Sleep disturbances in CHARGE syndrome: types and relationships with behavior and caregiver well-being

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LIST OF ABBREVIATIONS

DBC	Developmental Behaviour Checklist
DBC-P	Developmental Behavior Checklist – Parent/Carer Version
SDSC	Sleep Disturbances Scale For Children

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Children with CHARGE syndrome frequently develop moderate to severe behavior difficulties and are often diagnosed with obsessive–compulsive disorder, attention deficit disorder, Tourette syndrome, and autism. Anecdotal reports have indicated that sleep is also affected. However, the prevalence and types of sleep disturbance have not been identified. This study investigated sleep disturbances in 87 children with CHARGE syndrome, aged 6 to 18 years (mean 11y, SD 3y 8mo). There were 52 males and 35 females represented. Instruments included measures of sleep (Sleep Disturbances Scale for Children [SDSC]), behavior (Developmental Behaviour Checklist [DBC]), and carer well-being (Malaise Inventory). On the SDSC, 57.5% received scores considered significant for sleep disturbances, with disorders of initiating and maintaining sleep, sleep breathing, and sleep–wake transition being the most common. The SDSC was significantly correlated with the DBC (p=0.010) and the Malaise Inventory (p=0.003). Regression analysis found that both problem behavior and sleep disturbances contributed to the prediction of scores on the Malaise Inventory. Being both deaf and blind (p=0.001), experiencing frequent middle-ear infections (p=0.015), and starting to walk at an older age (p=0.007) were associated with more sleep disturbance. Craniofacial anomalies were not. The study highlights the importance of addressing the sleep difficulties associated with CHARGE syndrome relating both to airway management and to disorders of initiating sleep.

CHARGE syndrome was identified independently by Hall[1] and by Hittner and colleagues[2] in 1979, and the acronym was suggested by Pagon and colleagues in 1981,[3] based on common features: C, coloboma of the eye (missing part of iris and/or retina); H, heart defects; A, atresia of the choanae (bony or membranous blocking of nasal passage); R, retardation of growth and/or development; G, genitourinary anomalies; and E, ear anomalies and/or deafness.

CHARGE is a phenotypically heterogeneous syndrome with criteria that have been refined a number of times,[4] based on major and minor features (Table I). The incidence of CHARGE syndrome is generally estimated at 1 in 10 000 births, with a recent epidemiological survey in Canada reporting 1 in 8500.[5] A major gene for CHARGE syndrome, *CHD7*, was identified in 2004,[6] and approximately 65% of individuals have had *CHD7* mutations observed on chromosome 8q12.1.[7] *CHD7* encodes a protein of the chromodomain family, and these proteins affect chromatin structure and, hence, gene expression and, therefore, embryological development.[7]

Medical management of CHARGE syndrome is often focused on the multisensory impairments, swallowing difficulties, and heart, renal, and airway complications, including choanal atresia and cleft palate. Intensive medical management in the first 4 years of life is critical to survival and long-term well-being.

Children with CHARGE syndrome frequently develop moderate to severe behavior difficulties and may be diagnosed with obsessive–compulsive disorder, attention deficit disorder, Tourette syndrome, and autistic-like behaviors, including problems with language processing, social interaction, and self-stimulatory behaviors.[8] A wide range of cognitive ability is found in CHARGE syndrome from profound impairment to above-average IQ.[9]

Anecdotal reports indicate that sleep may be affected. The only published evidence for sleep problems in CHARGE syndrome was a study of 30 adolescents and young adults, of whom 13 were reported to have sleep apnea.[10] Given the prevalence of sleep difficulties among children in the general population, as well as studies demonstrating a high rate of sleep difficulties in children with disabilities,[11,12] it would not be surprising to find that sleep is a problem with children who have CHARGE syndrome. We speculate, in addition, that certain characteristics of CHARGE syndrome may lend themselves to sleep problems. First, deaf–blindness is a very common characteristic of CHARGE syndrome. Although there is no evidence that being deaf may negatively affect sleep, there is emerging evidence that visual impairment can.[13] The mechanisms underlying this are not entirely clear and need to be explored, but are at least partly chronobiological. Second, children with CHARGE syndrome may have various craniofacial abnormalities, including cleft deformities and choanal atresia, both of which have been associated with sleep-disordered breathing and obstructive sleep apnea.[14,15] Third, otitis media is a common occurrence in CHARGE syndrome. Anecdotal parent reports indicate that the pain from ear infections can interfere with sleep. The relationship between pain and disturbed sleep is well established[16] and may explain this finding.

With CHARGE syndrome having a highly variable phenotype, it would be expected that sleep disturbance would vary considerably among children with CHARGE syndrome. One marker that has been identified in several studies as predicting how well children with CHARGE syndrome develop is the age when they first walk.[8,9,17] Therefore it is of interest to learn whether this is a marker for sleep disturbance as well.

Well-being of primary carers is important, especially if children have behavioral difficulties. The impact of child sleep disturbance on parental well-being is probably complex.[18] Sleep deprivation in carers affects not only their own well-being but their emotional strength in consistently responding to children with behavioral issues.

The present study had the following aims: to document the possible extent of sleep disturbance in CHARGE syndrome; to test the relationships between sleep disturbance and daytime challenging behavior and parental well-being; to look for a relationship between sleep disturbance and deaf–blindness, choanal atresia, and ear infections; and to look at the association of age of walking with sleep disturbance.

Table I: Major and minor symptoms of CHARGE syndrome found in study participants

Features	Percentage affected (*n*=87)
Major	
Coloboma	84
Characteristic CHARGE ear	83
Choanal atresia or stenosis	60
Cranial nerve anomalies	
Sensorineural hearing loss	85
Facial palsy	48
Anosmia	40
Vestibular problems	85
Minor features	
Delayed motor milestones	99
Growth deficiency	82
Frequent middle ear infections	79
Heart defect	78
Swallowing problems	70
Genital hypoplasia	62–44 males (85%), 10 females (29%)
Spine anomalies	31
Renal problems	30
Cleft lip or palate	29
Tracheosophageal fistula	22
Hand anomalies	17

METHOD

Participants

Materials were mailed to parents of 102 children aged 6 to 18 years. All parents were members of the CHARGE Syndrome Foundation, and all of the children had received a medical diagnosis of CHARGE syndrome by a physician. Membership in the Foundation is open to anyone with an interest in CHARGE syndrome. Dues are set at US$20 so as not to discourage families from joining. Although it is possible that there may be some bias in terms of which parents join, the full range of CHARGE syndrome is seen in these children. In addition, this set of parents tends to be highly motivated to participate in research.

Measures

The CHARGE syndrome history questionnaire[9] was used to gather information on basic demographics and the child's CHARGE syndrome features.

The Malaise Inventory is a 24-item questionnaire that was developed by Rutter et al.[19] as a brief measure of mothers' mental well-being. The items refer to emotions and somatic complaints. The factor structure and internal consistency of the Malaise Inventory have been evaluated, and there is general support for a single factor (although second factors can also be derived) and acceptable internal consistency.[20] Test–retest correlations have been found between 0.80 over 1 year[21] and 0.91 over a shorter period.[19] A score of 7 or greater is generally considered to be an indication of psychiatric distress.[20]

The Developmental Behaviour Checklist, second edition (DBC)[22] was developed to measure the behavioral problems of children and adults with intellectual disabilities. It is completed by either the parent or carer or the teacher. There are 96 items scored in five subtests (disruptive/antisocial, self-absorbed, communication disturbance, anxiety, and social relating). The scales were derived through factor analysis[22] and were confirmed by Hastings et al.,[23] who also replicated high levels of internal consistency. The present study used only the parent/carer version (DBC-P). Norms on the DBC-P are based on an epidemiological study in New South Wales, Australia, constructed to as closely as possible constitute a representative sample of individuals in and out of institutions who have various degrees of intellectual disability from mild to profound. A score of 46 or higher is generally considered to be clinically significant on the DBC-P.

The Sleep Disturbance Scale For Children (SDSC);[24] is a 26-item scale used to categorize sleep disorders in children. Sleep is classified by six factor-analytically derived categories: disorders of initiating and maintaining sleep; sleep breathing disorders; disorders of arousal; sleep–wake transition disorders; disorders of excessive somnolence; and sleep hyperhydrosis. Bruni et al.[24] indicate that a T score of 55 is a good cut-off for clinical significance. They do not provide cut-offs for the subscales. Internal consistency of the items is acceptable.[24]

This project was reviewed and approved by the Institutional Review Board at Central Michigan University. Informed consent was given by the parents of participants.

Statistics

Descriptive statistics were used to present the degree of difficulties in sleep, behavior, and parent well-being. Correlations were used to look at relationships between these three variables, and with age of walking. Stepwise regression analysis was used to examine the relative contributions of behavior and sleep to parent well-being. Mean differences in sleep difficulties for the four CHARGE syndrome characteristics were examined by *t*-test.

RESULTS

Materials were returned by 89 parents (87%), of which 87 were usable; the majority were completed by the mother (89.7%). Most of the children were male (*n*=52; 59.8%), they came from 27 US states, and were predominantly white (*n*=77; 88.5%). Ages ranged from 6 to 18 years, with a mean of 11y 1mo (SD 3y 8mo). Although the *CHD7* gene was found in 2004, genetic testing of children with CHARGE syndrome is not yet widespread, particularly among the older children. For the children in this study, 50 had never been tested, 14 did not provide information on testing, and 23 had been tested, with 16 positive and seven negative results, for a 70% rate of positives. The percentage of participants with the various major and minor CHARGE syndrome features is shown in Table I.

Table II shows the results for the SDSC, DBC-P, and Malaise Inventory, along with the percentages of participants who scored at a clinical level, where available.

On the SDSC, 57.5% of the children obtained a total score higher than the clinical cut-off of a T score of 55. Table II includes the percentage of participants who scored at least 1SD above the mean (a T score of 60 or above). Looking at the subscales, the highest score was for disorders of initiating and maintaining sleep, with 57.5% of participants scoring at least 1SD above the mean. The average for sleep breathing disorders was 1SD above the mean. Sleep–wake transition disorders with a T score of 57 was the third highest subscale score. The other sleep disturbances, disorders of arousal, excessive somnolence, and sleep hyperhydrosis, had mean scores near the population mean.

Because the range of intellectual ability is quite large in CHARGE syndrome, participants were compared with the total sample norms on the DBC-P, recognizing that they might not apply accurately to participants whose intellectual ability was in the normal range. Nearly half of the children had a clinical score of 46 or above (58th centile) on the DBC-P. Cut-off scores are not provided for the subtests, so Table II includes the centile scores for the current participants based on the table of norms provided in the manual.[22] Centile scores were above the 50th centile for the subscales of self-absorbed, communication disturbance, and social relating (Table II), with the highest centile (64) for the self-absorbed subscale.

To test whether a relationship existed between sleep problems and behavior, correlations were calculated between the SDSC and the DBC-P (Table III). Total sleep scores were significantly associated with total DBC-P scores so that, as sleep disturbance increased, so did behavioral difficulties. Total sleep scores were also significantly associated with the self-absorbed subtest on the DBC-P.

Table II: Results for SDSC, DBC-P, and Malaise Inventory, with percentages of participants who scored at a clinical level, where available

Scale	Mean	SD		'Clinical' %
SDSC (T scores)			≥60%[a]	
Initiating/maintaining	62.05	15.31	57.5	
Breathing	59.63	15.21	37.9	
Arousal	48.57	5.87	4.6	
Sleep–wake	57.08	13.77	36.8	
Somnolence	51.76	11.62	17.2	
Hyperhydrosis	49.91	10.01	11.5	
Total	59.29	13.11	41.4	57.5[b]
DBC (raw scores)			Centile[c]	
Disruptive/antisocial	10.80	7.60	46	
Self-absorbed	16.66	10.97	64	
Communication	6.53	4.45	62	
Anxiety	3.84	2.98	48	
Social relating	4.76	3.80	56	
Total	44.13	23.83	56	49.4[d]
Malaise Inventory (raw scores)				
Total	4.99	4.01		33.3[e]

Data from 87 participants. [a]Percentage of children obtaining a score 1SD or greater above the mean. [b]Percentage of children obtaining a total SDSC T score above 55. [c]Cut-off scores are not provided for DBC subtests, so centile scores are given based on table of norms provided in the DBC manual.[22] [d]Percentage of children obtaining a DBC-P score of 46 or above (58th centile).[e]Percentage of parents/carers obtaining Malaise Inventory scores of ≥7. DBC, Developmental Behaviour Checklist; SDSC, Sleep Disturbances Scale For Children.

Table III: Correlations between sleep problems (Sleep Disturbances Scale For Children [SDSC] score) and behavior (Development Behaviour Checklist [DBC] score)

SDSC category	DBC subtest					
	Total	Disruptive	Absorbed	Communicate	Anxiety	Social
Sleep total	0.276	0.136	0.444	0.030	0.103	0.127
p value	***0.010***	*0.209*	***<0.001***	*0.785*	*0.342*	*0.240*
Initiating	0.429	0.290	0.566	0.152	0.220	0.228
p value	***<0.001***	***0.006***	***<0.001***	*0.161*	***0.041***	***0.034***
Breathing	0.140	0.023	0.245	0.038	–0.040	0.109
p value	*0.197*	*0.833*	***0.022***	*0.727*	*0.715*	*0.316*
Arousal	–0.065	–0.059	–0.033	–0.125	0.030	–0.103
p value	*0.552*	*0.587*	*0.762*	*0.249*	*0.782*	*0.344*
Sleep–wake	0.099	0.060	0.225	–0.120	0.023	–0.040
p value	*0.362*	*0.581*	***0.036***	*0.270*	*0.833*	*0.714*
Somnolence	0.043	–0.043	0.124	–0.027	0.045	0.005
p value	*0.695*	*0.694*	*0.254*	*0.800*	*0.682*	*0.960*
Hyperhydrosis	0.003	–0.058	0.073	0.020	–0.079	0.069
p value	*0.981*	*0.591*	*0.499*	*0.855*	*0.466*	*0.525*

Data from 87 participants; *p* values in bold represent statistical significance.

The sleep disturbance type most associated with behavior difficulties was problems with initiating and maintaining sleep, which was highly correlated with total behavior and the subtests of self-absorbed, anxiety, and social relating. Sleep breathing disorders and sleep–wake transition disorders were also significantly associated with self-absorbed

behavior. Self-absorbed behavior was, therefore, associated with total sleep disturbance and the problems of initiating and maintaining sleep, sleep breathing disorders, and sleep–wake transition disorders.

Scores on the Malaise Inventory ranged from 0 to 16. One-third of the parents had scores in the 'clinical' range of 7 or greater (Table II). Table IV shows the relationships found between sleep problems and the Malaise Inventory. Parent well-being was associated with total sleep disturbance scores and with problems initiating and maintaining sleep. It was not significantly associated with the other subscales of the SDSC.

Table IV also shows the relationships between behavior difficulties and the Malaise Inventory. Total scores on the DBC-P and all five subtests were significantly correlated with scores on the Malaise Inventory.

Because sleep problems are associated with behavior difficulties, the association between sleep problems and the Malaise Inventory could be attributed to the behavior difficulties alone, and not the actual sleep disturbances. To test this, a stepwise regression analysis was calculated to see how well behavior difficulties and sleep disturbance predicted scores on the Malaise Inventory. The regression for behavior difficulties alone (DBC-P total scores) was significant: R^2 =0.19, $F_{(1,85)}$=13.2, p<0.001. Including both behavior difficulties and sleep disturbance (total scores on the SDSC) in the model was also significant: R^2=0.23, $F_{(2,84)}$=12.6, p<0.001. R^2 change was calculated to assess the effect of sleep disturbance added to the first equation (which included only behavior difficulties): R^2 change=0.041, F change=4.53 (1,84), p<0.05. This was also significant. Therefore, in this study, sleep disturbance contributed significantly to parent well-being beyond the contribution of behavior difficulties.

Table IV also shows the analysis with age of walking, which was significantly related to both behavior and sleep difficulties. Mean age of walking in this study was 3y 3mo. Children who walk later have an increased likelihood of behavior and sleep difficulties.

The relationship between sleep disturbance and being deaf–blind, having choanal atresia, cleft palate, and ear infections, was investigated by t-tests for mean difference (Table V). Eighteen children were identified as deaf–blind (defined as having no better than both moderate hearing impairment in the best ear and moderate vision impairment in the best eye). This group was found to have significantly higher total scores on the SDSC. Surprisingly, there was no significant difference for children who had either choanal atresia or cleft palate. Because we expected a relationship due to sleep breathing problems, we did additional analyses with that subscale, and again the differences were not significant (t=0.603, p=0.55 for choanal atresia; t=1.72, p=0.09 for cleft palate). Finally, children with 'frequent' middle-ear infections had higher sleep total scores than those without.

DISCUSSION

Over half of the children with CHARGE syndrome in our sample had sleep disturbance scores in the clinical range. CHARGE syndrome is not unique in this. Others have

Table IV: Correlations for Malaise Inventory and age of walking with sleep problems (Sleep Disturbances Scale For Children [SDSC] score) and behavior (Development Behaviour Checklist [DBC] score)

	SDSC category						
	Total	Initiating	Breathing	Arousal	Sleep–Wake	Somnolence	Hyperhydrosis
Malaise inventory	0.316	0.385	0.216	0.080	0.152	0.120	–0.029
p value	**0.003**	**<0.001**	**0.044**	0.459	0.159	0.268	0.788
Age of walking	0.289	0.329	0.132	–0.094	0.130	0.075	0.259
p value	**0.007**	**0.002**	0.222	0.387	0.231	0.489	**0.016**
	DBC subtest						
	Total	Disruptive	Absorbed	Communicate	Anxiety	Social	
Malaise Inventory	0.435	0.361	0.398	0.316	0.234	0.265	
p value	**<0.001**	**0.001**	**<0.001**	**0.003**	**0.029**	**0.013**	
Age of walking	0.217	0.034	0.392	0.006	0.045	0.284	
p value	**0.043**	0.756	**<0.001**	0.954	0.676	**0.008**	

Data from 87 participants; *p*-values in bold represent statistical significance.

found sleep disturbances in a number of syndromes, with particularly high percentages in autism.[25] Given the prevalence of autistic-like behaviors in CHARGE syndrome, this finding may be significant. It is important to note that the measure used to assess sleep (SDSC) is a screening and research tool, but not a clinical diagnostic instrument. The results suggest that sleep is a problem, but the problem needs to be verified in each individual case. Nevertheless, the pediatrician should be alert to indications of possible sleep disturbance in patients with CHARGE syndrome, particularly problems with initiation and maintenance of sleep, and sleep breathing difficulties.

As we had anticipated, being deaf–blind was related to significantly higher scores on the SDSC. Previous work has suggested that the degree of visual impairment and the association of multiple disabilities result in an increased prevalence of sleep disorders.[13] Whether the problem is due to a lack of visual cues, enough light and dark contrast, or even behavioral difficulties not directly related to the visual impairment, is not known. However, management requires interdisciplinary collaboration using an array of approaches to sleep disorders.[13] The prevalence in this study of reported sleep breathing disorders highlights the need for early evaluation. Previous work has demonstrated a significant association between choanal atresia and a number of medical comorbidities, including otitis media with effusion as well as upper and lower airway disease.[15] Although we did not find a relationship between choanal atresia or cleft palate and sleep disturbance, that may be because the children in this study were no younger than 6 years, and so repairs to the choanae and palate would probably have been a number of years behind them.

The previous work on choanal atresia and its relationship with otitis media is nevertheless intriguing and may account for the association between ear infections and sleep difficulty that we found. These associations are likely to reflect an upper airway that predisposes to breathing difficulties in sleep in the child with CHARGE syndrome. We did not ask about tonsils and adenoids in this study, but anecdotal reports from parents indicate that removal has improved sleep breathing in at least some children.

We also speculate that the relationship found between disturbed sleep and ear infections may be related to pain making sleep difficult. More work is needed on the experience of pain in children with CHARGE syndrome, and how such experience might be related to sleep difficulties.

As in other studies, age of walking continues to be a useful marker for behavioral problems in CHARGE syndrome. Pediatricians should be alert to the child's progress in walking. The mean age for walking in CHARGE syndrome in our study as well as others is about 3 years,[8,9] and so delays beyond that age should be of particular concern.

Correlational studies sometimes oversimplify the possible nature of relationships. We found a link between challenging behavior and sleep disturbance, but it is not clear whether one causes the other or whether the causative association may go either way at different times. Other variables may also affect the relationship. However, the prevalence of behavioral difficulties in CHARGE syndrome and the challenges that these create for parents suggest that any relationship that may affect the severity of the behavior should be carefully considered and monitored. Self-absorbed behavior in particular may be associated with a sleep disturbance. The self-absorbed subtest includes such behaviors as pica, humming, biting, hitting, screaming, chewing, and head banging. These are quite likely to be the kinds of behaviors that create considerable difficulty for parents, and our finding that they are related to sleep difficulties as well only increases the challenge that parents face. Other researchers have also found an association between sleep problems and the total behavior, disruptive, and self-absorbed scales on the DBC in children with intellectual disabilities.[26]

Table V: Mean differences in Sleep Disturbances Scale For Children scores for specific CHARGE characteristics

	n	Mean	SD	*t*	df	*p*
Deaf–blind	18	68.56	14.65			
Not deaf–blind	69	56.87	11.62	3.59	85	0.001
Choanal atresia	52	59.94	13.29			
No choanal atresia	35	58.31	12.96	0.57	85	0.573
Cleft palate	25	60.52	15.30			
No cleft palate	62	58.79	12.22	0.58	85	0.581
Ear infections	69	61.01	13.48			
No ear infections	18	52.67	9.17	2.48	85	0.015

df, degrees of freedom.

Because challenging behavior is so clearly associated with parent well-being, we wondered whether the problem of sleep was due only to its association with behavior. Our finding that sleep problems added to the regression equation seems to point to how important sleep issues are for parents. Coping with child behavior after a poor night of sleep oneself must be extremely difficult. When the child's behavior is exacerbated by lack of sleep on the child's part, the overall situation may become unmanageable. Although it may be tempting for pediatricians to want to address the behavior first, significant gains in all areas might be made by addressing the sleep issue. Pediatricians consulting on either sleep or behavior should inquire about the other.

Limitations

It is important to recognize that, although well over half of the children in this study scored at a 'clinical' level for sleep disturbance, nearly half did not. CHARGE is a highly variable syndrome, and it is difficult to generalize to 'most' cases.

Additionally, caution is required in consideration of the instruments used. The norms for the DBC-P are for children with intellectual disability, and, although the items do an excellent job of capturing the behavioral concerns in CHARGE syndrome, the norms do not reflect all children with CHARGE syndrome. In addition, the SDSC development was based on children who were younger than 16 years, and some of the participants in the present study were older than that. If type of sleep disturbance varies by age, then our data may be less accurate for the older children. Finally, all of these instruments were based on parent report, which is potentially biased. It is interesting to consider how lack of sleep, for example, might have influenced how parents completed the instruments.

However, even with these limitations, it is clear from the results of this study that parents are very concerned with sleep problems in their children with CHARGE syndrome.

CONCLUSION

This paper highlights the importance of screening for sleep disturbance in children with CHARGE syndrome. Poor-quality sleep is associated with behavioral difficulties as well as affecting parent mental health. The early identification and instigation of appropriate therapies may reduce the negative consequences of poor sleep for these children.

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