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Understanding obstructive sleep apnea in children with CHARGE syndrome

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ABSTRACT

Objective: CHARGE syndrome occurs in approximately 1 in 8500 live births and is diagnosed clinically by combinations of major characteristics: choanal atresia, coloboma, characteristic ears, cranial nerve abnormalities and distinct temporal bone anomalies. More than 50% of children with CHARGE syndrome experience sleep disturbances, with obstructive sleep apnea being one diagnosis. Objectives of this study were to develop a better understanding of the prevalence, symptomatology and treatments of sleep apnea in CHARGE syndrome. Secondary aims were to determine the usefulness of questionnaires examining obstructive sleep apnea in a CHARGE syndrome population.

Methods: Parents of 51 children with CHARGE syndrome (aged 0–14 years) were recruited between May 2010 and July 2011. Genetic testing and/or clinical criteria confirmed diagnosis of CHARGE syndrome. Questionnaires completed by parents included one covering CHARGE characteristics and three previously validated questionnaires: the Brouilette Score Questionnaire, the Pediatric Sleep Questionnaire and the OSA-18 Quality of Life Questionnaire. SPSS 19.0 was used for statistical calculations.

Results: Previous diagnosis of obstructive sleep apnea was present in 65% of the study population. Treatments included continuous positive airway pressure, tonsillectomy and/or adenoidectomy, and tracheostomy. Brouilette scores identified the presence of obstructive sleep apnea in the CHARGE syndrome population studied and indicated statistically significant ($p = <0.001$) improvements following treatment, which were comparable to the general population. Only the subscales of snoring and daytime sleepiness were useful in identifying obstructive sleep apnea using the Pediatric Sleep Questionnaire. The OSA-18 Questionnaire indicated that residual symptoms affecting quality of life may be present in the CHARGE syndrome population after treatment for obstructive sleep apnea.

Conclusions: Obstructive sleep apnea appears to be prevalent in children with CHARGE syndrome. All conventional treatments for obstructive sleep apnea reduce symptomatology. Brouilette scores are useful in identifying obstructive sleep apnea in the CHARGE syndrome population. The Pediatric Sleep Questionnaire could be useful once modified. The OSA-18 Questionnaire would be most useful as a means to measure quality of life gains following treatment.

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1. Introduction

CHARGE syndrome can be diagnosed clinically by the presence of combinations of major characteristics: choanal atresia, coloboma, characteristic ears, cranial nerve abnormalities [1] and distinct associated temporal bone anomalies [2]. Minor features include cardiovascular malformations, genital hypoplasia, cleft lip and/or palate, growth deficiency and developmental delay. CHARGE syndrome can also be genetically identified by mutations in the CHD7 gene on chromosome 8q12, a member of the chromodomain helicase DNA-binding (CHD) genes, which have roles in early embryonic development [3]. Many features of CHARGE syndrome require surgical, behavioral and pharmacological interventions, as well as extensive medical management unique to each child as they develop. With a birth incidence approaching 1 in 8500, CHARGE syndrome is among the more common recognized genetic disorders [4].

Individuals with CHARGE syndrome have multiple issues that are of interest to otolaryngologists. Primary management of infants with CHARGE syndrome often requires airway stabilization, as choanal atresia or stenosis, cleft lip and palate and

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laryngotracheomalcia can all contribute to respiratory distress and cyclical cyanosis [5]. Over 85% of children with CHARGE syndrome have hearing loss severe enough to affect acquisition of speech and language [6]. This hearing loss may be sensorineural loss, from abnormalities of cranial nerve (CN) VIII or structural abnormalities of the inner ear (absent semicircular canals, atresia of the oval window, cochlear dysplasia) or it may be conductive loss from chronic serous otitis media or ossicular chain malformation. This hearing loss leads to audiological evaluation and treatment involving pressure equalization tubes, hearing aids and cochlear implantation [1,7–10]. Individuals with CHARGE syndrome may also be affected by glossoptosis, but more commonly neurogenic swallowing problems are present, which have been attributed to cranial nerve IX/X anomalies [7] and can lead to poorly coordinated sucking and swallowing, nasal regurgitation and aspiration of oral secretions [11].

A study by Hartshorne et al. in 2009 revealed that 58% of children with CHARGE syndrome have sleep disturbances, with sleep breathing disorders, disorders initiating and maintaining sleep and sleep-wake transition disorders being most common [12]. Sleep and behavior anomalies in children with CHARGE syndrome have been linked to sleep related problems with airway management due to tracheal anomalies and low muscle tone [12,13]. Over 20% of children with cleft lip and palate have symptoms of sleep disordered breathing and obstructive sleep apnea, while over all, 13% of syndromic patients have abnormal sleep studies [14]. A study examining adolescents and older individuals with CHARGE syndrome revealed that 15 of 30 participants reported sleep problems and the majority of these participants experienced sleep apnea specifically [13]. Most studies report a prevalence of childhood obstructive sleep apnea (OSA) from 1% to 4% [15]. These studies suggest that sleep disorders, specifically sleep breathing disorders like sleep apnea are more probable in children with CHARGE syndrome than in the general population.

In children, OSA can have daytime symptoms of sleepiness, which could be manifested as labile mood, aggressiveness, hyperactivity and inattention [16]. Three risk factors contributing to OSA in the pediatric population are craniofacial abnormalities, altered soft tissue size of structures of the upper airway and neurologic disorders [17]. Obese children are also at increased risk of obstructive sleep apnea and are at greater risk of developing excessive daytime sleepiness [16,18]. In pediatric patients, the primary pathophysiological mechanism of OSA is hypertrophy of adenoid and tonsilar tissue in the upper airway, although the 3-dimensionality of these tissues and the way they overlap are also important [17]. Therefore, removal of this tissue is often considered for first-line therapy, although 20% of patients will have remaining abnormalities on polysomnography [19]. It would be expected that surgical treatment would be less effective in those with craniofacial anomalies since OSA has also been linked to the airway narrowing and decreased neuromotor tone that this population also struggles with [17]. Despite these risks for persistent evidence of ongoing sleep disorder based on polysomnography in some patients, particularly those with craniofacial syndromes, there is evidence that clinical improvement related to the removal of tonsil and adenoid tissue in children with CHARGE syndrome does have benefits. In a small sample size study of 3 patients with CHARGE syndrome, post-operative airway problems were significantly reduced after patients underwent adenotonsillectomy [20]. Also, anecdotal reports indicate that parents have also noticed improved sleeping, less snoring and less waking due to coughing for CHARGE syndrome patients after tonsillectomy and adenoidectomy [20].

The present study was an attempt to develop a better understanding of the prevalence, symptomatology and the treatment of sleep apnea in a large number of children with CHARGE syndrome. The effectiveness of treatments and the relationship of OSA with CHARGE syndrome characteristics related to airway obstruction are examined and discussed. Quality of life following treatment is compared to the general pediatric population. Secondary aims were to evaluate the usefulness of standardized questionnaires examining OSA in the CHARGE syndrome population.

2. Methods

2.1. Subjects

Inclusion criteria were that the children must be between the ages of 0 and 14 years, with a confirmed clinical or genetic diagnosis of CHARGE syndrome. Clinical diagnosis met current criteria based on major and minor features of CHARGE syndrome and genetic diagnosis involved a mutation of the CHD7 gene. The study was advertised through the CHARGE Syndrome Foundation, CHARGE Syndrome Yahoogroups Listserv, CHARGE Syndrome Facebook group and the CHARGE Syndrome Twitter page, to ensure a wide population inclusion. The first 53 participants to respond to the study advertisement and match inclusion criteria were administered the questionnaires, answered by their parents over the phone with a research assistant, or in person at the 2011 International CHARGE Syndrome Conference. Approval for this study was granted from the IWK Health Center's Research Ethics Board, Halifax, Nova Scotia.

2.2. Questionnaires

One parent of each participant was asked to complete the questionnaires over the phone or in person. The first questionnaire reviewed the child's relevant CHARGE syndrome characteristics, height and weight, demographics, previous OSA diagnoses and treatments. The three additional questionnaires are previously validated sleep surveys: (1) Brouilette score, (2) Pediatric Sleep Questionnaire and (3) OSAS Quality of Life Survey, OSA-18. All questionnaires were sent to the parents to review prior to the telephone interview. Parents were asked to recall and note any changes in their child's sleep habits after any treatment for OSA.

The Brouilette score comes from a standardized questionnaire in which parents evaluate their child's difficulty breathing in sleep and snoring on a scale of 0–3 (never to always). Parents also evaluate if their child stopped breathing during sleep on a scale of 0–1 (yes or no). A mathematical formula is used to produce a Brouilette score, where a score >3.5 is highly predictive of OSA and a score <-1 indicates that OSA is unlikely [21]. When possible, Brouilette scores were calculated before and after treatment and were compared to scores in the general population.

The Pediatric Sleep Questionnaire (PSQ) is a validated scale examining childhood sleep related breathing disorders, snoring, sleepiness and behavior. Answers are yes or no, graded 1 or 0. If the total mean score of all questions is >0.33, this indicates pediatric OSA. The snoring, sleepiness and behavioral subscales of the PSQ are statistically significant for identifying sleep-related breathing disorders on their own [22]. PSQ scores were calculated before and after treatment when parent felt confident in their recollection of symptoms prior to their child's treatment for OSA.

The OSA-18 survey examines sleep disturbance, physical symptoms, emotional distress, daytime function and caregiver concerns and is scored with a 7-point scale for each section. An OSA-18 summary score of >60 is abnormal and indicates a negative impact on quality of life [23]. OSA-18 scores were

calculated after treatment and compared to the general pediatric population.

2.3. Statistics

Descriptive statistics were used to present main features of the general data. The data set was analyzed by version 19.0 of SPSS for Windows. Mean differences were examined by *t*-test. A *p*-value of <0.05 was considered statistically significant.

3. Results

Questionnaires surveying CHARGE syndrome characteristics and sleep related issues were completed for 53 children. Two of the 53 participants were excluded due to lack of a definitive diagnosis of CHARGE syndrome. Of the 51 included participants, 19 were female (37%). Study participants ranged in age from 20 months to 14 years of age, with a mean age of 6 years 3 months (SD 3 years 6 months). Participants came from Canada, the United States, the United Kingdom and Denmark. Thirty-two of the 51 participants tested positive for the CHD7 gene mutation in CHARGE syndrome. The remaining 19 participants were diagnosed clinically. The participants' major and minor CHARGE syndrome features are shown in Table 1. Frequencies in the study were compared to those in previously published literature and were found to be comparable, except for a lower prevalence of developmental disorders at 90%, and an increased frequency of cardiovascular malformations and orofacial clefts. There were no large difference in frequency of features between genetically ($n = 32$) and clinically diagnosed ($n = 19$) participants beyond increased rates of facial clefts (31% vs. 16%) and renal anomalies (44% vs. 21%) in the genetically diagnosed. The clinically diagnosed and genetically diagnosed were grouped together as our total population ($n = 51$).

Of the 51 participants, 33 had a previous diagnosis of OSA. For 29 of the 51 children, the presence or absence of OSA was diagnosed via polysomnography, whereas in 22 cases this distinction was made on a clinical basis. Ten of these affected children had tried treatments of continuous positive airway pressure (CPAP), 27 underwent adenoidectomy and/or tonsillectomy for obstructive symptoms, and 9 children underwent tracheostomy. Some of these children had tried progressive combinations of the above treatments. Of the 51 children in the study, 18 had not received a diagnosis of OSA. Only two of the children were overweight with BMI's over the 95th percentile. The remaining children's weights were in the normal range.

Table 1
Major and minor characteristics of CHARGE syndrome including study population frequencies and estimated CHARGE population frequencies from previously published literature.

Features	Study population frequency[a] ($n = 51$)	Estimated population frequency [4]	Estimated population frequency [1]
Major			
Coloboma	40 (78%)	77%	80–90%
Choanal atresia or stenosis	28 (55%)	64%	50–60%
Characteristic CHARGE ear	50 (98%)	96%	90%
Cranial nerve dysfunction	44 (86%)	91%	70–90%
Minor			
Genital hypoplasia	29/51 (57%)	38%	70–80%
Males	24/32 (75%)	65%	
Females	5/19 (26%)	8%	
Developmental delay	46 (90%)	N/A	100%
Cardiovascular malformations	47 (92%)	84%	75–85%
Growth deficiency	36 (71%)	58%	70%
Orofacial cleft	13 (25%)	18%	15–20%
Tracheoesophageal fistula	11 (22%)	19%	15–20%
Distinctive face	42 (82%)	55%	70–80%
Renal anomalies	18 (35%)	36%	15–25%

[a] Of the 51 study participants, 32 were diagnosed genetically and 19 were diagnosed clinically.

Table 2
Brouilette scores for children before and after treatment for OSA and comparisons of scores to the general pediatric population.

Group	Mean scores before surgery	Mean scores after surgery	*p*-Value
Children with OSA ($n = 19$)	2.20	−1.51	<0.001[#]
Children without OSA ($n = 18$)	−1.58		
Children with tracheostomy ($n = 4$)	3.26	−2.24	
Children with tonsillectomy and/or adenoidectomy ($n = 15$)	1.89	−1.47	<0.001[#]
General pediatric population with tonsillectomy and/or adenoidectomy [24]	2.72	−2.19	

[#] Significant difference in scores before and after treatment in the study population.

A Brouilette score of >3.5 is highly predictive of OSA and a score <-1 indicates that OSA is unlikely. Brouilette scores are compared in Table 2. Parents of 19 children reported that they were able to remember their child's symptoms both before and after treatment. Brouilette scores prior to treatment for OSA were calculated where the mean score was 2.20, which suggests the presence of OSA. The mean score following treatment was −1.51, indicating an absence of OSA. A matched samples *t*-test indicated that these score improvements are significant ($t = 9.00$, $p = <0.001$). The mean Brouilette score of the 18 children without a diagnosis of OSA was −1.58, which is an appropriate score for children without OSA.

Of the 9 participants with a tracheostomy, 4 parents were able to remember symptoms to calculate Brouilette scores before and after tracheostomy. For these four children, the mean Brouilette score prior to tracheostomy was 3.26, which is suggestive of OSA. The mean Brouilette score following tracheostomy was −2.24, indicating an absence of OSA. Fifteen participants had Brouilette scores calculated before and after tonsillectomy and/or adenoidectomy. The mean score before treatment was 1.89, which is suggestive of OSA. The mean score following treatment was −1.47, which is an improvement strong enough to indicate absence of OSA. Paired Samples *t*-test showed that post tonsillectomy and/or adenoidectomy scores were significantly different from the pre-treatment scores, indicating a statistically significant improvement ($t = 7.72$, $p = <0.001$).

In the general pediatric population the mean Brouilette score prior to tonsillectomy and or adenoidectomy for children diagnosed with OSA is 2.72 [25]. The mean Brouilette score following treatment is −2.19. Mean scores of the CHARGE syndrome population are not statistically different from that of the general pediatric population (pre-removal $t = -1.91$, $p = 0.077$, post-removal $t = 1.83$, $p = 0.088$) indicating that the score improvements of the general population are not statistically different from the score improvements of this CHARGE syndrome population.

Relationships were expected between the presence of OSA and the CHARGE syndrome characteristics related to airway obstruction, including choanal atresia, cleft palate and frequent middle ear infections. Children with choanal atresia and OSA had a mean Brouilette score of 1.76, the same as those without choanal atresia. Children with orofacial anomalies and OSA had a mean Brouilette score of 2.21, compared to 1.68 for those children without orofacial clefts. Children with frequent otitis media had a mean Brouilette score of 1.84, compared to 1.49 for those without frequent otitis

Table 3
Pediatric Sleep Questionnaire (PSQ) subscale scores before and after tonsillectomy and/or adenoidectomy ($n = 16$).

Symptom category subscale	Mean scores before surgery	Mean scores after surgery	p-Value
Snoring[a]	2.88	0.69	<0.001[#]
Breathing problems	1.75	0.62	<0.001[#]
Mouth breathing	1.31	1.06	0.104
Daytime sleepiness[a]	2.62	1.69	0.011[#]
Inattention/hyperactivity[a]	4.19	4.12	1.00
Other symptoms	1.62	1.62	0.333

[a] Subscales previously significantly associated with sleep related breathing disorders on their own in previous literature.
[#] Significant difference in scores before and after treatment in the study population.

Table 4
OSA-18 Questionnaire summary scores compared between the study population without an OSA diagnosis and those treated for OSA. Total mean scores >60 are abnormal and indicate a continued negative impact on quality of life from OSA following treatment.

OSA-18 Scale Health Related Quality of Life Score	Children without diagnosed OSA ($n = 15$)	Children treated[a] for OSA ($n = 33$)
>80 (large impact)	0 (0%)	4 (12%)
60–80 (moderate impact)	6 (40%)	7 (21%)
<60 (small impact)	9 (60%)	22 (67%)

[a] Treatments = continuous positive airway pressure (CPAP), tonsillectomy and/or adenoidectomy, tracheostomy.

media. Investigations with t-tests found no significant differences between scores for children with choanal atresia, cleft palate, or frequent middle ear infections and those without these characteristics (choanal atresia $t = 0.00547$, $p = 0.996$, orofacial cleft $t = 0.875$, $p = 0.446$, otitis media $t = 0.796$, $p = 0.443$).

A PSQ score >0.33 indicates pediatric OSA. The mean total PSQ score for children with diagnosed OSA before treatment ($n = 28$) was 0.64. Following treatment the mean score dropped to 0.45. The mean total PSQ score for participants without diagnosed OSA ($n = 17$) was 0.50. Sixteen children with diagnosed OSA had their PSQ scores evaluated both before and after treatment. The results are shown in Table 3. It is important to note that the snoring and daytime sleepiness subscales do show improvement before and after treatment. These subscales have been significantly associated with sleep related breathing disorders on their own in the general population in previous literature [23]. The breathing problem subscale also shows significant improvement. The other subscales show no statistically significant improvement following treatment.

An OSA-18 health-related quality-of-life summary score >60 is abnormal and indicates a negative impact on quality of life. Scores were calculated following treatment only. The mean OSA-18 summary score for the 33 children treated for OSA was 53. A mean OSA-18 summary score of 51 was calculated for 15 children without a diagnosis of OSA. The OSA-18 summary scores for the study population are shown in Table 4. Following treatment for OSA, 67% of children had symptoms that had only a small impact on quality of life, 21% had symptoms in the moderate range and 12% had residual symptoms having a large impact on their quality of life. For children without a diagnosis of OSA, 60% of children had symptoms having only a small impact on quality-of-life, 40% had symptoms in the moderate range and 0% had residual symptoms having a large impact on their quality of life.

Table 5 compares OSA-18 total mean scores and subscale scores between the CHARGE syndrome population and those for the general pediatric population in previously published literature. One sample t-tests were used to test if the sample means differed from those in the literature. The total mean scores, along with the physical symptom and caregiver concern subscales scores were significantly different than those of the general pediatric population following treatment.

4. Discussion

From this study we report a high prevalence of OSA in children with CHARGE syndrome. Sixty-five percent of our study population had a diagnosis of OSA. Children with CHARGE syndrome display many of the classic symptoms of OSA, including sleep disturbances like snoring, pauses in breathing and difficulty breathing. However, parents and professionals note that emotional symptoms are often associated with poor sleep. Changes in mood, displays of hyperactive behavior, and symptoms affecting daytime function like sleepiness and shortened attention span are difficult to distinguish from typical CHARGE syndrome characteristics and behaviors.

Only two of the children in the study were overweight with BMI's over the 95th percentile. This may be due to the fact that the children in this study were young. Children with CHARGE syndrome tend to decline away from the normal growth curve after birth and then catch up in growth with progressive obesity occurring in the late teenage years [26]. Although obese children are at increased risk of sleep apnea, weight did not affect the sleep apnea symptoms in our study population.

Children with a diagnosis of sleep apnea had been treated with various combinations of CPAP, tracheostomy, and tonsillectomy and/or adenoidectomy. Parents noted that CPAP did help with symptoms of OSA, but compliance was an issue if children were scared of the mask or tried to remove it. Children who had a tracheostomy or tonsillectomy and/or adenoidectomy had a clear reduction in OSA symptoms. However, parents noted that many of their children had residual symptoms following treatments for OSA with tonsillectomy and/or adenoidectomy. This treatment still has a significant role in this population, but it may be recommended that these children have a follow-up sleep study and possible additional treatment.

Many children with suspected OSA do not have access to polysomnography. However, the alternate screening method for OSA involves the use of questionnaires that previously were untested in a CHARGE syndrome population. The Brouilette Score questionnaire was found to be useful in identifying OSA in CHARGE

Table 5
Mean subscale OSA-18 Questionnaire scores for the study population children diagnosed with OSA ($n = 33$) vs. those scores of the general pediatric population. Total mean scores >60 are abnormal and indicate a continued negative impact on quality of life from OSA following treatment.

	Total mean score	Sleep disturbances	Physical symptoms	Emotional symptoms	Daytime function	Caregiver concerns
Sample	53.1	10.7	13.9	9.2	8.5	10.8
General pediatric population [25]	41.0	8.4	8.9	8.4	7.4	7.8
p-Value	0.011[*]	0.068	<0.001[*]	0.532	0.268	0.031[*]

[*] Statistically significant.

syndrome in its current format as the questions address symptoms regarding breathing and sleep that are independent of typical CHARGE syndrome characteristics. The mean score prior to treatment for children with a diagnosis of OSA was suggestive for the presence of OSA. The mean score following treatment indicated an absence of OSA and therefore successful treatment outcomes. The mean Brouilette scores obtained for children without a diagnosis of OSA confirmed the lack of OSA.

Children who had a tracheostomy had a reduction in Brouilette scores from a mean of 3.26 to −2.24, indicating an absence of OSA post-treatment. This score reduction is expected since tracheostomy effectively eliminates the cause of OSA. Children who had tonsillectomy and/or adenoidectomies had a reduction in Brouilette scores from a mean of 1.89 to −1.47, indicating an absence of OSA post-treatment. Although this improvement is not as great as that of those receiving a tracheostomy, it is a statistically significant improvement. This score improvement was not significantly different than that of the general population, indicating that the use of this questionnaire is as useful in the CHARGE syndrome population as in the general pediatric population.

It has been hypothesized that choanal atresia, cleft palate and otitis media are associated with sleep disturbances in CHARGE syndrome [12]. Children with orofacial clefts and frequent otitis media had higher mean Brouilette scores than children without these traits. However, no statistically significant difference was found between Brouilette scores for children with CHARGE syndrome with choanal atresia, cleft palate, or frequent middle ear infections and children with CHARGE syndrome without these traits. This is possibly due to many of these children having had successful surgical repairs prior to OSA diagnosis and treatment and therefore these traits are no longer greatly affecting their OSA symptoms. This conclusion is in agreement with other studies examining sleep disturbances in CHARGE syndrome [12]. However, ear infections have been associated with sleep disturbances in CHARGE syndrome before, although this is likely due to pain, and the Brouilette score examines only physical airway related OSA symptoms, explaining the lack of correlation [12].

The Pediatric Sleep Questionnaire was not found to be as strong a measure of OSA as the Brouilette score in this population, since many of the questions assessed symptoms of OSA that could not be analyzed separately from typical CHARGE syndrome characteristics. Parents note that it is difficult to answer the questions in the behavioral and other symptom categories on the PSQ since typical CHARGE syndrome characteristics may be mistaken for OSA behavioral symptoms in these categories. For example, children with CHARGE syndrome have problems tracking their behavior in terms of task attainment and have problems controlling impulses, following social rules and focusing on activities [27]. These behaviors lead to confusion on the behavioral subscale of the PSQ. Therefore, the current scoring systems used by this questionnaire may not accurately reflect sleep issues in this population. This may explain why the PSQ scores for children with CHARGE syndrome without a diagnosis of OSA are 0.50, which is high enough to be considered diagnostic of OSA on this questionnaire. The snoring, breathing problem and daytime sleepiness scales addressed symptomatology separate from CHARGE characteristics. The subscales of snoring, breathing problems and daytime sleepiness showed significant differences in scores before and after treatment. The snoring and daytime sleepiness subscales have been significantly associated with sleep related breathing disorders in a general population on their own, indicating that it may be possible to modify the PSQ for the CHARGE syndrome population to include only these two subscales.

The OSA-18 Quality of Life Questionnaire does contain questions regarding symptoms that are difficult to distinguish from general CHARGE syndrome characteristics, so we expected that scores might be elevated. However, summary scores from the OSA-18 Questionnaire are still useful in evaluating quality-of-life issues. Examining the distribution of the scores showed that none of the children without a diagnosis of OSA have any symptoms that have more than a moderate impact on their quality of life. Unfortunately, 12% of children who have been treated for OSA still experience symptoms that have a large impact on their quality of life as assessed by sleep disturbances, physical and emotional symptoms, daytime function and caregiver concerns. This is important to consider when decisions are made regarding the treatment and follow-up of OSA in this population and in educating parents on possible outcomes and realistic expectations of treatment.

When the OSA-18 Quality of Life Questionnaire results for the CHARGE syndrome population were compared to the general pediatric population, the physical symptoms subscale was statistically significantly elevated. This elevation was likely due to increased scores from typical CHARGE syndrome characteristics like frequent colds and nasal discharge, as well as difficulties swallowing. The statistically significant elevation in scores on the caregiver concerns subscale were likely due to questions about how much caregivers worry about their child's general health, which is likely higher in the CHARGE syndrome population than in the general pediatric population. The elevation of these two subscales explains the elevation in the total mean OSA-18 Questionnaire scores. It would be most useful to complete OSA-18 Questionnaires both before and after treatment to determine gains in quality of life following treatment for OSA for this population.

The advertisement for participants in this study did mention sleep apnea as the topic of research, which could potentially have elevated the uptake of children with sleep apnea in the study. The study is based on retrospective parental observations and responses, which could lead to bias. A long-term longitudinal study would be the next step in this research direction and could address these biases. Further investigation is also necessary in children older than 14 with CHARGE syndrome, to determine the applicability of this study's results to the general CHARGE population.

5. Conclusion

OSA is very prevalent in children ages 0–14 with CHARGE syndrome. All treatment modalities (CPAP, tonsillectomy, adenoidectomy, tracheostomy) show improvements in symptomatology. The Brouilette score is useful in identifying OSA in the CHARGE syndrome population in its current form. The Pediatric Sleep Questionnaire subscales of snoring and daytime sleepiness appear to be useful in identifying pediatric OSA in children with CHARGE syndrome. The OSA-18 Health Related Quality of Life Questionnaire would be most useful if administered both before and after treatment as a way to measure quality of life gains following treatment and to identify those children with residual symptoms causing significant impacts on their quality of life. Parents should be given appropriate information about reasonable expectations regarding treatment, as residual symptoms may be present, prompting recommendation of follow-up sleep studies.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Appendix A

The Pediatric Sleep Questionnaire (PSQ) is a validated scale examining childhood sleep related breathing disorders, snoring, sleepiness and behavior. Answers are yes or no, graded 1 or 0. If the total mean score of all questions is >0.33, this indicates pediatric OSA.

Pediatric Sleep Questionnaire	Yes/no
While sleeping, does your child…	
…snore more than half the time?	Y/N
…always snore?	Y/N
…snore loudly?	Y/N
…have "heavy" or loud breathing?	Y/N
…have trouble breathing, or struggle to breathe?	Y/N
Have you ever…	
…seen your child stop breathing during the night?	Y/N
Does your child…	
…tend to breathe through the mouth during the day?	Y/N
…have a dry mouth on waking up in the morning?	Y/N
…occasionally wet the bed?	Y/N
Does your child…	
…wake up feeling *un*refreshed in the morning?	Y/N
…have a problem with sleepiness during the day?	Y/N
Has a teacher or other supervisor commented that your child appears sleepy during the day?	Y/N
Is it hard to wake your child up in the morning?	Y/N
Does your child wake up with headaches in the morning?	Y/N
Did your child stop growing at a normal rate at any time since birth?	Y/N
Is your child overweight?	Y/N
This child often…	
…does not seem to listen when spoken to directly	Y/N
…has difficulty organizing task and activities	Y/N
…is easily distracted by extraneous stimuli	Y/N
…fidgets with hands or feet or squirms in seat	Y/N
…is 'on the go' or often acts as if 'driven by a motor'	Y/N
…interrupts or intrudes on others (e.g. butts into conversations or games)	Y/N

Chervin et al. [22].

The OSA-18 survey examines sleep disturbance, physical symptoms, emotional distress, daytime function and caregiver concerns and is scored with a 7-point scale for each section. An OSA-18 summary score of >60 is abnormal and indicates a negative impact on quality of life.

OSAS Quality of Life Survey (OSA-18)	1 = never 2 = hardly ever 3 = a little bit 4 = some of time 5 = a good bit 6 = most of time 7 = always
Sleep disturbances	
During the past four weeks, how often has your child had…	
…loud snoring?	
…breath holding spells or pauses in breathing at night?	
…choking or made gasping sounds while asleep?	
…restless or frequent awakenings from sleep?	
Physical symptoms	
During the past four weeks, how often has your child had…	
…mouth breathing because of nasal obstruction?	
…frequent colds or upper respiratory infections?	
…nasal discharge or runny nose?	
…difficulty in swallowing foods?	
Emotional symptoms	
During the past four weeks, how often has your child had…	
…mood swings or temper tantrums?	
…aggressive or hyperactive behavior?	
…discipline problems?	
Daytime function	
During the past four weeks, how often has your child had…	
…excessive daytime sleepiness?	
…a poor attention span or concentration?	
…difficulty getting up in the morning?	
Caregiver concerns	
During the past four weeks, how often have the problems described above…	
…caused you to worry about your child's general health?	
…created concern that your child is not getting enough air?	
…interfered with your ability to perform daily activities?	
…made you frustrated?	

Franco et al. [23].

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