In many instances, they were already awake for a longer period before they started to make noise, sometimes up to an hour.

4. Discussion

In this randomized controlled study on the effect of a behavioral intervention program for sleep problems in children with AS, we showed a positive effect on total sleep time assessed by diary and actigraphy and wake after sleep onset assessed by diary, actigraphy and videosomnography within the intervention group, using classical comparative groups analysis and single case analysis. The positive effect on total sleep time assessed by actigraphy and wake after sleep onset assessed by diary and actigraphy was persistent over time (primary outcome). We also found a positive and persistent effect on sleep hygiene and some quality of life domains of both

Table 2
Change in sleep parameters from baseline to T12 and baseline to T26.

		Intervention group (N = 9)[f]		Control group (N = 9)[f]	
Primary outcome		T12	T26	T12	T26
TST	DIARY	43	15.8	10.5	1
median difference in minutes		(27–59.5)	(−4.9 to 40)	(−26.5 to 47.5)	(−47 to 32.9)
(Q1-Q3)		7.1(7–8)	6.7(6–8)	6.6(4–7)	6.9(6–7)
mean nights	ACT	40	34	14.5	13
(n, range)		(−32.1 to 135.3)	(−29.3 to 112.8)	(−17.5 to 61.4)	(−40.8 to 41.3)
		5.8(5–7)	5.8(4–7)	6.2(3–7)	5.5(5–7)
	VIDEO	59	23	26.5	11
		(−39.8 to 80.5)	(−41.3 to 50)	(−39.3 to 41.9)	(−49 to 31)
		5.7(2–8)	6.3(5–7)	6.4(4–7)	6.9(6–7)
WASO	DIARY	-34	-33.3	6	-10.5
median difference in minutes		(−83 to 0)	(−84.8 to 0)	(−44 to 32.5)	(−48.5 to 4.5)
(Q1-Q3)		7.1(7–8)	6.7(6–8)	6.6(4–7)	6.9(6–7)
mean nights	ACT	-6.5	4	-22	-26
(n, range)		(−98.1 to 16)	(−84.3 to 15.3)	(−46.4 to 51.1)	(−30.5 to −4.3)
		5.8(5–7)	5.8(4–7)	6.8(6–7)	5.5(5–7)
	VIDEO	**-36.5** *	-11	12	-18
		(−60 to −7.5)	(−46.3 to 1)	(−53.4 to 49.8)	(−74.5 to 16)
		5.7(2–8)	6.3(5–7)	6.4(4–7)	6.9(6–7)
SOL	**DIARY**	0	**0**[#]	0	11
median difference in minutes		(−90 to 0)	(−4.3 to 0)	(−31 to 9.5)	(1.5 – 21.9)
(Q1-Q3)		7.1(7–8)	6.7(6–8)	6.6(4–7)	6.9(6–7)
mean nights	**ACT**	-0.5	**-1**[#]	-2	21
(n, range)		(−11.3 to 9.6)	(−10.5 to 3.5)	(−2 to 9.8)	(9.3 – 29.8)
		5.8(5–7)	5.8(4–7)	6.5(3–7)	5.5(5–7)
	VIDEO	-2.5	-1	-1	8.5
		(−35.8 to 5)	(−38.3 to 5.8)	(−28 to 6)	(2.5–17)
		6.2(5–7)	6.7(6–8)	6.9(4–7)	6.9(6–7)
awakenings	DIARY	0	0	0	0
median difference in numbers (SD)		(−1.5 −1)	(−2 to 0)	(−0.5 to 1)	(−1 to 0)
mean nights		7.1(7–8)	6.7(6–8)	6.6(4–7)	6.9(6–7)
(n, range)	**VIDEO**	-1.5	**-1** *	0	-1
		(−3.8 to −0.8)	(−4.5 to −0.5)	(−2.1 to 2)	(−3 to −0.5)
		5.8(4–7)	6.3(5–7)	6.4(4–7)	6.9(6–7)
CSI *mean difference (SD)*		-0.3(2.5)	-0.4 (2.3)	-1.3 (3.5)	-2.3 (3.2)
Secondary outcome					
visits parents	**VIDEO**	-0.5	**-1** *	0	0
median difference in numbers (SD)		(−3.5 to 0.8)	(−3.5 to −0.3)	(−1.5 to 0.4)	(−2 to 0)
mean nights		6.2(2–7)	6.6(5–7)	6.4(4–7)	6.9(6–7)
(n, range)					
TST parent	DIARY	24	24	13	6
median difference in minutes (Q1-Q3)		(−6.3 to 111)	(−6.3 to 111.5)	(−40.5 to 49)	(−24.9 to 66.4)
mean nights		7(7–7)	6.5(5–7)	6.2(4–7)	6.6(6–7)
(n, range)					
WASO parent		-30	-30	0	-5
median difference in minutes (Q1-Q3)		(−63 to 11.8)	(−63 to 11.8)	(−21.5 to 6.5)	(−16 to 0)
mean nights		7(7–7)	6.5(5–7)	6.2(4–7)	6.6(6–7)
(n, range)					
awakenings parent		-0.5	-0.3	0	0
median difference in numbers (SD)		(−1.5 to 0)	(−1 to 0.1)	(−0.5 to 0)	(−1 to 0.4)
mean nights		7(7–7)	6.5(5–7)	6.2(4–7)	6.6(6–7)
(n, range)					

ACT = actigraphy, TST = total sleep time, WASO = wake after sleep onset, SOL = sleep onset latency, CSI = composite sleep index
[#] $p < 0.05$ Mann-Whitney test (difference between groups)
* $p < 0.05$ Wilcoxon signed rank test (change within group)
f actigraphy data was sufficient for analysis for 12 participants at T12 (6 in each group) and 8 at T26 (4 in each group)

child and parent ("Parental Impact and Vitality") within the intervention group (secondary outcome). We did not find significant improvement within the control group on any of the primary and secondary parameters apart from two domains of the ITQOL, "Temperament & Mood" at T12 and T26 and "Parental Impact" at T26. The improvement of "Parental Impact" was significantly larger in the intervention group at both T12 and T26.

Furthermore, we saw a significant difference of effect of intervention between the groups on sleep onset latency measured by diary and actigraphy at T26, which was not significant at T12 (Table 2, Fig. 3A). We hypothesize that changing certain patterns and parent-child interactions need time to lead to effect. The effect on sleep onset latency in the intervention group can be considered even stronger since the sleep onset latency at baseline was already near normal assessed by both diary and videosomnography in the intervention group.

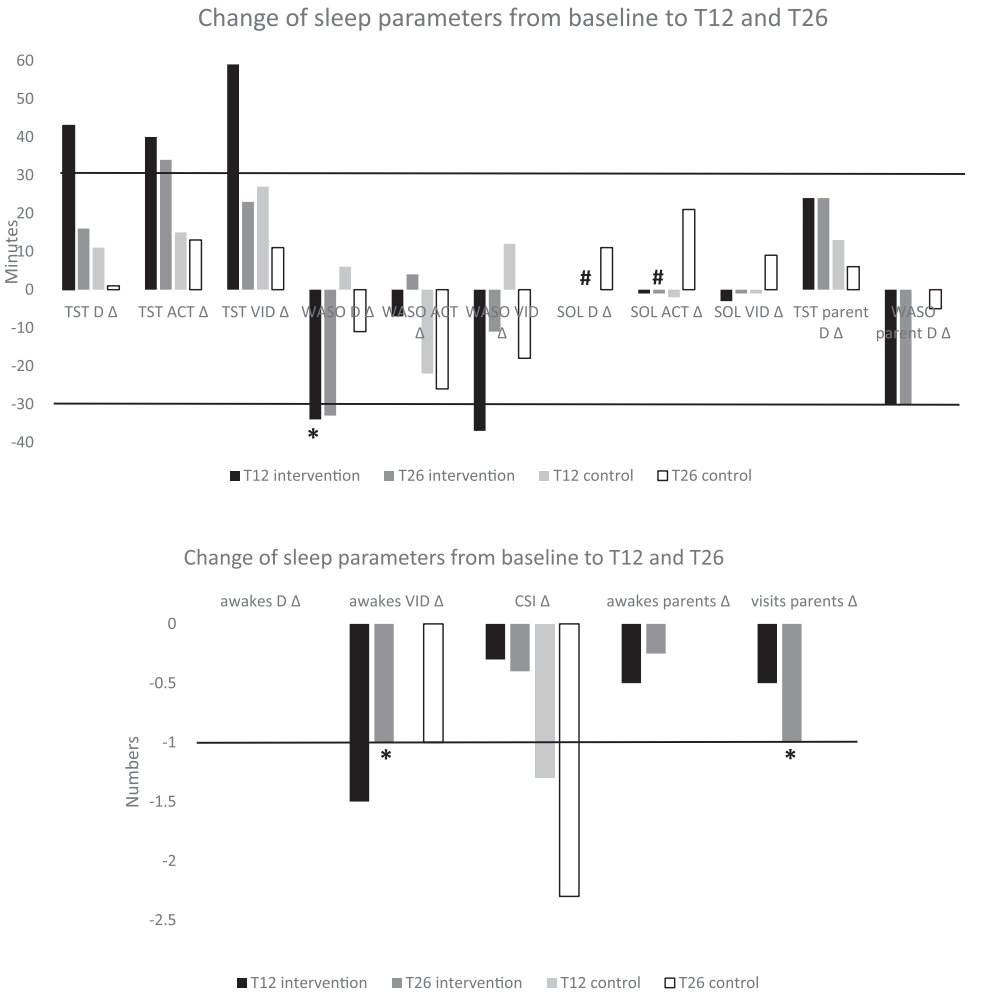

Fig. 3. **A** Change of sleep parameters baseline to T12 and baseline to T26 in median differences. Δ = difference between baseline and T12 or T26, ACT = actigraphy, TST = total sleep time, D = diary, VID = videosomnography, WASO = wake after sleep onset, SOL = sleep onset latency. # $p < 0.05$ Mann-Whitney test (between groups). * $p < 0.05$ Wilcoxon signed rank test (within group). **B** Change of sleep parameters from baseline to T12 and baseline to T26. Δ = difference between baseline and T12 or T26, D = diary, VID = videosomnography, CSI = composite sleep index. * $p < 0.05$ Wilcoxon signed rank test (within group).

Table 3
Questionnaires total raw scores at baseline and versus postintervention and at follow-up.

	Baseline		T12		T26	
	I	C	I	C	I	C
Raw scores	Mean (SD)	Mean (SD)	Mean difference (SD)	Mean difference (SD)	Mean difference (SD)	Mean difference (SD)
SHBK[f] (sleep hygiene)	117.4 (5.1)	116.4 (6.0)	8.3 (5.7)*	1.9 (6.2)	9.3 (8.1)*	1.7 (7.1)
ABC (daily behavior)	37.6 (24.0)	40 (12.3)	-7.4 (22.0)	1.4 (14.7)	1.6 (28.6)	4.1 (14.1)
NOSI-K (parenting stress index)	74.3 (14.2)	71.1 (18.5)	-6.1 (11.6)	6.9 (15.2)	-1.0 (27.1)	7.9 (20.7)
ITQOL (quality of live child)						
Overall health	64.3 (27.5)	64.4 (22.7)	-3.6 (9.5)	-9.4 (12.9)	2.9 (24.8)	1.3 (20.8)
Physical abilities	60.4 (18.4)	58.6 (19.3)	-5.6 (28.3)	-2.1(14.8)	8.3 (15.7)	3.5 (11.9)
Overall growth and development	55.6 (14.5)	65.6 (20.4)	0 (9.6)	0.6 (19.5)	7.5 (16.0)	0.6 (15.7)
Bodily discomfort, pain	60.9 (14.1)	68.1 (17.8)	6.3 (30.6)	0 (24.1)	20.3 (24.0)*	1.6 (17.0)
Temperament, mood	53.1 (10.9)	58.3 (18.3)	13.5 (11.5)*	10.9 (6.7)*	22.9 (12.0)*	17.7 (10.4)*
Combined behavioral scale	56.6 (13.6)	59.2 (8.4)	0.2 (0.1)*	0.2 (0.4)	0.4 (0.3)*	0.1 (0.3)
Global behavior	44.4 (26.7)	42.8 (20.5)	0 (16.0)	0.7 (28.4)	7.5 (13.9)	4.4 (29.0)
General health perception	36.3 (17.1)	54.7 (24.6)	0.4 (0.5)	-0.1 (0.5)	0.5 (0.5)	0.5 (0.5)
Parental impact	40.63 (17.5)	54.6 (29.5)	28.1 (15.4)#/*	-2.1 (24.7)	31.3 (17.7)#/*	13.5 (9.9)*
Family cohesion	65.6 (19.0)	62.8 (31.4)	13.1 (24.3)	3.1 (18.3)	8.8 (18.5)	17.5 (26.2)
SF-36 (quality of live parents)						
Physical functioning	27.0 (3.0)	24.2 (7.2)	1.0 (2.4)	1.9 (6.4)	-2.1 (6.3)	3.9 (7.4)
Role limitations due to physical health	5.0 (1.9)	6.9 (1.5)	1.0 (1.7)	0.9 (1.9)	1.3 (2.2)	0.4 (1.5)
Role limitations due to emotional problems	4.9 (1.6)	4.4 (1.2)	0.5 (1.1)	0.9 (1.5)	0.3 (1.3)	1.3 (1.6)
Vitality	11.1 (4.4)	14.4 (4.0)	3.0 (3.4)*	0.5 (3.5)	2.9 (2.9)*	0.9 (1.9)
Physical health	54.6 (7.4)	56.2 (10.7)	4.1 (5.9)	5.3 (9.1)	4.6 (9.2)	4.7 (11.0)
Mental health	46.1(9.3)	47.9 (9.3)	6.5 (5.4)*	4.0 (8.3)	4.0 (9.1)	3.6(7.2)
Mental health subscale	23.1 (4.5)	22.0 (4.7)	2.0 (4.0)	1.6 (3.1)	0.5 (5.4)	1.1(3.3)
Social functioning	7.0 (1.8)	7.0 (2.4)	1.0 (0.9)*	1.0 (2.7)	0.9 (1.9)	0.4 (2.9)
Pain	8.0 (1.3)	8.6 (2.3)	0.8 (1.5)	1.3 (2.1)	0.6 (1.4)	0.1 (2.8)
General health	14.6 (2.7)	16.6 (3.8)	1.4 (2.7)	0.3 (2.4)	2.4 (3.7)	0.5 (3.5)

I = intervention group, C = control group, SHBK = Children's Sleep Hygiene Scale, ABC = Aberrant Behavior Checklist, NOSI-K = Parenting Stress Index, ITQOL = Infant Toddler Quality of Life Questionnaire, SF-36 = 36-item Short Form Health Survey
# $p < 0.05$ Mann-Whitney test (between groups)
* $p < 0.05$ Wilcoxon signed rank test (within group)
[f] SHBK total raw score without item 8 and 12

Parents in the intervention group were actively encouraged to decrease their nighttime visits. Although this did not lead to a significant decrease at T12, it might be responsible for the significant decrease in nighttime visits and presumably for the decrease in number of awakenings at T26. Secondly, it might also be responsible for the significant improvement of wake after sleep onset of the child at both T12 and T26 by breaking the negative feedback loop. The significant and persistent effect on wake after sleep onset in the children, could have led to less broken nights for parents and children and this might be related to the improvement on the quality of life on several domains in the intervention group. Also when children were awake at night, they appeared more calm on video footage, probably making parents assume that their child was asleep. This might explain the higher total sleep time found in the diaries compared to the videosomnography data, which suggests less fragmented sleep for parents. The positive and persistent effect on the domains "Parental Impact" (ITQOL) and "Vitality" (SF-36) might be a result of this improved quality of sleep. Sleep hygiene was significantly and persistently improved in the intervention group, which also might be associated with the improvement in sleep onset latency and wake after sleep onset duration. We did see a positive effect on TST and WASO of the parents in the intervention group, but it was not significant, possibly also related to a significant shorter TST at baseline.

Measuring sleep objectively is challenging. Polysomnography is the gold standard, but also interferes with sleep as AS children will often not accept the electrodes or cap and sleep differently in a sleep lab. We chose to assess sleep duration with a combination of parental observation by sleep diary, motion detection with actigraphy and investigator observation by videosomnography. The advantage of this combination is registering real live situation at home. The diary reflects the parents' perception of (the absence of) sleep and videosomnography, in this study supported by indicated moments of movement by actigraphy, reflects the actual sleep duration, adding information about the sleep behavior and child-parent dyads. Disadvantages of actigraphy are that the actigraph was

Table 4

A *NAP clinical effect and stability results diary at T12 and T26*

DIARY

	TST child		WASO child		SOL child		#awake child		TST parent		WASO parent		#awake parent	
N with positive effect/ N total	I	C	I	C	I	C	I	C	I	C	I	C	I	C
Clinical T12	*5/7*	4/9	*4/7*	4/9	3/7	2/9	3/7	1/9	*3/5*	2/9	2/5	2/9	1/5	2/9
Stable T12	*4/7*	3/9	*4/7*	4/9	*4/7*	4/9	3/7	3/9	2/5	1/9	*3/5*	4/9	*3/5*	1/9
Both clinical & stable T12	**4/7**	3/9	**4/7**	4/9	3/7	2/9	3/7	1/9	2/5	1/9	2/5	2/9	1/5	0/9*
Clinical T26	2/6	2/8	*3/6*	3/8	1/6	1/8	2/6	1/8	*3/6*	2/8	2/6	2/8	2/6	2/8
Stable T26	*3/6*	2/8	*3/6*	*4/8*	2/6	1/8	2/6	3/8	2/6	2/8	*4/6*	2/8	*3/6*	1/8
Both clinical & stable T26	2/6	2/8	**3/6**	3/8	1/6	1/8	2/6	1/8	2/6	2/8	2/6	2/8	2/6	1/8

B *NAP clinical effect and stability results videosomnography at T12 and T26*

VIDEO

	TST child		WASO child		SOL child		#awake child		#visit parent	
N with positive effect/ N total	I	C	I	C	I	C	I	C	I	C
Clinical T12	4/9	2/8	*5/9*	3/8	2/9	2/8	*5/9*	2/8	3/9	2/8
Stable T12	3/9	1/8	4/9	2/8	3/9	3/8	*5/9*	2/8	*5/9*	2/8
Both clinical & stable T12	3/9	1/8	4/9	2/8	2/9	1/8	4/9 *	2/8	3/9	2/8
Clinical T26	*5/9*	2/7	4/9	*6/7*	3/9	1/7	*8/9*	*4/7*	4/9	2/7
Stable T26	4/9	1/7	3/9	3/7	4/9	1/7	*5/9*	3/7	*6/9*	2/7
Both clinical & stable T26	4/9	1/7	3/9	3/7	3/9	1/7	**5/9**	3/7	4/9	2/7

C *NAP clinical effect and stability results actigraphy at T12 and T26*

ACTIGRAPHY

	TST child		WASO child		SOL child	
N with positive effect/ N total	I	C	I	C	I	C
Clinical T12	*3/5*	2/6	2/6	2/5	0/5	1/6
Stable T12	*3/5*	*3/6*	*3/6*	1/5	2/5	1/6
Both clinical & stable T12	**3/5**	2/6	2/6	1/5	0/5	1/6
Clinical T26	*2/4*	0/4	*2/4*	*2/4*	0/4	0/4
Stable T26	*2/4*	0/4	*2/4*	1/4	*2/4*	0/4
Both clinical & stable T26	**2/4**	0/4	**2/4**	1/4	0/4	0/4

Italic = stable OR clinical effect, Bold = stable AND clinical effect in ≥50% of the children
NAP = Non-Overlap of All Pairs, I = intervention group, C = control group, TST = total sleep time, WASO = wake after sleep onset, SOL = sleep onset latency, #awakes = number of awakenings, #visits = number of visits, * not the same children

not well tolerated by the children with AS; in our study only a maximum of half of the children accepted the actiwatch. Secondly,it does not reliable register number of awakenings, as was also seen in previous studies (Elbaz et al., 2012; Sitnick et al., 2008), which are one of the biggest problems of sleep in children with AS. The disadvantage of videosomnography is that it is not always clear whether the child is asleep, for example because the child's face is turned away from the camera. The advantage of videosomnography over actigraphy is that it is more accurate about sleep duration, e.g. if the child lies still, but with eyes open or if it is moving in his or her sleep. In children with AS the latter is more prevalent, as we also clinically observed in this study (and which can lead to underestimation of sleep with actigraphy). A comparative study of these three methods of sleep assessment confirmed our clinical impression of overestimation of sleep duration and underestimation of waking periods by diary compared to videosomnography (Camerota et al., 2018). A study in children with AS assessing sleep with actigraphy and diary showed the need of more insight in the frequent nighttime awakenings. (Trickett et al., 2019). We think videosomnography is a good alternative for actigraphy for future studies to this problem. Unfortunately, videosomnography is very time consuming to analyze if used in a research setting. Development of computerized analysis of videosomnography would be helpful. Using the videosomnography to educate the parents, however, was very helpful for them to understand the behavioral patterns in their absence (e.g. throwing the pacifier out of the bed deliberately) and to see that their child was in fact warm and safe, supporting parents in being able to change sleep routines. In clinical care, videosomnography can be assessed at a much higher speed and probably less than seven nights are enough to get a good enough clinical impression of the behavioral sleep patterns.

We did not find an effect on the other primary outcome, sleep behavior as measured with the CSI. The questionnaire is used often in children with intellectual disability and sleep problems (Wiggs & Stores, 1998). We also use the CSI in clinical care, as only five questions give an indication of the presence and character of sleep problems. However, based on our data we hypothesize that this measure might not be sensitive enough for change in clinical trials.

In our opinion, the effect of the intervention is most likely due to a combination of the personal and persistent support of the behavioral therapist with individual tailored advices, direct observation of the bedtime routine, discussion of video observations with reassurance and the use of specific behavioral techniques as needed. In this study extinction and bed time fading were most used. In the

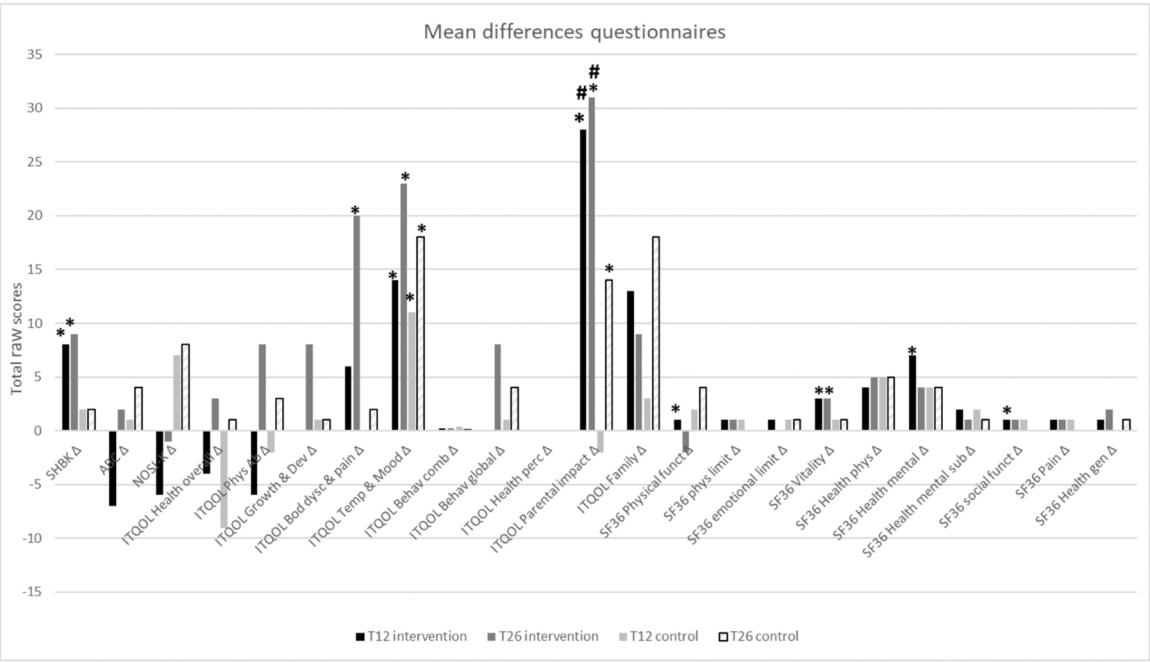

Fig. 4. Mean differences total raw scores all questionnaires. Δ = difference between baseline and T12 or T26, SHBK = Children's Sleep Hygiene Scale, ABC = Aberrant Behavior Checklist, NOSI-K = Parenting Stress Index, ITQOL = Infant Toddler Quality of Life Questionnaire, SF-36 = 36-item Short Form Health Survey. # $p < 0.05$ Mann-Whitney test (between groups). * $p < 0.05$ Wilcoxon signed rank test (within group).

control group, parents of some children reported to have changed the sleep routines on their own after receiving the report of the baseline assessment. Since there was no significant positive effect on the sleep parameters within this group, the additional effect of personalized and persistent instruction, feedback and support seems to make the difference. Parents highly appreciated the conclusions from the baseline video footage and were very relieved to hear their child was safe and warm at night, had no seizures and did not harm him/herself. When this footage was watched with the therapist, parents were often positively surprised by what their child did and they saw that (s)he was also able to fall back asleep by him/herself. Parents told us that not going to the child at awake moments at night was one of the most difficult things to do. Most of the parents went anyway, but later and less frequent, so called "differentiated extinction" after intervention. Many indicated that they could differentiate between "calling for attention" and "calling because something is off" and handled accordingly. Parents reported fear of missing seizures of the child, smearing or being cold without blankets as reasons for checking on their child. Watching and discussing the video with the therapist was reported as reassuring. Also, the parents told us that they were only able to implement the advices once they could no longer endure the sleep problems, intrinsic motivation being an important success factor. This was also seen in the study of Allen (Allen et al., 2013), parents found sticking to the new strategies really challenging and required weekly contact with the therapist to maintain them, even when the effects were positive.

Based on our data and experience we advise a stepped-care approach with psycho-education offered to all parents with a child with AS, including information on sleep hygiene, emphasizing the importance of diminishing parental nighttime visits to prevent stimulating a negative feedback loop. In children with mild problems, three nights videosomnography might be enough to analyze the behavioral problems and give parents specific advice. For children with more serious sleeping problems, personal guidance of a behavioral therapist including house visits and the use of specific behavioral techniques proved effective in this study.

We are aware that sleep problems in AS are not solely behavioral, but also have a physical component like gastro-esophageal reflux and epilepsy and a molecular-biological component as the involvement of UBE3A in the circadian rhythm is getting more clear (Ehlen et al., 2015; Shi et al., 2015, 2022). Remarkable in this study is that children slept even less than parents thought. They were often awake for 30–60 min, quietly in their bed before alarming their parents. We also observed hypermotor sleep behavior, long periods of quietly lying awake (especially in the second half of the night) and shorter sleep periods than normal for age. We do not have polysomnography data for a more quantitative and objective analysis, but sleep seemed to be more fragmented, which is supported by the observed high number of awakenings. But even in the presence of physical and molecular-biological factors interfering with sleep, behavioral factors can certainly attribute to sleep problems. This study adds to the empirical support (Allen et al., 2013) that behavioral intervention always should be considered.

4.1. Strengths and limitations

This is the largest study on diminishing sleeping problems in AS children so far, adding evidence to the provisional positive effect of behavioral intervention. We used randomization to an intervention or control group, stratification with age, a standardized behavioral intervention program, single blinded analysis of data and clearly predefined and objective outcome measures. We analyzed changes of the parameters from baseline to 12 and 26 weeks at three levels: intervention group compared to the control group, change within the groups separately and within the children themselves. The NAP analysis added information about both clinical relevance and effect size on individual basis to the findings of the classic comparative analysis, supporting the clinical impact of these findings. The interobserver agreement for the videosomnography outcome measures was high. This is also the first study that used video-somnography next to diary, actigraphy and questionnaires to assess sleep duration and behavior. A novel aspect of this study is that we also used clips from the video footage to give concrete feedback to the parents as part of the intervention program. This was very well received by parents as they responded positively to the footage and indicated to the therapist that this was helpful in understanding of and persevering in the behavioral intervention rationale.

The actigraphy data are based on small numbers, so it is hard to draw conclusions from, even when the results were in line with the results of the diary and videosomnography.

We coded sleep very strictly and only coded “awake” when we were sure they were awake (intentional movement or sounds). This may have resulted in an overestimation of TST and underestimation of WASO and #awake. This only affects interpretation of the baseline data, since it was of course the same for both intervention and control group.

We did not reach our target inclusion of 18 children in each group, which was calculated with an expected total sleep time of 8 h (SD 1.8 h) based on published data (Walz et al., 2005). Our participants showed a mean total sleep time of 9.8 h (SD 1.6 h) and had a younger age, which might explain the difference in total sleep time, in addition to our strict definition of being awake when showing intentional movement or vocalization. In retrospect, an improvement of 1.8 h and therefore the calculated power seems less realistic to achieve. Despite having a smaller sample, we were still able to show a positive effect of behavioral intervention.

We did not objectively verify which intervention elements were most effective or important according to parents, which could be useful in further optimize the behavioral intervention program.

Lastly, some parents of the control group used the baseline evaluation report to change things in sleep hygiene by themselves, which potentially reduced the difference in effect between the groups.

5. Conclusion

The results of this RCT indicate that behavioral intervention has a positive and persistent effect on total sleep time and wake after sleep onset in children with AS, on sleep hygiene and several quality of life domains of child and parents.

We advise a stepped-care approach to diminish sleep problems in children with AS. This should include psycho-education on sleep for all parents, evaluation of sleep behavior by a behavioral therapist with videosomnography followed by individual behavioral advice and the use of specific behavioral techniques in children with respectively moderate and more severe sleep problems.

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Data availability

Data will be made available on request.

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What this paper adds

Sleep problems in children with Angelman Syndrome (AS) are highly prevalent and are stated as unmet needs by parents. Behavioral factors seem to be involved. An earlier study found a positive effect for behavioral therapy, but with limited evidence due to study limitations. We performed a RCT with a standardized behavioral intervention program of 10 weeks and use of both parent reported and objective outcome measures on sleep duration of child and parent, sleep hygiene, daily behavior of the children, quality of life of child and parent, and parental stress. This study showed a positive and persistent effect of behavioral intervention on both primary (total sleep time, wake after sleep onset) and secondary outcomes (sleep hygiene and several quality of life domains of child and parents) on sleep problems. Videosomnography was used for both assessment of sleep duration with a high interobserver agreement, and serving as feedback in reassuring and instructing parents.

This papers supports the evidence for and implementation of a behavioral intervention program with psychoeducation for all parents with a child with AS, and behavioral intervention by a behavioral therapist with use of videosomnography, individual behavioral advice and specific behavioral techniques as needed for children with sleep problems. Although sleep problems seem to be a specific symptom in AS, our results may translate to other children with intellectual disability and sleep problems.

References

Allen, K. D., Kuhn, B. R., DeHaai, K. A., & Wallace, D. P. (2013). Evaluation of a behavioral treatment package to reduce sleep problems in children with Angelman Syndrome. https://doi.org/S0891-4222(12)00256-9 [pii] *Research in Developmental Disabilities, 34*(1), 676–686. https://doi.org/10.1016/j.ridd.2012.10.001.

Aman, M. G., Singh, N. N., Stewart, A. W., & Field, C. J. (1985). The aberrant behavior checklist: A behavior rating scale for the assessment of treatment effects. *American Journal of Mental Deficiency, 89*(5), 485–491. ⟨https://www.ncbi.nlm.nih.gov/pubmed/3993694⟩.

Beygo, J., Buiting, K., Ramsden, S. C., Ellis, R., Clayton-Smith, J., & Kanber, D. (2019). Update of the EMQN/ACGS best practice guidelines for molecular analysis of Prader-Willi and Angelman syndromes. *European Journal of Human Genetics, 27*(9), 1326–1340. https://doi.org/10.1038/s41431-019-0435-0

Bindels-de Heus, K., Mous, S. E., Ten Hooven-Radstaake, M., van Iperen-Kolk, B. M., Navis, C., Rietman, A. B., Ten Hoopen, L. W., Brooks, A. S., AS, E. E. C. f, Elgersma, Y., Moll, H. A., & de Wit, M. Y. (2020). An overview of health issues and development in a large clinical cohort of children with Angelman syndrome. *American Journal of Medical Genetics A, 182*(1), 53–63. https://doi.org/10.1002/ajmg.a.61382

Boer, F. (2011). *Slaapproblemen bij kinderen* (1st ed.). Lannoo Campus.

Braam, W., Didden, R., Smits, M. G., & Curfs, L. M. (2008). Melatonin for chronic insomnia in Angelman syndrome: A randomized placebo-controlled trial. *Journal of Child Neurology, 23*(6), 649–654.

Bruni, O., Ferri, R., D'Agostino, G., Miano, S., Roccella, M., & Elia, M. (2004). Sleep disturbances in Angelman syndrome: A questionnaire study. *Brain and Development, 26*(4), 233–240.

Burnham, M. M., Goodlin-Jones, B. L., Gaylor, E. E., & Anders, T. F. (2002). Nighttime sleep-wake patterns and self-soothing from birth to one year of age: A longitudinal intervention study. *Journal of Child Psychology and Psychiatry, 43*(6), 713–725. https://doi.org/10.1111/1469-7610.00076

Camerota, M., Tully, K. P., Grimes, M., Gueron-Sela, N., & Propper, C. B. (2018). Assessment of infant sleep: How well do multiple methods compare?. https://doi.org/5067292 [pii] *Sleep, 41*(10). https://doi.org/10.1093/sleep/zsy146.

Clayton-Smith, J. (1993). Clinical research on Angelman syndrome in the United Kingdom: Observations on 82 affected individuals. *American Journal of Medical Genetics, 46*(1), 12–15. https://doi.org/10.1002/ajmg.1320460105

Conant, K. D., Thibert, R. L., & Thiele, E. A. (2009). Epilepsy and the sleep-wake patterns found in Angelman syndrome. *Epilepsia, 50*(11), 2497–2500.

de Brock, A. J. L. L., Vermulst, A. A., Gerris, J. R. M., & Abidin, R. R. (1992). *NOSI, Nijmeegse Ouderlijke Stress Index. Experimentele versie. Handleiding*. Swets & Zeitlinger.

Didden, R., Korzilius, H., Smits, M. G., & Curfs, L. M. (2004). Sleep problems in individuals with Angelman syndrome. *American Journal on Mental Retardation, 109*(4), 275–284.

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*(4), 255–272.

Egan, M., Farrell, K., Hoey, E., McGuire, B. E., & Lydon, H. K. (2020). Interventions to improve sleep for individuals with Angelman syndrome: A systematic review. https://doi.org/S0891-4222(19)30221-5 [pii] *Research in Developmental Disabilities, 97*, Article 103554. https://doi.org/10.1016/j.ridd.2019.103554.

Ehlen, J. C., Jones, K. A., Pinckney, L., Gray, C. L., Burette, S., Weinberg, R. J., Evans, J. A., Brager, A. J., Zylka, M. J., Paul, K. N., Philpot, B. D., & DeBruyne, J. P. (2015). Maternal Ube3a loss disrupts sleep homeostasis but leaves circadian rhythmicity largely intact. https://doi.org/35/40/13587 [pii] *The Journal of Neuroscience, 35*(40), 13587–13598. https://doi.org/10.1523/JNEUROSCI.2194-15.2015.

Elbaz, M., Yauy, K., Metlaine, A., Martoni, M., & Leger, D. (2012). Validation of a new actigraph motion watch versus polysomnography on 70 healthy and suspected sleep-disordered subjects. *Journal of Sleeping Research, 21*, 218-218. <Go to ISI>://WOS:000307963201070.

Gadoth, N., & Oksenberg, A. (2014). Sleep and sleep disorders in rare hereditary diseases: A reminder for the pediatrician, pediatric and adult neurologist, general practitioner, and sleep specialist. *Frontiers in Neurology, 5*, 133. https://doi.org/10.3389/fneur.2014.00133

Goldman, S. E., Bichell, T. J., Surdyka, K., & Malow, B. A. (2012). Sleep in children and adolescents with Angelman syndrome: association with parent sleep and stress. *Journal of Intellectual Disability Research, 56*(6), 600–608.

Grieco, J. C., Romero, B., Flood, E., Cabo, R., & Visootsak, J. (2019). A conceptual model of angelman syndrome and review of relevant clinical outcomes assessments (COAs). *Patient, 12*(1), 97–112. https://doi.org/10.1007/s40271-018-0323-7

Grigg-Damberger, M., & Ralls, F. (2013). Treatment strategies for complex behavioral insomnia in children with neurodevelopmental disorders. *Current Opinion in Pulmonary Medicine, 19*(6), 616–625. https://doi.org/10.1097/MCP.0b013e328365ab89

Heald, M., Adams, D., & Oliver, C. (2020). Profiles of atypical sensory processing in Angelman, Cornelia de Lange and Fragile X syndromes. *Journal of Intellectual Disability Research, 64*(2), 117–130. https://doi.org/10.1111/jir.12702

IBM SPSS Statistics for Windows. In. (2017). (Version 25) IBM Corp.

Iglowstein, I., Jenni, O. G., Molinari, L., & Largo, R. H. (2003). Sleep duration from infancy to adolescence: Reference values and generational trends. *Pediatrics, 111*(2), 302–307. https://doi.org/10.1542/peds.111.2.302

Ipsiroglu, O. S., Hung, Y. H., Chan, F., Ross, M. L., Veer, D., Soo, S., Ho, G., Berger, M., McAllister, G., Garn, H., Kloesch, G., Barbosa, A. V., Stockler, S., McKellin, W., & Vatikiotis-Bateson, E. (2015). "Diagnosis by behavioral observation" home-videosomnography - a rigorous ethnographic approach to sleep of children with neurodevelopmental conditions. *Frontiers in Psychiatry, 6*, 39. https://doi.org/10.3389/fpsyt.2015.00039

Jan, J. E., Owens, J. A., Weiss, M. D., Johnson, K. P., Wasdell, M. B., Freeman, R. D., & Ipsiroglu, O. S. (2008). Sleep hygiene for children with neurodevelopmental disabilities. https://doi.org/122/6/1343 [pii] *Pediatrics, 122*(6), 1343–1350. https://doi.org/10.1542/peds.2007-3308.

Kazdin, A. E. (2010). *Single-Case Research Designs* (2nd ed.). Oxford University Press Inc.

Khan, N., Cabo, R., Tan, W. H., Tayag, R., & Bird, L. M. (2019). An observational study of pediatric healthcare burden in Angelman syndrome: Results from a real-world study. *Orphanet Journal of Rare Diseases, 14*(1), 239. https://doi.org/10.1186/s13023-019-1210-6, 10.1186/s13023-019-1210-6 [pii].

Landgraf, J. M. (2007). *Infant and Toddler Quality of Life Questionnaire (ITQOL): Manual (H. Raat, M. L. Essink-Bot, & H. A. Moll, trans.)*. HealthAct CHQ Inc.

LeBourgeois, M. K. (2001). *Children's sleep hygiene scale. Caretaker-report form for 2- to 12-year-old children*. University of Southern Mississippi: Sleep Research Laboratory.

Maas, A. P., Didden, R., Korzilius, H., Braam, W., Collin, P., Smits, M. G., & Curfs, L. M. (2011). Psychometric properties of a sleep questionnaire for use in individuals with intellectual disabilities. https://doi.org/S0891-4222(11)00270-8 [pii] *Research in Developmental Disabilities, 32*(6), 2467–2479. https://doi.org/10.1016/j.ridd.2011.07.013.

Malow, B. A., Byars, K., Johnson, K., Weiss, S., Bernal, P., Goldman, S. E., Panzer, R., Coury, D. L., Glaze, D. G., & Sleep Committee of the Autism Treatment, N.. (2012). A practice pathway for the identification, evaluation, and management of insomnia in children and adolescents with autism spectrum disorders. https://doi.org/peds.2012-0900I [pii] *Pediatrics, 130*(Suppl 2), S106–S124. https://doi.org/10.1542/peds.2012-0900I.

McHorney, C. A., Ware, J. E., Jr., & Raczek, A. E. (1993). The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care, 31*(3), 247–263. https://doi.org/10.1097/00005650-199303000-00006

Miano, S., Bruni, O., Leuzzi, V., Elia, M., Verrillo, E., & Ferri, R. (2004). Sleep polygraphy in Angelman syndrome. *Clinical Neurophysiology, 115*(4), 938–945.

Owens, J. A., & Mindell, J. A. (2011). Pediatric insomnia. https://doi.org/S0031-3955(11)00027-7 [pii] *Pediatric Clinics of North America, 58*(3), 555–569. https://doi.org/10.1016/j.pcl.2011.03.011.

Parker, R. I., & Vannest, K. (2009). An improved effect size for single-case research: Nonoverlap of all pairs. https://doi.org/S0005-7894(08)00081-6 [pii] *Behavior Therapy, 40*(4), 357–367. https://doi.org/10.1016/j.beth.2008.10.006.

Pelc, K., Cheron, G., Boyd, S. G., & Dan, B. (2008). Are there distinctive sleep problems in Angelman syndrome? *Sleep Medicine, 9*(4), 434–441.

Pereira, J. A., Ravichandran, C. T., Mullett, J., McDougle, C. J., & Keary, C. J. (2020). Characterization of sleep habits and medication outcomes for sleep disturbance in children and adults with Angelman syndrome. *American Journal of Medical Genetics A, 182*(8), 1913–1922. https://doi.org/10.1002/ajmg.a.61642

Peters, S. U., Beaudet, A. L., Madduri, N., & Bacino, C. A. (2004). Autism in Angelman syndrome: Implications for autism research. https://doi.org/CGE362 [pii] *Clinical Genetics, 66*(6), 530–536. https://doi.org/10.1111/j.1399-0004.2004.00362.x.

Quante, M., Kaplan, E. R., Cailler, M., Rueschman, M., Wang, R., Weng, J., Taveras, E. M., & Redline, S. (2018). Actigraphy-based sleep estimation in adolescents and adults: A comparison with polysomnography using two scoring algorithms. https://doi.org/nss-10-013 [pii] *Nature and Science of Sleep, 10*, 13–20. https://doi.org/10.2147/NSS.S151085.

Sateia, M. J., Buysse, D. J., Krystal, A. D., Neubauer, D. N., & Heald, J. L. (2017). Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: An American academy of sleep medicine clinical practice guideline. *Journal of Clinical Sleep Medicine, 13*(2), 307–349. https://doi.org/10.5664/jcsm.6470jc-00382-16

Shi, S. Q., Bichell, T. J., Ihrie, R. A., & Johnson, C. H. (2015). Ube3a imprinting impairs circadian robustness in Angelman syndrome models. https://doi.org/S0960-9822(14)01650-9 [pii] *Current Biology, 25*(5), 537–545. https://doi.org/10.1016/j.cub.2014.12.047.

Shi, S. Q., Mahoney, C. E., Houdek, P., Zhao, W., Anderson, M. P., Zhuo, X., Beaudet, A., Sumova, A., Scammell, T. E., & Johnson, C. H. (2022). Circadian rhythms and sleep are dependent upon expression levels of key ubiquitin ligase Ube3a. *Frontiers in Behavioral Neuroscience, 16*, Article 837523. https://doi.org/10.3389/fnbeh.2022.837523

Simonds, J. F., & Parraga, H. (1982). Prevalence of sleep disorders and sleep behaviors in children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry, 21*(4), 383–388. https://doi.org/10.1016/s0002-7138(09)60942-0

Sitnick, S. L., Goodlin-Jones, B. L., & Anders, T. F. (2008). The use of actigraphy to study sleep disorders in preschoolers: some concerns about detection of nighttime awakenings. *Sleep, 31*(3), 395–401. https://doi.org/10.1093/sleep/31.3.395

Spruyt, K., Braam, W., & Curfs, L. M. (2018). Sleep in Angelman syndrome: A review of evidence. https://doi.org/S1087-0792(17)30017-5 [pii] *Sleep Medicine Reviews, 37*, 69–84. https://doi.org/10.1016/j.smrv.2017.01.002.

Spruyt, K., & Curfs, L. M. (2015). Non-pharmacological management of problematic sleeping in children with developmental disabilities. *Developmental Medicine & Child Neurology, 57*(2), 120–136. https://doi.org/10.1111/dmcn.12623

Takaesu, Y., Komada, Y., & Inoue, Y. (2012). Melatonin profile and its relation to circadian rhythm sleep disorders in Angelman syndrome patients. *Sleeping Medicine*.

Thibert, R. L., Larson, A. M., Hsieh, D. T., Raby, A. R., & Thiele, E. A. (2013). Neurologic manifestations of Angelman syndrome. https://doi.org/S0887-8994(12)00483-3 [pii] *Pediatric Neuro Pediatric Neurology, 48*(4), 271–279. https://doi.org/10.1016/j.pediatrneurol.2012.09.015.

Thorpy, M. J. (2012). Classification of sleep disorders. *Neurotherapeutics, 9*(4), 687–701. https://doi.org/10.1007/s13311-012-0145-6

Tietze, A. L., Blankenburg, M., Hechler, T., Michel, E., Koh, M., Schluter, B., & Zernikow, B. (2012). Sleep disturbances in children with multiple disabilities. https://doi.org/S1087-0792(11)00035-9 [pii] *Sleep Medicine Reviews, 16*(2), 117–127. https://doi.org/10.1016/j.smrv.2011.03.006.

Trickett, J., Heald, M., & Oliver, C. (2017). Sleep in children with Angelman syndrome: Parental concerns and priorities. https://doi.org/S0891-4222(17)30190-7 [pii] *Research in Developmental Disabilities, 69*, 105–115. https://doi.org/10.1016/j.ridd.2017.07.017.

Trickett, J., Heald, M., Oliver, C., & Richards, C. (2018). A cross-syndrome cohort comparison of sleep disturbance in children with Smith-Magenis syndrome, Angelman syndrome, autism spectrum disorder and tuberous sclerosis complex. *Journal of Neurodevelopmental Disorders, 10*(1), 9. https://doi.org/10.1186/s11689-018-9226-0

Trickett, J., Oliver, C., Heald, M., Denyer, H., Surtees, A., Clarkson, E., Gringras, P., & Richards, C. (2019). Multi-method assessment of sleep in children with angelman syndrome: A case-controlled study. *Frontiers in Psychiatry, 10*, 874. https://doi.org/10.3389/fpsyt.2019.00874

Walz, N. C., Beebe, D., & Byars, K. (2005). Sleep in individuals with Angelman syndrome: Parent perceptions of patterns and problems. *American Journal on Mental Retardation, 110*(4), 243–252.

Ware, J. E., Jr., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care, 30*(6), 473–483. ⟨https://www.ncbi.nlm.nih.gov/pubmed/1593914⟩.

Wheeler, A. C., Sacco, P., & Cabo, R. (2017). Unmet clinical needs and burden in Angelman syndrome: a review of the literature. *Orphanet Journal of Rare Diseases, 12*(1), 164. https://doi.org/10.1186/s13023-017-0716-z

Wiggs, L., & Stores, G. (1996). Severe sleep disturbance and daytime challenging behaviour in children with severe learning disabilities. *Journal of Intellectual Disability Research, 40*(*Pt 6*), 518–528. https://doi.org/10.1046/j.1365-2788.1996.799799.x

Wiggs, L., & Stores, G. (1998). Behavioural treatment for sleep problems in children with severe learning disabilities and challenging daytime behaviour: Effect on sleep patterns of mother and child. *Journal of Sleep Research, 7*(2), 119–126. https://doi.org/10.1046/j.1365-2869.1998.00107.x

Willgoss, T., Cassater, D., Connor, S., Krishnan, M. L., Miller, M. T., Dias-Barbosa, C., Phillips, D., McCormack, J., Bird, L. M., Burdine, R. D., Claridge, S., & Bichell, T. J. (2021). Measuring what matters to individuals with angelman syndrome and their families: Development of a patient-centered disease concept model. https://doi.org/10.1007/s10578-020-01051-z [pii] 1051[pii] *Child Psychiatry & Human Development, 52*(4), 654–668. https://doi.org/10.1007/s10578-020-01051-z.

Williams, C. A., Beaudet, A. L., Clayton-Smith, J., Knoll, J. H., Kyllerman, M., Laan, L. A., Magenis, R. E., Moncla, A., Schinzel, A. A., Summers, J. A., & Wagstaff, J. (2006). Angelman syndrome 2005: Updated consensus for diagnostic criteria. *American Journal of Medical Genetics, 140*(5), 413–418.