Screening for Obstructive Sleep Apnea in Treacher-Collins Syndrome

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Objectives/Hypothesis: This study evaluated the accuracy of established obstructive sleep apnea syndrome (OSAS) questionnaires based on presenting symptoms and complaints as screening tools for OSAS in Treacher-Collins syndrome (TCS).

Study Design: Cross-sectional cohort study.

Methods: In 35 TCS patients (13 children, 22 adults) in whom diagnostic polysomnographic results on OSAS were available, the Brouillette score was evaluated in children and the Epworth Sleepiness Scale in adults.

Results: The total Brouillette score showed a sensitivity of 50%, specificity of 71%, and positive and negative predictive values of 60% and 63%, respectively. The answer “No” to the question as to whether a child snored could rule out OSAS in children, and showed positive and negative predictive values of 55% and 100%, respectively. The Epworth Sleepiness Scale showed a sensitivity of 0%, specificity of 92%, and positive and negative predictive values of 0% and 57%, respectively. A positive answer to the question of whether a person falls asleep while sitting and talking to someone (sometimes or more) was able to predict OSAS in adults; this question had positive and negative predictive values of 100% and 72%, respectively.

Conclusions: This cross-sectional cohort study showed that the Brouillette score and the Epworth Sleepiness Scale are of minimal usefulness in TCS. Diagnosis of OSAS based solely on complaints is not reliable, probably due to habituation. Therefore, for a good evaluation and optimal multidisciplinary treatment of this chronic disease in TCS, all newly referred pediatric and adult TCS patients should be screened for OSAS at least once with polysomnography.

Key Words: Treacher-Collins syndrome, obstructive sleep apnea, Epworth Sleepiness Scale, Brouillette score, screening.

Level of Evidence: 2b

INTRODUCTION

Treacher-Collins syndrome (TCS) is a rare congenital craniofacial syndrome. Deformities can range from minor defects in the periorbital region to a full clinical presentation, which is characterized by defects such as mandibular hypoplasia and hypoplasia/aplasia of zygoma, microtia, and middle ear deformities.1 TCS is an autosomal dominant disorder of craniofacial development with an incidence of 1 in 50,000 live births.2 In more than 60% of cases there is no previous family history, and the condition is thought to arise as the result of a de novo mutation. Loss-of-function mutations are generally found in the TCOFI gene; however, alterations in the POLR1D and POLR1C genes have been demonstrated to cause TCS as well.3,4

Patients with craniofacial syndromes frequently suffer from obstructive sleep apnea syndrome (OSAS). OSAS is characterized by breathing cessation (apneas) or reduction (hypopneas) as a result of complete or partial upper airway obstruction. This disorder is one of the most frequent forms of sleep-disordered breathing, and is associated with major physical and functional impairment due to the disturbed sleep patterns.5 OSAS is a frequent finding in TCS.6–9 Severities range from mild to severe in pediatric and adult TCS patients, of which a considerable number suffer from severe OSAS.

Definitive diagnosis and grading of OSAS requires polysomnography (PSG), which is considered the gold standard for diagnosis. Normally, diagnosis is often supported by symptoms like snoring and excessive sleepiness in adults.10,11 In children, symptoms can be apneas, snoring, and increased respiratory effort, which can lead to failure to thrive, recurrent respiratory infections, feeding difficulties, and disturbed cognitive functions such as attention deficit and impaired concentration and memory.12 However, symptoms as presented often remain unrecognized in patients with OSAS.13

Because the presence of symptoms/complaints in a normal population can be suggestive for OSAS and
OSAS with the gold standard (i.e., PSG). which we established the prevalence and severity of this, the same TCS cohort was investigated in whether it is possible to predict OSAS with two validated questionnaires. Given the high prevalence of OSAS in TCS, it is essential to clarify whether symptoms/complaints of OSAS are of diagnostic value. Therefore, the present study aimed to: 1) determine whether it is possible to predict OSAS with two validated OSAS questionnaires, 2) explore differences in outcomes of these questionnaires (symptoms), and 3) determine the frequency of different symptoms. To establish this, the same TCS cohort was investigated in which we established the prevalence and severity of OSAS with the gold standard (i.e., PSG).

MATERIALS AND METHODS

Patient Selection

We conducted a cross-sectional cohort study to establish the complaints associated with OSAS in a population diagnosed with TCS. Patients were included if they were diagnosed with TCS and treated by the multidisciplinary craniofacial team of the Erasmus MC. The group was divided into pediatric and adult patients (cutoff at age ≥18 years). The study was approved by the ethical committee of the Erasmus MC (MEC-2008-402).

Polysomnography

A clear objective diagnosis of OSAS through PSG was available for 35 TCS patients (13 children, 22 adults) (Table I). Current guideline standards were used for the diagnosis of OSAS for children according to the consensus.10,17–19 For children the obstructive Apnea-Hypopnea Index (AHI) was used. Central apneas were not included. An obstructive AHI score >1 was defined as mild OSAS. An AHI ≥5 and <24 was defined as moderate OSAS, and a score ≥24 as severe OSAS. For adults, the diagnosis of OSAS was according to the Adult OSA Task Force of the American Academy of Sleep Medicine.20,21 OSAS was defined as mild for AHI ≥5 and <15, moderate for AHI ≥15 and ≤30, and severe for AHI >30 per hour.

Questionnaires

Pediatric questionnaire. Brouillette et al. developed an OSAS score to predict the presence of OSAS with a high sensitivity in normal children. To make a clear inventory of the complaints associated with OSAS in this cohort we used the Brouillette score for pediatric patients.22 The parents of these children answered the questions. The Brouillette score is calculated using the following formula: 1.42 D + 1.41 A + 0.71 S – 3.83. Where D stands for difficulty in breathing and S for snoring, using different scores for the frequency of the complaint (never = 0, sometimes = 1, often = 2, always = 3); A stands for apnea and is scored 0 if apnea does not occur and scored 1 if it does. A Brouillette score below –1 is defined as no OSAS, between –1 and 3.5 as suggestive for OSAS, and >3.5 as OSAS.22

Children were divided into an OSAS group and a non-OSAS group based on the PSG results. Adult questionnaire. Daytime sleepiness was assessed using the Epworth Sleepiness Scale. The Epworth Sleepiness Scale provides a rapid and quantifiable assessment of subjective sleepiness as cardinal daily symptom of OSAS.11,23 Adults were asked, “How likely are you to doze off or fall asleep in the following situations?” in eight different situations. The following situations were described according to the Epworth Sleepiness Scale: 1) sitting and reading, 2) watching television, 3) sitting inactive in a public place (for instance at a theater or meeting), 4) as a passenger in a car for an hour without a break, 5) lying down to rest in the afternoon when circumstances permit, 6) sitting and talking to someone, 7) sitting quietly after a lunch without alcohol, and 8) in a car while stopped for a few minutes in traffic. The total score of the Epworth Sleepiness Scale is the sum of the responses to the eight individual items and ranges from 0 to 24. Values >10 indicate significant sleepiness and a relation with OSAS and prompts further evaluation; values ≥16 indicate a high level of daytime sleepiness. Adults were divided into an OSAS group and a non-OSAS group.

Statistical Analysis

Accuracy of the questionnaires was determined by using contingency tables to calculate the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of total scores and separate items of the questionnaires, as appropriate. To calculate the above-mentioned values, a cutoff ≥–1 was used (suggestive for OSAS) in the total Brouillette score. A cutoff ≥1 was used per question in the Epworth Sleepiness Scale. A cutoff ≥10 was used for the total score in this questionnaire. The unpaired t test with equal variances with two-tailed significance was used to compare differences in mean scores in all questionnaires between the OSAS group and the non-OSAS group. The Bonferroni correction for significance for multiple testing was used in all questionnaires. A P value ≤.05 was defined as significant. Analyses were performed using SPSS 17.0 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

Population

In the period from 1974 through 2010, 58 patients were diagnosed with TCS. Of these, four died and 19 did not participate due to emigration (one patient), lack of correct personal details (three patients), unwillingness to participate (14 patients), and loss to follow-up (one patient). Of the 54 patients, 35 (65%) were included in the present study. Of these 35 patients, 34 underwent PSG. In one patient no PSG was performed due to

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Mild OSAS, % (No.)</th>
<th>Moderate OSAS, % (No.)</th>
<th>Severe OSAS, % (No.)</th>
<th>Total, % (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCS children, n = 13</td>
<td>8 (1/13)</td>
<td>38 (5/13)</td>
<td>8 (1/13)*</td>
<td>54 (7/13)</td>
</tr>
<tr>
<td>TCS adults, n = 22</td>
<td>14 (3/22)</td>
<td>0 (0/22)</td>
<td>27 (6/22)</td>
<td>41 (9/22)</td>
</tr>
<tr>
<td>Total, n = 35</td>
<td>11 (4/35)</td>
<td>14 (5/35)</td>
<td>20 (7/35)</td>
<td>46 (16/35)</td>
</tr>
</tbody>
</table>

*One patient received immediate treatment for severe airway obstruction, therefore no polysomnography prior to treatment was available.

OSAS = obstructive sleep apnea syndrome; TCS = Treacher-Collins syndrome.
severe airway problems which necessitated immediate tracheotomy; therefore, this patient was considered to have severe OSAS.

All patients filled out the questionnaires on the same day that the PSG was performed. This cohort comprised 13 children (five boys) and 22 adults (10 males). Median age of the pediatric group was 12 years (range, 0–17 years), and median age of the adult group was 37 years (range, 20–60 years).

**Questionnaires**

**Pediatric questionnaire.** Parents of all 13 pediatric TCS patients filled out the Brouillette score. Although children with OSAS scored higher than children in the non-OSAS group, the difference was not significant (0.42 vs. 1.81, \( P = .094 \)) (Table II). The total Brouillette score showed a low sensitivity (50%), specificity (71%), and a low PPV and NPV (60% and 63%, respectively). The most frequent complaint in children was snoring. PPV of the three separate symptoms as used in this questionnaire ranged from 55% to 67%, of which snoring scored lowest.

**Adult questionnaire.** All 22 adults who underwent PSG completed the full Epworth Sleepiness Scale. The mean scores of the OSAS and non-OSAS groups on the total Epworth Sleepiness Scale showed no significant difference (4.2 vs. 4.7, \( P = .729 \)) (Table III). The total score of the Epworth Sleepiness Scale showed a sensitivity, PPV, and NPV of 0%, 0%, and 57%, respectively.

When taking the severe OSAS group separately (as a subset) and comparing the mean total scores of the total Epworth Sleepiness Scale of the severe OSAS group with the non-OSAS group, again no significant difference was found (4.3 vs. 4.7, \( P = .824 \)). The question concerning whether a person was falling asleep while sitting and talking to someone showed the best PPV and NPV (100% and 72%, respectively); the score on this question showed a significant difference between the OSAS group and the non-OSAS group (0.4 vs. 0.0, \( P = .035 \)). The other question showing a significant difference was sitting quietly after a lunch

**TABLE II.**

Brouillette Score and Separate Items as Tools for Predicting Obstructive Sleep Apnea Syndrome in Children With Treacher-Collins Syndrome (\( n = 13 \)).

<table>
<thead>
<tr>
<th>Brouillette Score and Separate Items, OSAS ( [n = 6] ), Non-OSAS ( [n &gt; 7] )</th>
<th>OSAS, Mean (SD)</th>
<th>Non-OSAS, Mean (SD)</th>
<th>( P ) Value</th>
<th>Se, % (No.)</th>
<th>Sp, % (No.)</th>
<th>PPV, % (No.)</th>
<th>NPV, % (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty in breathing +</td>
<td>1.33 (1.37)</td>
<td>0.29 (0.49)</td>
<td>—</td>
<td>67 (4/6)</td>
<td>71 (5/7)</td>
<td>67 (4/6)</td>
<td>71 (5/7)</td>
</tr>
<tr>
<td>Apnea +</td>
<td>0.67 (0.52)</td>
<td>0.29 (0.49)</td>
<td>—</td>
<td>67 (4/6)</td>
<td>71 (5/7)</td>
<td>67 (4/6)</td>
<td>71 (5/7)</td>
</tr>
<tr>
<td>Snoring +</td>
<td>2.00 (0.89)</td>
<td>1.14 (0.90)</td>
<td>—</td>
<td>100 (6/6)</td>
<td>29 (2/7)</td>
<td>55 (6/11)</td>
<td>100 (2/2)</td>
</tr>
<tr>
<td>Total Brouillette score &gt; −1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>50 (3/6)</td>
<td>71 (5/7)</td>
<td>60 (3/5)</td>
<td>63 (5/8)</td>
</tr>
<tr>
<td>Total Brouillette score</td>
<td>0.42 (2.62)</td>
<td>−1.81 (1.76)</td>
<td>.094</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

OSAS = obstructive sleep apnea syndrome; SD = standard deviation; Se = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value.

**TABLE III.**

Epworth Sleepiness Scale in Adults With Treacher-Collins Syndrome (\( n = 22 \)); Comparison of Mean Scores, Frequency of Separate Items, and Tools for Predicting Obstructive Sleep Apnea Syndrome in Treacher-Collins Syndrome Adults.

<table>
<thead>
<tr>
<th>ESS Items, OSAS ( [n = 9] ), Non-OSAS ( [n = 13] )</th>
<th>OSAS, Mean (SD)</th>
<th>Non-OSAS, Mean (SD)</th>
<th>( P ) Value</th>
<th>OSAS Frequency Scored, % (No.)</th>
<th>Non-OSAS Frequency Scored, % (No.)</th>
<th>Se, % (No.)*</th>
<th>Sp, % (No.)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
<td>0.89 (0.33)</td>
<td>0.85 (1.14)</td>
<td>.901</td>
<td>89 (8/9)</td>
<td>46 (6/13)</td>
<td>89 (8/9)</td>
<td>54 (7/13)</td>
</tr>
<tr>
<td>Watching television</td>
<td>0.67 (0.71)</td>
<td>1.08 (0.86)</td>
<td>.253</td>
<td>56 (5/9)</td>
<td>77 (10/13)</td>
<td>56 (5/9)</td>
<td>23 (3/13)</td>
</tr>
<tr>
<td>Sitting inactive in a public place</td>
<td>0.33 (0.71)</td>
<td>0.46 (0.97)</td>
<td>.738</td>
<td>22 (2/9)</td>
<td>23 (3/13)</td>
<td>22 (2/9)</td>
<td>77 (10/13)</td>
</tr>
<tr>
<td>As a passenger in a car for an hour without a break</td>
<td>0.67 (0.50)</td>
<td>0.31 (0.48)</td>
<td>.106</td>
<td>67 (6/9)</td>
<td>31 (4/13)</td>
<td>67 (6/9)</td>
<td>69 (9/13)</td>
</tr>
<tr>
<td>Lying down to rest in the afternoon</td>
<td>0.89 (1.05)</td>
<td>1.23 (1.09)</td>
<td>.473</td>
<td>56 (5/9)</td>
<td>69 (9/13)</td>
<td>56 (5/9)</td>
<td>31 (4/13)</td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
<td>0.44 (0.53)</td>
<td>0.00 (0.00)</td>
<td>.035</td>
<td>44 (4/9)</td>
<td>0 (0/13)</td>
<td>44 (4/9)</td>
<td>100 (13/13)</td>
</tr>
<tr>
<td>Sitting quietly after a lunch without alcohol</td>
<td>0.11 (0.33)</td>
<td>0.62 (0.65)</td>
<td>.028</td>
<td>11 (1/9)</td>
<td>54 (7/13)</td>
<td>11 (1/9)</td>
<td>46 (6/13)</td>
</tr>
<tr>
<td>In a car while stopped for a few minutes in traffic</td>
<td>0.22 (0.67)</td>
<td>0.15 (0.38)</td>
<td>.761</td>
<td>11 (1/9)</td>
<td>26 (2/13)</td>
<td>11 (1/9)</td>
<td>84 (11/13)</td>
</tr>
<tr>
<td>Total ESS score ( ^1 )</td>
<td>4.22 (2.33)</td>
<td>4.69 (3.45)</td>
<td>.729</td>
<td>0 (0/9)</td>
<td>92 (12/13)</td>
<td>0 (0/1)</td>
<td>57 (12/21)</td>
</tr>
</tbody>
</table>

\(^1\)Cutoff for sensitivity and specificity for the separate items of the ESS; scores >1 are used.

\(^1\)Cutoff for sensitivity and specificity for the total ESS score; scores >10 are used.

ESS = Epworth Sleepiness Scale; OSAS = obstructive sleep apnea syndrome; SD = standard deviation; Se = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value.
without alcohol, which was scored higher in the non-OSAS group (0.1 vs. 0.6, \( P = .028 \)).

DISCUSSION

The results of this cross-sectional cohort study show that the Epworth Sleepiness Scale and the Brouillette score are not useful in predicting OSAS in adults and children with TCS. The lack of differences between the severity of symptoms/complaints in the OSAS group and the non-OSAS group resulted in low values of sensitivity, PPV and NPV, and of the total scores of these two questionnaires.

Whereas the sensitivity of the Brouillette score in normal healthy children with OSAS is reported to be around 89\%, in the present study the sensitivity was very low.\(^22,24\) This might be because the most frequently scored complaint was snoring in children with TCS. The total score of this screening tool probably failed in our population because nearly all of the children in the present study snored.

Although the snoring question was not specific, the NPV of this question was high (100\%), indicating that the answer “yes” to this question was not helpful, whereas the answer “no” was able to rule out OSAS in children.

The fact that almost all children snored is in accordance with a study in children with syndromic craniosynostosis, in which 77\% of the children were reported to snore; therefore, this item could not be used to discriminate between OSAS and non-OSAS.\(^25\) That same study found that asking parents whether the child has difficulty (or not) in breathing during sleep can exclude the presence of clinically significant OSAS.\(^25\) For this particular question we found a low sensitivity of 67\% and an NPV of 71\%.

Considering the low predictive values of the total score, the Brouillette score missed around 40\% of the OSAS cases in children, based on the cutoff values as used in that score.

Currently, the most widely used self-reporting scale for excessive daytime sleepiness is the Epworth Sleepiness Scale as subjective screening for OSAS in normal healthy patients. However, we found that this scale has no sensitivity and no PPV (both 0\%) to detect OSAS. Two items of the Epworth Sleepiness Scale showed a significant difference between the OSAS group and the non-OSAS group. Of these items, the question as to whether a person falls asleep while sitting and talking to someone (sometimes or more) showed the best PPV (100\%). Although a positive answer to this question indicates the presence of OSAS, a negative answer did not rule out OSAS. Of all the eight questions, this latter question implies the most extreme daytime sleepiness and suggests hypersomnia/menolence may still be a symptom of OSAS in our population. However, we think this is to a lesser overall degree than expected in a normal OSAS population, because all our total sleepiness scores were relatively low.

Surprisingly, the second significant item, falling asleep while sitting quietly after a lunch without alcohol, scored significantly higher in the non-OSAS group (showing very low PPV and NPV) and is therefore not useful for screening.

A possible explanation for the fact that the Epworth Sleepiness Scale in adult TCS patients is not discriminative for OSAS is that the patients are accustomed to these symptoms, probably having experienced them from birth. Furthermore, we have to bear in mind that the questionnaires were not filled in due to referral to a specialist because of complaints, but because we requested them to do so.

Limitations

Due to the relatively small study population the results of this study should be interpreted with caution.

CONCLUSION

This cross-sectional cohort study shows that the Epworth Sleepiness Scale and the Brouillette score are of minimal usefulness in TCS. A negative answer to the question regarding snoring can rule out OSAS in children; however, although this question is helpful the PSG is still required as it is the only reliable screening tool. A diagnosis of OSAS based solely on complaints is not reliable, probably due to habituation. Therefore, for a good evaluation and optimal multidisciplinary treatment of this chronic disease in TCS, all newly referred pediatric and adult TCS patients should be screened for OSAS at least once with PSG. Future research should focus on the impact on the quality of life of these OSAS-related symptoms/complaints, rather than using these as a screening method for TCS.

BIBLIOGRAPHY


