

SLEEP PROBLEMS IN INDIVIDUALS WITH 11q TERMINAL DELETION DISORDER (JACOBSEN SYNDROME)

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Summary: *Sleep problems in individuals with 11q terminal deletion disorder (Jacobsen syndrome):* Characteristics of sleep and sleep problems were investigated in 43 individuals with 11q terminal deletion disorder (Jacobsen syndrome). Data were collected using a sleep questionnaire. Ten individuals (23%) had a sleep problem. Settling problems, frequent night waking and early waking occurred in 2 (4%), 7 (16%) and 2 (6%) individuals, respectively. Twenty-two individuals (54%) had a history of sleep problems. Twenty-five individuals (60%) showed restless sleep and 23 individuals (54%) slept in an unusual position. Apart from frequent coughs, no significant relationships were found between the presence of a sleep problem and other variables, such as age, level of ID, breathing problems, heart defects, constipation, daytime activity and behavioral diagnosis, restless sleep and sleeping in an unusual positions.

Key-words: 11q terminal deletion disorder – Jacobsen syndrome – Sleep problems – Sleep questionnaire.

INTRODUCTION

11q terminal deletion disorder (Jacobsen syndrome) is a rare genetic disorder, caused by a terminal deletion in the long arm of chromosome 11. It is characterized by psychomotor retardation, congenital heart defects, blood dyscrasias (Paris-Trousseau syndrome) and craniofacial anomalies. Seizures are uncommon in this syndrome. Cognitive level in individuals with Jacobsen syndrome usually ranges from near normal intelligence to moderate intellectual disability (see e.g. Grossfeld *et al.* (6)).

Sleep problems may be part of genetic syndromes associated with intellectual disability. Compared to matched controls, prevalence of specific sleep problems has been found to be higher among individuals with a genetic disorder than in those without a disorder. A relatively high prevalence of sleep problems were found in Down, fragile-X, Smith-Magenis, Prader-Willi, Angelman and Rett syndrome (e.g. 2-4, 7, 9-11). Little is known about the characteristics of sleep or the frequency of sleep problems in Jacobsen syndrome. Our knowledge on sleep problems in individuals with Jacobsen syndrome is primarily based on anecdotal information and clinical experience, suggesting that sleep problems in individuals with Jacobsen syndrome may be prevalent. Furthermore, it is not known what other neurocognitive and/or medical

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problems may be associated with sleep problems in these patients. To date, no study has been performed that characterizes sleep and sleep problems in individuals with Jacobsen syndrome, and factors that may be related to sleep problems in this group. Therefore, in the present study, (a) characteristics of sleep and sleep problems were investigated in a relatively large sample ($N = 43$) of individuals with Jacobsen syndrome, (b) parental management with their child's sleep problem was investigated, and (c) relationships between the presence of a sleep problem and other variables (e.g., age, level of intellectual disability and medical problems) were explored.

METHOD

PARTICIPANTS AND PROCEDURE

A standardized sleep questionnaire (see *Sleep Questionnaire*) was sent to parents who were members of the American 11q Research and Resource Group. Only individuals with a terminal deletion at chromosome 11q (Jacobsen syndrome) and who were living at home with their parents were included. Parents were asked to complete the Sleep Questionnaire.

MATERIALS

Sleep Questionnaire

The Sleep Questionnaire was adapted from Wiggs and Stores (14), Didden, Korzilius, Van Aperlo, Van Overloop and De Vries (5) and Didden *et al.* (4) and consisted of five parts. Part one addresses demographic information (e.g., presence of seizure disorder and heart defect). The second part covers current (i.e. last three months) behaviors related to settling to sleep, night waking and early waking. Questions about frequency of occurrence (e.g., "How often does your child wake in the night?") were assessed on a 7-point scale, from "Never" to "Daily". Questions about duration (e.g., "How long does it usually take to resettle her?") were assessed on a 5-point scale, from "Few minutes" to "More than two hours". In part three, parents were asked to fill in at what times their child usually goes to bed and wakes up in the morning, among other items. The fourth part assessed the frequency of occurrence of several behaviors related to sleep (e.g., "Grinds teeth in sleep", "Reluctant to go to bed") on a 7-point scale, from "Never" to "Daily". According to Wiggs & Stores (15) behaviors that occurred only 'Sometimes' ("Once or twice a week") and those that occur-

red 'Often' ("Three to six times a week" or "Daily") are distinguished. Finally, the last part contains items about parents' impression of their child's current or past sleep problems, as well as treatment of the child's sleep problem and family's sleep.

The items of the fourth part, some items of the third part and one of the second part of the questionnaire can be clustered into six sleep 'factors' (12). These factors are indicative for "Poor quality sleep", "Anxieties about sleep", "Parasomnias", "Disordered breathing", "Early waking" and "Narcolepsy".

Definition of a sleep problem

Criteria for the definition of a sleep problem were established by Wiggs and Stores (14) and Didden *et al.* (4, 5). Three types of sleep problems were distinguished. Severe *settling problems* occurred three or more nights a week, whereby the individual took more than 1 hour to fall asleep and parents were disturbed during this time. Mild *settling problems* occurred one or two nights a week and falling asleep took more than 30 minutes. *Night waking* was defined as severe if it occurred three or more nights a week, and if the individual woke up for more than a few minutes and disturbed parents during that time (e.g. co-sleeping, crying). Finally, *early waking* was defined as severe if the individual woke up before 5:00 a.m. and stayed awake three or more nights a week. Night waking or early waking was considered a mild problem if it occurred once or twice a week. A sleep problem was diagnosed if an individual had at least one of the above three types of sleep problems.

DATA ANALYSIS

Paired sample *t*-tests were performed for the sleep factors. For nominal data a Chi-square test was performed. In case differences could not be tested with Chi-square tests, due to low cell frequencies, two-tailed Fisher's Exact Tests were conducted. This test only produces a significance level and no formal test statistic. For age in months an Independent Samples *t*-test (Student's *t*) was performed and for ordinal data, such as level of intellectual disability, a Mann-Whitney test was performed. SPSS (version 12.0) was used to analyze the results.

RESULTS

POPULATION

Out of 95 questionnaires that were sent to parents of individuals with this syndrome, 43 were returned (response rate: 45%). A total of 43 individuals participated in this study. Fourteen individuals were male. The sex ratio was .48 and this ratio is not statistically different (binomial test, test proportion .65, $p = .44$) from the male to female sex ratio of .53 found by Grossfeld *et al.* (6). Their mean age was 10 years and 4 months (range: 1 yr 7 months to 25 yrs 10 months, $SD = 5$ yrs 11 months). Six participants were 18 years or older. Mean age at which Jacobsen syndrome was diagnosed was 1 year and 8 months (range: 0 months to 13 yrs 6 months, $SD = 3$ yrs 6 months). All participants were initially confirmed as having Jacobsen syndrome by karyotype analysis. Further mapping of the breakpoint was performed either by FISH or CGH (using microarrays). The range of the deletions was from about 7 to 16 megabases.

Level of cognitive functioning was known for 18 participants (42%) of whom 5 had mild intellectual disability (IQ 55-70), 5 had moderate intellectual disability (IQ 40-55), 2 had severe intellectual disability (IQ 25-40) and 1 had profound intellectual disability (IQ < 25). Five participants had an IQ level that was greater than 70. Parents of 12 children (28%) mentioned that their child had a behavioral diagnosis, for example Attention-Deficit Hyperactivity Disorder, Autistic Spectrum Disorder and/or Obsessive-Compulsive Disorder.

Of the participants, 25 (61%, $n = 41$) had a (congenital) heart defect and 10 (26%, $n = 39$) had breathing problems. Six participants (15%, $n = 41$) had a history of seizures and none of them showed epileptic seizures (one as a result of medication) at the time of the study. Twenty participants (47%) had recurrent constipation problems. According to the Centers for Disease Control and Prevention Growth Charts: United States for boys and girls aged 2 to 20 years (8) 5 participants (16%, $n = 32$) were overweight (Body Mass Index for age > 95th percentile). None of the participants was blind. Twenty individuals (47%) had a hearing impairment. Five had a moderate to severe hearing loss, 9 had a mild hearing loss, one had a variable hearing loss and for 5 individuals the level of hearing loss was unknown. Most individuals ($n = 38$) were able to walk independently (93%), whereas 1 individual crawled and 2 were wheelchair dependent (for 2 toddlers it was not applicable because of their age).

DESCRIPTION OF SLEEP PROBLEMS

Sleep problems

Table I shows percentages of individuals with different types of (combinations of) sleep problems. *Severe* settling problems and frequent night waking were found in 1 (2%) and 3 (7%) participants, respectively. None of the participants had a severe type of early waking. *Mild* settling problems, frequent night waking and early waking were found in 1 (2%), 4 (9%) and 2 (6%) participants respectively. Totally, 10 (23%) participants had a mild or severe sleep problem.

Out of the 34 children who woke up at night, 14 (41%) children called out for their parent, 10 (29%) did nothing, 9 (27%) started to cry, 6 (18%) played with toys, and 5 (15%) went out of their bed and wandered about. In case parents responded to their child's night waking ($n = 35$), 17 (49%) patted or cuddled their child, 16 (46%) provided food and/or drinks, 16 (46%) put their child back into bed immediately, 13 (37%) lied with their child on the child's bed, 11 (31%) settled their child in the parent's bed, and 9 (26%) talked, sang a lullaby or read a story to their child.

Table I: Number and percentage of individuals with types of (combinations of) sleep problems

Type (s) of sleep problem	Mild n (%)	Severe n (%)	Total n (%)
Settling problems	1 (2%)	1 (2%)	2 (4%)
Frequent night waking	4 (9%)	3 (7%)	7 (16%)
Early waking	2 (6%)	0	2 (6%)
Frequent night waking and early waking	1 (3%)	0	1 (3%)
Settling problems or frequent night waking or early waking	6 (14%)	4 (9%)	10 (23%)

Sleep behaviors and type of sleep disturbance

Types and percentages of sleep behaviors that occurred sometimes ("Once or twice a week") or often ("Three to six times a week" or "Daily") are shown in Table II. For example, 21 participants (50%, $n = 42$) were reported often to be restless during sleep, and 13 (35%, $n = 37$) appeared often to be more active than other individuals during daytime. Most striking was the finding that 23 participants (54%) were reported to sleep in unusual positions, such as lying all over bed and

Table II: Number and percentage of individuals exhibiting sleep behaviors by frequency of occurrence*

	1-2 per week	More than 3 times per week	Total
Sleep behavior	n (%)	n (%)	n (%)
<i>Poor quality sleep</i>			
Restless sleep	4 (10%)	21 (50%)	25 (60%)
Wakes up in a bad mood	-	-	6 (17%)
Wakes up tired	-	-	5 (13%)
Seems drowsy, but can stop themselves from sleeping ^{ab}	2 (6%)	2 (6%)	4 (12%)
Daytime naps ^{ab}	-	-	1 (3%)
<i>Anxieties about sleep</i>			
Insists on bedtime ritual before going to sleep	0	18 (44%)	18 (44%)
Needs security object before going to sleep	1 (2%)	16 (38%)	17 (41%)
Insists on sleeping with somebody else at sleep onset/in night	2 (5%)	8 (20%)	10 (25%)
Afraid of the dark	0	3 (8%)	3 (8%)
Doesn't want to go to bed because afraid	0	2 (5%)	2 (5%)
Expresses fear that if goes to sleep they might die	0	0	0
<i>Parasomnias</i>			
Grinds teeth	3 (8%)	8 (20%)	11 (28%)
Talks in sleep	2 (5%)	5 (12%)	7 (17%)
Bangs head in sleep or going off to sleep	0	3 (7%)	3 (7%)
Walks in sleep	0	1 (3%)	1 (3%)
Wakes in night complaining of nightmares ^d	0	0	0
Wakes during the night screaming in terror ^c	0	0	0
<i>Disordered breathing</i>			
Snores loudly	1 (3%)	7 (18%)	8 (20%)
Gags or chokes	1 (2%)	1 (2%)	2 (5%)
Repeatedly stops breathing for 15-30 seconds	0	1 (3%)	1 (3%)
<i>Early waking</i>			
Wakes in the morning before 5 a.m. and stays awake	2 (6%)	0	2 (6%)
<i>Narcolepsy</i>			
Has urges to go to sleep and can't stop themselves ^{ab}	0	1 (3%)	1 (3%)
Upon waking or going off to sleep, feels paralyzed	0	1 (3%)	1 (3%)
Muscles become so weak that she/he falls to the ground ^b	0	0	0
<i>Other</i>			
Sleeps in unusual positions	-	-	23 (54%)
Appears more active than other children ^b	2 (5%)	13 (35%)	15 (41%)
Wets bed ^a	2 (6%)	12 (35%)	14 (41%)
Quick movements of arms or legs	3 (7%)	12 (29%)	15 (37%)
Reluctant to go to bed	2 (6%)	6 (17%)	8 (23%)
Needs sleep medication	0	2 (5%)	2 (5%)
Bites tongue	0	0	0

* A dash indicates that data were not obtained for these sleep behaviors. ^aIndividuals five years or older; ^bDuring the day; ^cFirst half of the night; ^dLast half of the night

upside down (9 participants, 21%), on knees with bottom up (6 participants, 14%), and completely hidden under the blanket (3 participants, 7%). Three participants (7%) used medication to improve sleep (2 used clonidine; 1 used melatonin), and parents of 2 of these participants (5%, $n = 41$) reported that their child needed sleep medication (i.e., clonidine) on a daily basis.

As described previously, sleep behaviors were clustered into six sleep factors (see Table II). Those factors correspond to different types of sleep disturbance. The mean scores (expressed as the percentage of maximum score) and *SD*'s on the sleep factors were: Poor quality sleep 27.6 (21.1); Anxieties about sleep 20.8 (18.0); Parasomnias 8.5 (12.8); Disordered breathing 9.3 (20.4); Early waking 5.6 (23.2); and Narcolepsy 2.6 (9.0).

Parent's perception of sleep problems

Parents were asked whether they thought that their child had a current sleep problem (no criteria or definition of a sleep problem were provided to them). This question was answered affirmatively by parents of 11 children (26%, $n = 42$). According to them 5 children had problems with settling to sleep, 5 with frequent night waking and 6 with early waking. Additionally, parents of 4 children mentioned that co-sleeping was a problem.

Parents of another 11 children (all of whom didn't report a current sleep problem) reported a past sleep problem. In the past, the following sleep problems were present: 7 children had problems settling to sleep, 5 had frequent night waking problems and 5 had problems with early waking. Parents of 6 children mentioned that co-sleeping had been a problem in the past. Current or past sleep problems lasted 1 year or longer in 17 children (89%, $n = 19$). Parents of 19 children (46%, $n = 41$) reported that their children never had a sleep problem.

Treatment of sleep problems

Parents of 11 children (55%, $n = 20$) with current or past sleep problems had asked for advice or help about treatment of those problems. Sleep medication was used most often, that is in 7 of the 11 individuals. Medication was effective in reducing sleep problems of 4 individuals (2 of them used clonidine, 1 used melatonin and in 1 individual this was not specified). One individual underwent adenoidectomy (operation) and this was effective. Parents of 3 children received psychological help and this was effective in reducing sleep problems for 1 individual. An example of psychological treatment was stimulus control (establishing an appropriate bedtime routine). Education/general advice and homeopathic remedy were also mentioned for 5 and 3 individu-

als respectively, and both types of help were not effective in reducing sleep problems.

STATISTICAL ANALYSIS

Upon being asked whether their child had a current sleep problem, parents mentioned sleep problems in 26% of the cases. According to the objective criteria for a sleep problem (see *Definition of a Sleep Problem*), the prevalence rate of sleep problems was 23%. This difference is not statistically significant ($p = 1.00$, two-tailed Fisher's exact test). However, of the 10 participants currently having a sleep problem according to the objective criteria, only 2 parents mentioned that their child had a sleep problem.

According to the objective criteria, 3 (25%, $n = 12$) individuals with a behavioral diagnosis had a sleep problem, compared to 7 (23%, $n = 31$) individuals without a behavioral diagnosis. This difference is not statistically significant ($p = 1.00$, two-tailed Fisher's exact test).

No differences were found in the occurrence ("sometimes/often" compared to "infrequent") of single sleep behaviors between individuals with and without a behavioral diagnosis.

Six (24%, $n = 25$) individuals with restless sleep had a sleep problem. This does not statistically differ from the 4 (24%, $n = 17$) individuals without restless sleep ($p = 1.00$, two-tailed Fisher's exact test). Seven (30%, $n = 23$) individuals with an unusual sleeping position had a sleep problem, compared to 3 (15%, $n = 20$) individuals without an unusual sleeping position. This difference is not statistically significant ($p = .29$, two-tailed Fisher's exact test). In addition, no significant difference was found between individuals with or without restless sleep and sleeping in an unusual position (60% versus 41% respectively, $p = .35$, two-tailed Fisher's exact test).

No differences were found in the occurrence ("sometimes/often" compared to "infrequent") of single sleep behaviors between individuals with and without sleep problems.

Furthermore, no significant relationships were found between the presence of a sleep problem and other variables, such as breathing problems, heart defects, constipation problems, overweight, medication use, having a room of their own, having a bed time routine and daytime activity. Seven (41%, $n = 17$) individuals with frequent coughs had sleep problems, compared to 2 (9%, $n = 22$) individuals without frequent coughs ($p = .03$, two-tailed Fisher's exact test). This difference is statistically significant.

There was no significant relationship between the presence of a sleep problem and age in months, $t(41) = 1.63$, $p = .11$. (two-tailed). When

a division into age groups ("infant", "toddler", "preschooler", "school aged", "adolescent" and "adult") was made, there also was no statistically significant difference, $z = -1,95$ ($p = .05$, two-tailed). None of the adult (age > 215 months) participants ($n = 6$) had a sleep problem. There was no significant relationship between the presence of a sleep problem and level of ID ($n = 18$), $z = -1,71$ ($p = .09$, two-tailed). When a division was made into three groups ("IQ > 70", "mild/moderate ID" and "severe/profound ID"), none of the participants with an IQ > 70 had a sleep problem, 1 (10%, $n = 10$) from the participants with a mild/moderate ID had a sleep problem and 2 (67%, $n = 3$) from the participants with a severe/profound ID.

A relatively high mean score on one or more of the sleep factors indicate that this type of sleep disturbance is more prevalent in this sample than other types of sleep disturbance. Results of paired t -tests (using Bonferroni correction for the number of comparisons) revealed that the mean score of the sleep factor group Poor quality sleep was statistically different from the other sleep factor groups except for anxieties about sleep (all p 's < .001). The mean score for Poor quality sleep were higher than the mean scores for Parasomnias, Disordered breathing, Early waking and Narcolepsy. In addition the mean score of Anxieties about sleep was higher than the mean scores for Parasomnias, Early waking and Narcolepsy (all p 's < .001).

DISCUSSION

The present study is the first to systematically investigate sleep and sleep problems in a large sample of individuals with Jacobsen syndrome. We used a standardized questionnaire for data collection. According to well-established criteria (see 4, 5, 14) 10 individuals (i.e., 23% of the sample) had a mild or severe sleep problem at the time of the study. Settling problems, frequent night waking and early waking were found in 2, 7, and 2 individuals, respectively, and 1 participant had both night waking and early waking problems. According to the parents, 22 (54%) individuals with Jacobsen syndrome experienced sleep problems at some point in their lives and in 17 individuals (89%) current or past problems had lasted more than 1 year.

Remarkable were the high percentages on the items "Sleeping in an unusual position" (53%) and "Restless sleep" (60%). Lower percentages on restless sleep are reported in other studies using the same questionnaire: 41% (children with severe intellectual disability (14)), 21% (children with intellectual disability (5)), 45% (children with autistic

spectrum disorders (15)), 25% (individuals with Angelman syndrome (4)) of the samples, respectively. Restless sleep may indicate poor sleep quality or non-restorative sleep. Restlessness in sleep in individuals with Jacobsen syndrome has to be clarified by objective observation, such as actigraphy or video recording during the night.

It is known that sleep problems in children with Autistic Spectrum Disorders or Attention-Deficit Hyperactivity Disorder are highly prevalent (1, 15). In this sample, no difference in the presence of a sleep problem or sleep behaviors between individuals with or without a behavioral diagnosis was found. This might be because individuals with a behavioral diagnosis in this sample received treatment (medication) for their behavior disorders.

The treatment of a sleep problem should be based on a careful assessment and, if possible, identification of an underlying diagnosis. For an overview of assessment and treatment of a sleep problem in individuals with intellectual disability see Wiggs (13). Clinical practitioners managing a patient with Jacobsen syndrome, should determine the underlying cause for specific sleep problems and sleep behaviors in these patients. Medical problems should be identified and treated accordingly. Behavioral problems can be treated with behavior modification procedures, and possibly medications. For example, a suitable treatment for anxiety problems is gradual withdrawal. For limit setting disorders and sleep onset association problems stimulus control and extinction procedures are suitable procedures.

Future studies should be conducted to compare characteristics of sleep and type of sleep problems in individuals with Jacobsen syndrome to those exhibited by individuals with other genetic disorders or nonspecific intellectual disabilities. The purpose is to determine if sleep is part of the behavioral phenotype in Jacobsen syndrome. Additional individuals will be studied to determine a possible causal relationship between severity of intellectual impairment and sleep problems. Furthermore, future investigation of sleep (architecture) by polysomnography may increase our understanding of the nature and cause(s) of sleep characteristics (for example restless sleep) in individuals with Jacobsen syndrome.

ACKNOWLEDGEMENTS

The authors would like to thank all the participants of the study. We wish to express special thanks to Linzee Carroll and other members of the American 11q Research and Resource Group who aided in the distribution of the questionnaire.

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