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Evaluation of behavioral change after adenotonsillectomy for obstructive sleep apnea in children with autism spectrum disorder

（閉塞性睡眠時無呼吸のある自閉スペクトラム症児のアデノイド扁桃摘出術後の行動変化の検討）

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Evaluation of behavioral change after adenotonsillectomy for obstructive sleep apnea in children with autism spectrum disorder

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ABSTRACT

Background and objective: Obstructive sleep apnea (OSA) may affect daily cognitive functioning in children. The aims of our study were two-fold. The first aim was to detect, using the Child Behavior Checklist (CBCL), whether adenotonsillectomy (AT) for the treatment of OSA improved the behavior of children with autism spectrum disorder (ASD). The second aim was to identify characteristics for behavioral improvement following the treatment of OSA in these children with ASD.

Methods: The behaviors of ASD children aged 5–14 years diagnosed as having OSA (n = 30) were evaluated using CBCL before and after AT. CBCL evaluation of ASD children without OSA at two time points with the same interval served as a control (n = 24). We statistically examined the two groups. In addition, we conducted a paired *t*-test to assess changes in CBCL Tscores between the improved group and unchanged/deteriorated group to identify characteristics that may affect behavioral changes following OSA treatment.

Results: After AT, T-scores of the CBCL scales were significantly improved in the OSA group, but no change was observed in the control. A paired *t*-test revealed that the improved group had significantly higher scores on the CBCL pre-AT than the unchanged/deteriorated group in ASD children with OSA after OSA treatment.

Conclusions: Behavioral problems were significantly improved following AT in ASD children with OSA. Early detection and treatment of children with OSA is essential to prevent behavioral problems and to support mental development.

What this paper adds?

Pediatric obstructive sleep apnea (OSA) has been associated with deficits in behavior and emotion regulation, selection, sustained attention and scholastic performance. When comparing children's neurobehavioral functioning before and after adenotonsillectomy (AT), many studies have reported improvement of cognitive function, behavior and learning. However, no studies have been

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conducted to evaluate the effect of AT on the behavior of children in Japan. And there are no studies investigating the effect of AT on behavioral problems in children with autism spectrum disorder (ASD), although it was recently suggested that the frequency of OSA is higher in ASD than community samples. This study sought to determine whether AT for the treatment of OSA improved the behavior of children with ASD, and to identify the characteristics that may affect behavioral improvement in children with ASD after treatment of OSA by AT. We analyzed Child Behavior Checklist (CBCL) scores before and after AT in ASD children with OSA. After AT, Tscores of the CBCL scales were significantly improved in ASD children with OSA. We revealed that the improved group shown significantly higher scores on the CBCL pre-AT than the unchanged/deteriorated group in ASD children with OSA after OSA treatment. We believe that our study makes a significant contribution to the literature because, to the best of our knowledge, it is the first to report the efficacy of the treatment of OSA as a means of improving the behavior of children with ASD.

1. Introduction

In the third edition of the International Classification of Sleep Disorders (ICSD-3), the prevalence of pediatric obstructive sleep apnea (OSA) is estimated to be 1–4% (American Academy of Sleep Medicine, 2014). In children, OSA has been associated with not only daytime sleepiness but also metabolic problems, e.g., obesity (Bhattacharjee et al., 2010; Mitchell & Kelly, 2007; O'Brien, Sitha, & Bauer, 2006; Tauman, Gulliver, & Krishna, 2006), cardiovascular accidents (Marcus, 2001), and growth problems (Marcus, 2001). In addition, OSA may affect daily cognitive functioning in children and lead to attention problems, hyperactivity, impulsivity, or aggression (American Academy of Sleep Medicine, 2014).

Sleep-disordered breathing (SDB) ranges in severity from primary snoring, which is not associated with any gas exchange abnormalities or sleep disturbance as detected on conventional polysomnography (PSG), to OSA, which is characterized by not only snoring, but also apnea, intermittent hypoxia, hypercarbia, and/or repeated arousals from sleep (Gozal, 2001). A review of 61 studies, and others that focused on the relationship between childhood SDB and neurobehavioral functioning, reported that SDB was associated with deficits in such variables as behaviors, emotional regulation, scholastic performance, sustained or selective attention, alertness, and so on (Beebe, 2006; Blunden et al., 2000; Giordani et al., 2008; O'Brien et al., 2004; Zhao et al., 2008). Symptoms were not, however, affected by the severity of SDB (Blunden et al., 2000; Giordani et al., 2008; O'Brien et al., 2004; Zhao et al., 2008).

The diagnostic criteria, causal factors, and first-line treatment of childhood OSA are different from those of adults (Chervin et al., 2005). For example, the diagnostic criterion for the apnea-hypopnea index (AHI), which represents the number of apnea and hypopnea events per hour, is five in adult OSA, and only one in childhood OSA (American Academy of Sleep Medicine, 2014). In addition, childhood OSA is mainly caused by hypertrophy of the adenoid and/or palatine tonsils, therefore, the current standard treatment for childhood OSA is adenotonsillectomy (AT) rather than continuous positive airway pressure (CPAP), which is the first-line treatment for adult OSA (Marcus et al., 2012).

Many studies, including the randomized Childhood Adenotonsillectomy Trial (CHAT) (Marcus et al., 2013), have reported improvements in cognitive function, behavior, and learning after surgical intervention with AT (Ericsson, Lundeborg, & Hultcrantz, 2009; Friedman et al., 2003; Goldstein et al., 2002; Huang et al., 2007; Li et al., 2006; Malow et al., 2006; Marcus et al., 2013).

We previously reported the case of an obese child with severe OSA whose hyperactivity was improved after introducing CPAP for the treatment of OSA (Miyoshi et al., 2006). However, no studies have been conducted to evaluate the effect of OSA treatment on the behavior of children in Japan.

Several studies have reported an improvement in children's behavior after treatment of these symptoms (Tordjman et al., 2013; Cohen et al., 2014). Huang et al. (2007) reported that AT is more effective for behavioral improvement in children with attention deficit hyperactivity disorder (ADHD) and mild OSA than methylphenidate. Concerning autism spectrum disorder (ASD), it highly comorbid with sleep problems such as sleep-wake rhythm disturbances, insomnia, and parasomnia (Richdale & Schreck, 2009; Malow & McGrew, 2008). Furthermore, the severity of sleep problems in ASD has been found to be significantly correlated with behavioral problems (Hirata et al., 2016). Recently, we found that the prevalence of OSA is higher in ASD than community samples (Hirata et al., 2016). Thus, we hypothesized that treatment of OSA may also improve behaviors in ASD children with OSA. AT is a difficult procedure for ASD children, because such novel events may provoke in them a great deal of anxiety; this being in addition to the intrinsic risks of AT procedures, such as bleeding, throat pain, and respiratory complication (Baugh et al., 2011). If we can predict the efficacy of AT, we can avoid unnecessary surgery or recommend an age for surgical intervention. Unfortunately, there is no literature which characteristic is sensitive for behavioral and cognitive impairments followed sleep improvement. However, obesity and OSA severity did not an affect to improvement in cognitive function and behavior after surgical intervention (Marcus et al., 2013; Huang et al., 2007). Thus, we examined characteristic which is the most recommendable case for AT, i.e. age, sex, obesity, OSA severity, or behavioral problems.

The aims of our short-term retrospective study were two-fold. The first aim was to determine whether AT for the treatment of OSA improves the behavior of Japanese children with ASD using the Child Behavior Checklist (CBCL). The second aim was to identify characteristics for behavioral improvement following the treatment of OSA in these children with ASD.

2. Methods

2.1. Study design and participants

Fifty-five children attended to in the pediatric developmental clinic at Osaka University Hospital or Ota Memorial Sleep Center from September 2007 to June 2014 were enrolled in this study. Patients were all children with ASD who were outpatient clinic during the study period. This was not a randomized study; if children have OSA, we could not leave them without treatment OSA. The control group thus comprised ASD children without OSA, and we examined whether the behavioral change observed was due to the natural course (i.e. vs. the control group) or due to an improvement of sleep. One child was excluded due to an invalid response on the CBCL. All children were Japanese. The clinical diagnosis of ASD was assessed by three pediatric neurologists according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5, American Psychiatric Association, 2013). Older cases whose initial diagnoses were made according to the DSM-IV-TR, prior to the release of DSM-5 in 2013, were re-diagnosed using DSM-5 criteria.

Thirty children were diagnosed as having OSA (OSA group). They usually experience loud snoring, choking, apnea, mouth opening, and leaning back of the head during sleep. Furthermore, some children show difficulties in waking up, even if they slept for a sufficient number of hours and a poor appetite at breakfast. On the other hand, they did not have symptoms such as difficulties falling asleep, sleep wake cycle abnormalities, and night awakening. For the diagnosis of OSA, PSG, cardiorespiratory monitoring, and pulse oximetry were performed for 19 (63.3%), three (10.0%), and eight (26.7%) children, respectively. Overnight pulse oximetry can be used as a substitute for PSG in children (Kaditis, Kheirandish-Gozal, & Gozal, 2015), and, for such cases, the 3% oxygen desaturation index (ODI) may be used as an approximate value of AHI (Oeverland et al., 2002). According to the ICSD-3, the criteria of childhood OSA are an apnea/hypopnea index of more than 1/hour and/or obstructive hypoventilation (hypercapnia ($PaCO2 > 50$ mmHg) in at least 25% of total sleep time, and one or more of the following: snoring, flattening of the nasal cavity pressure sensor signal during expiration, and indentation of the chest during exhalation). We defined OSA as an AHI/3% ODI > 1, rising end-tidal CO2 and/or hypertrophy of the adenoids, and/or palatine tonsils. Therefore, in the present study, AHI and ODI 3% are used together for the index of severity of OSA. Because hypertrophy of the adenoids and/or palatine tonsils was observed, all participants underwent AT performed by one of several otolaryngologists.

Twenty-four children with ASD but without OSA were recruited to comprise the control group. This comparison allowed us to establish whether observed changes in CBCL scores were due to the natural course or a result of the experimental intervention. Denial of OSA is confirmed by lack of hypertrophy of the tonsils and adenoid, and without characteristic symptoms such as: snoring, choking, apnea, mouth opening, sweating, and leaning back of the head during sleep.

All children were naive to medical treatment for ADHD-like symptoms. Furthermore, they all didn't have chromosomal abnormality or syndromic feature. Psycho-educational programs, including parent training and social skills training, were provided for seven out of 24 children and/or parents of children in the control group, but not for the children in the OSA group.

2.2. Evaluation of behavior in children with OSA before and after AT

We used the CBCL/4-18 Japanese Edition, which was originally developed by Achenbach (1991) and standardized by Itani et al. (2001) in Japan, to evaluate the emotional and behavioral problems of children with OSA and ASD. The Japanese version of the CBCL/4-18 showed that the Cronbach's alpha coefficient was 0.67–0.89 excluding thought problems (Itani et al., 2001). Furthermore, construct validity was confirmed from high correlation coefficients with scores from the Rutter Parent Questionnaire (Itani et al., 2001). Thus, the CBCL is useful to evaluate Japanese children's cognitive and behavioral problems. The CBCL/4-18 is organized into the following subscales: withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behavior, and aggressive behavior.

We scheduled to see the patient about once or twice within six months after AT. The behavioral assessment was conducted the first or second visit that was scheduled. Malow et al. (2006) reassessed a child's behavior using CBCL and the Autism Diagnostic Observation Schedule, one month and three months after AT, respectively. Too long interval is greatly affected by many environmental conditions. So, the CBCL was completed by the children's parents before AT (pre-AT) and within 6 months after AT (post-AT; mean $\pm$ standard deviation: 2.6 $\pm$ 1.1 months) in the OSA group; the interval between the baseline and the second evaluation was approximately 6 months in both the OSA and control group (5.9 $\pm$ 3.3 months and 5.8 $\pm$ 4.7 months, respectively; Table 1).

This study was approved by the Institutional Review Board of Osaka University Hospital and Ota Memorial Sleep Center.

2.3. Statistical analysis

Changes in CBCL T-scores between two time points were compared between the two groups using a paired *t*-test. In addition, we conducted a paired *t*-test to assess changes in CBCL T-scores between the improved group and unchanged/deteriorated group to

Table 1
Patient characteristics stratified by adenotonsillectomy and control.

	AT group (OSA)				control group (no OSA)				p value (AT group vs. control group)
	Total (n = 30)	Boy (n = 24)	Girl (n = 6)	p value (Boy vs. Girl)	Total (n = 24)	Boy (n = 12)	Girl (n = 12)	p value (Boy vs. Girl)	
age	7 y 3 m ± 2 y 5 m	7 y 3 m ± 2 y 8 m	7 y 3 m ± 1 y 1 m	0.97	7 y 5 m ± 2 y 0 m	7 y 11 m ± 2 y 6 m	6 y 11 m ± 1 y 4 m	0.26	0.77
AT age	7 y 6 m ± 2 y 5 m	7 y 6 m ± 2 y 8 m	7 y 5 m ± 1 y 2 m	0.93					
Kaup Index/Rohrer Index z-score	0.1 ± 1.3	0.0 ± 1.3	0.5 ± 1.4	0.44	0.3 ± 1.1	−0.1 ± 1.2	0.6 ± 1.0	0.14	0.67
obesity [n (%)]	4 (13.3)	3 (12.5)	1 (16.7)	0.79	3 (12.5)	1 (8.3)	2 (16.7)	0.54	0.93
AHI/3% ODI	11.5 ± 12.2	12.1 ± 12.9	11.4 ± 10.6	0.53					
Interval from AT to second CBCL (m)	2.6 ± 1.1	2.8 ± 1.1	2.0 ± 1.1	0.15					
Interval from baseline to second CBCL (m)	5.9 ± 3.3	6.3 ± 3.5	4.3 ± 2.2	0.12	5.8 ± 4.7	5.2 ± 4.7	6.5 ± 4.8	0.50	0.98

Abbreviations: CBCL, Child Behavior Checklist; AT, adenotonsillectomy; AHI, apnea-hypopnea index; 3% ODI, 3% oxygen desaturation index; y, year; m, month.
Values are expressed as mean ± standard deviation and N (%).

identify characteristics that may affect behavioral changes following OSA treatment.

Since obesity is a causal factor of OSA, we also used the z-score of the Kaup Index or Rohrer Index to estimate the degree of obesity among children under 7 years old and over 7 years old, respectively. In all participants, the normal ranges are more than 15 to fewer than 19 on the Kaup Index, and more than 115 to fewer than 145 on the Rohrer Index.

All data analyses were performed using SPSS for Windows software, version 20.0 (IBM Japan, Tokyo, Japan), and the significance level was set at $p < 0.05$ for all tests. Values are expressed as mean (M) ± standard deviation (SD).

3. Results

3.1. Demographic data of participants

Enrolled in the present study were 30 ASD children with OSA (OSA group) and 24 ASD children without OSA (control group). Intellectual disability was diagnosed in two children in the OSA group, and eight children in the control group.

The mean age of the participants was 7 years and 3 months (SD = 2 years and 5 months, range: 5–14 years) in the OSA group, and 7 years and 5 months (SD = 2 years and 0 months, range: 5–13 years) in the control group. The mean z-score of the Kaup Index/Rohrer Index was within the normal range for both groups. The sex ratio was not significantly different between the OSA group and the control group (Table 1). In the OSA group, the mean AHI/3% ODI was 11.5 (SD = 12.2, range: 0.7-59.9) per hour of sleep, and the mean age of children underwent AT at 7 years and 6 months (SD = 2 years and 5 months, range: 5–14 years) of age. We usually diagnosed children as having OSA if they showed an AHI/3% ODI > 1; however, we exceptionally diagnosed a child with AHI/3% ODI = 0.7 as having OSA who had producing loud snoring from infant, perspiring, frequent body movement, and Grade 2 progression of double tonsillar hypertrophy.

3.2. CBCL scores

The baseline T-scores, including the total scale and eight subscales, were not significantly different between the OSA group and control group (Table 2).

To investigate the behavioral changes following AT, we compared the T-scores of pre- and post-AT in the OSA group. As shown in Table 2, the T-scores of the total scale ($p < 0.01$) and the internalizing scale ($p < 0.05$) were significantly decreased after AT in the OSA group. Regarding the eight subscales, withdrawn ($p < 0.05$), social problems ($p < 0.01$), thought problems ($p < 0.05$), attention problems ($p < 0.01$), and aggressive behavior ($p < 0.05$) were significantly decreased after AT. The domain of “thought problems” showed the largest decrease (3.60 points) in the OSA group. On the other hand, neither the total scale nor subscales of CBCL showed significant differences between the two time points in the control group (Table 2, Figs. 1 and 2).

The severity of sleep disturbance may depend on OSA severity, whereby mild OSA may cause less sleep disturbances and behavioral problems. To clarify whether behavioral improvements after AT was related to the severity of OSA, we compared the CBCL scores of pre- and post-AT in ASD children with mild OSA (AHI/3% ODI < 5, n = 12). There are no criteria of severity of OSA in children, so we classified an AHI < 5 as mild OSA as did a previous study (Kang et al., 2017). Improvement was observed in the social problems score (pre-AT: 69.42 ± 12.63; post-AT: 65.92 ± 11.14; $p = 0.04$).

3.3. Characteristics associated with behavioral improvement after treatment of OSA in children with ASD

AT is the first-line choice for pediatric OSA (Marcus et al., 2013). However, as with any surgical intervention, it also carries some risks. Thus, it is clinically important to identify factors that make a patient a strong candidate and those that mean AT should be avoided. To this aim, we conducted a paired *t*-test to test the changes in CBCL T-scores between the improved group and unchanged/deteriorated group in order to identify the characteristics that may affect behavioral improvement in children with ASD after treatment of OSA by AT (Table 3).

The sex, AT age, the indices of obesity, and the severity of OSA as estimated based on AHI/3% ODI were not significantly different between the improved group and unchanged/deteriorated group (Table 3). In contrast, the pre-AT T-score of externalizing ($p < 0.01$), somatic complaints ($p < 0.05$), anxious/depressed ($p < 0.05$), social problems ($p < 0.01$), thought problems ($p < 0.01$), delinquent behavior ($p < 0.01$), and aggressive behavior ($p < 0.05$) were significantly higher in the improved group than unchanged/deterioration group (Table 3).

4. Discussion

4.1. Behavioral improvement following AT in ASD children

It is well-known that sleep problems including OSA may cause ADHD or ADHD-like symptoms in children, and many studies have

Table 2
The Change of the Scores on the Child Behavior Checklist.

	AT group (OSA) (n = 30)		control group (no OSA) (n = 24)
	T-score		T-score
Total Scale			
Pre-AT / Baseline	67.57 ± 8.71	**	68.13 ± 9.89
Post-AT / Second	63.30 ± 8.29		66.38 ± 7.80
Internalizing			
Pre-AT / Baseline	64.00 ± 9.28	*	60.79 ± 8.94
Post-AT / Second	60.40 ± 10.13		61.46 ± 9.25
Externalizing			
Pre-AT / Baseline	62.93 ± 12.07		63.25 ± 8.79
Post-AT / Second	60.23 ± 9.42		64.08 ± 8.82
Withdrawn			
Pre-AT / Baseline	64.37 ± 9.41	*	60.38 ± 7.76
Post-AT / Second	60.97 ± 8.80		60.21 ± 7.68
Somatic Complaints			
Pre-AT / Baseline	54.40 ± 7.02		56.46 ± 8.32
Post-AT / Second	54.63 ± 7.45		58.29 ± 8.64
Anxious / Depressed			
Pre-AT / Baseline	62.73 ± 9.86		60.33 ± 8.75
Post-AT/ Second	59.73 ± 9.57		60.63 ± 9.33
Social Problems			
Pre-AT / Baseline	65.97 ± 11.07	**	67.75 ± 8.11
Post-AT / Second	62.80 ± 9.55		68.38 ± 8.53
Thought Problems			
Pre-AT / Baseline	60.63 ± 10.14	*	59.00 ± 10.47
Post-AT / Second	57.03 ± 9.21		59.88 ± 9.28
Attention Problems			
Pre-AT / Baseline	65.97 ± 9.08	**	68.46 ± 8.74
Post-AT / Second	62.50 ± 8.25		67.71 ± 7.58
Delinquent Behavior			
Pre-AT / Baseline	59.80 ± 8.11		61.29 ± 6.55
Post-AT / Second	59.30 ± 8.19		59.50 ± 7.73
Aggressive Behavior			
Pre-AT / Baseline	63.50 ± 10.52	*	62.79 ± 8.72
Post-AT / Second	60.03 ± 7.57		64.33 ± 8.37

Abbreviations: OSA, obstructive sleep apnea; AT, adenotonsillectomy.
Values are expressed as mean ± standard deviation. *$p < 0.05$, **$p < 0.01$.

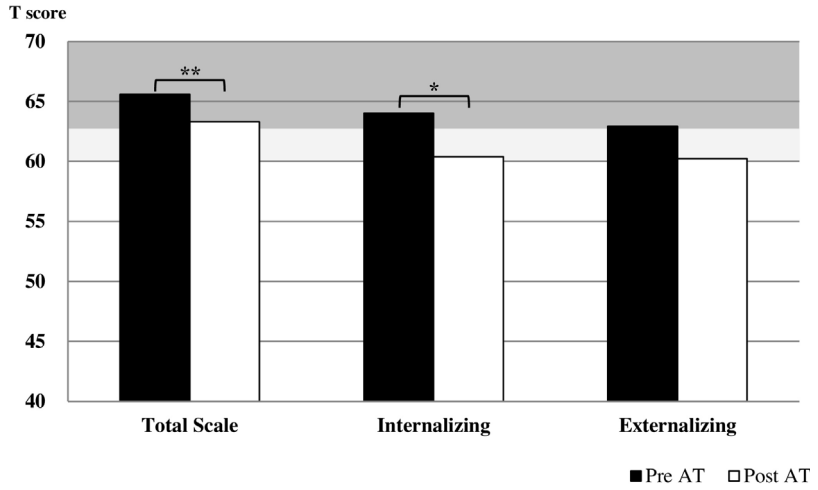

Fig. 1. The Change of the Scores on the Child Behavior Checklist (Total scale, Internalizing, and Externalizing).Abbreviations: AT, adenotonsillectomy.T-scores of the total scale and superordinate scales of Child Behavior Checklist (CBCL) for all participants before and after adenotonsillectomy (AT). Bars represent standard deviation. Dark gray, light gray, and white areas represent clinical, borderline, and normal ranges, respectively. $^{*}p < 0.05$, $^{**}p < 0.01$, n = 30.

reported that behavior improved after AT in children with OSA (Huang et al., 2007; Li et al., 2006; Malow et al., 2006; Wei et al., 2007). We confirmed that ADHD or ADHD-like symptoms are significantly decreased after AT in typically developing (TD) children (n = 57, Appendix A).

Malow et al., (2006) reported a notable example that autistic manifestation was decreased after AT for treatment of OSA in a 5-year-old female with ASD. In the present study, we also found a significant improvement of the features of ASD such as withdrawal behavior (derives little enjoyment from social activity, prefers to be alone, will not talk, secretive, shy, etc.), social problems (behaving immaturely, does not get along with others, is teased, not well-liked, etc.), and thought problems (absent-minded, self-injury, engages in repetitive and/or strange behaviors, etc.) besides ADHD-like symptoms after OSA treatment in 30 ASD children with OSA (Table 2).

Recent neuroimaging studies have revealed that abnormal brain function and/or networks, including those of the frontal lobe, are related to the social deficits of ASD (Murphy et al., 2014) and the symptoms of ADHD (Ortiz et al., 2015). On the other hand, sleep

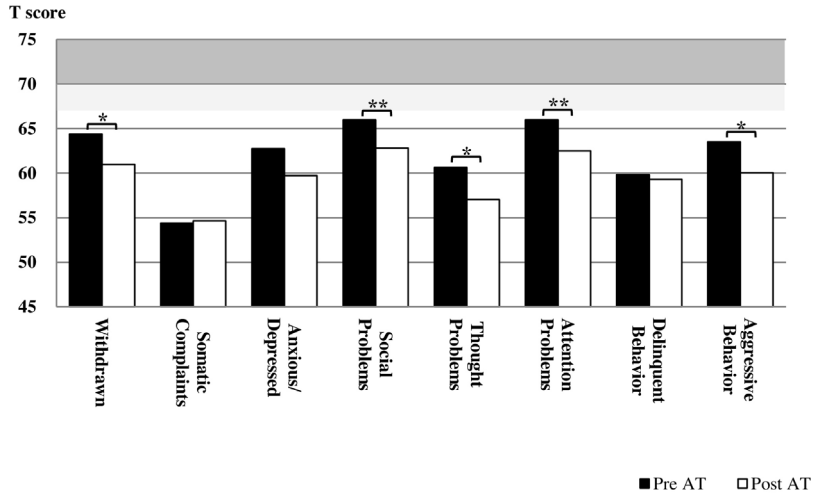

Fig. 2. The Change of the Scores on the Child Behavior Checklist (8 subscales).Abbreviations: AT, adenotonsillectomy.T-scores of the 8 subscales of Child Behavior Checklist (CBCL) before and after adenotonsillectomy (AT) for all participants. Bars represent standard deviation. Dark gray, light gray, and white areas represent clinical, borderline, and normal ranges, respectively. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, n = 30.

Table 3
Characteristics associated with behavioral improvement after treatment of OSA in children with ASD.

		sex (boy)	AT age	Kaup Index/ Rohrer Index z-score	AHI/3% ODI	baseline CBCL T-score
Total Scale	improved	20 (16)	7y 5m ± 1y 10m	0.08 ± 1.43	12.23 ± 13.66	68.80 ± 9.35
	unchanged and deteriorated	10 (8)	7y 9m ± 3y 5m	0.20 ± 0.96	10.17 ± 9.07	65.10 ± 7.05
	p value	1.00	0.77	0.78	0.63	0.24
Internalizing	improved	18 (13)	7y 2m ± 1y 11m	0.38 ± 1.45	12.81 ± 14.08	66.28 ± 9.75
	unchanged and deteriorated	12 (11)	8y 0m ± 3y 1m	−0.28 ± 0.87	9.64 ± 8.89	60.58 ± 7.67
	p value	0.19	0.38	0.13	0.46	0.09
Externalizing	improved	19 (15)	7y 7m ± 2y 0m	0.15 ± 1.44	11.56 ± 13.79	67.74 ± 9.80
	unchanged and deteriorated	11 (9)	7y 5m ± 3y 1m	0.06 ± 0.99	11.51 ± 9.45	54.64 ± 11.39
	p value	0.85	0.91	0.84	0.99	0.005
Withdrawn	improved	16 (12)	7y 3m ± 1y 10m	0.28 ± 1.54	14.09 ± 14.63	67.13 ± 10.56
	unchanged and deteriorated	14 (12)	7y 10m ± 3y 0m	−0.06 ± 0.91	8.63 ± 8.23	61.21 ± 6.97
	p value	0.46	0.53	0.47	0.21	0.08
Somatic Complaints	improved	9 (6)	7y 6m ± 2y 5m	−0.26 ± 1.11	11.11 ± 7.17	60.33 ± 8.34
	unchanged and deteriorated	21 (18)	7y 5m ± 2y 6m	0.28 ± 1.34	11.72 ± 13.97	51.86 ± 4.58
	p value	0.23	0.97	0.27	0.88	0.02
Anxious/ Depressed	improved	16 (12)	7y 6m ± 2y 0m	0.36 ± 1.54	13.49 ± 14.23	66.44 ± 9.47
	unchanged and deteriorated	14 (12)	7y 6m ± 2y 11m	−0.16 ± 0.86	9.30 ± 9.39	58.50 ± 8.80
	p value	0.46	1.00	0.26	0.35	0.02
Social Problems	improved	18 (13)	8y 0m ± 2y 6m	0.26 ± 1.38	11.68 ± 14.20	70.89 ± 9.97
	unchanged and deteriorated	12 (11)	6y 10m ± 2y 2m	−0.08 ± 1.13	11.33 ± 8.98	58.58 ± 8.37
	p value	0.19	0.19	0.47	0.94	0.001
Thought Problems	improved	12 (9)	7y 11m ± 2y 1m	−0.36 ± 1.21	10.13 ± 8.29	67.00 ± 9.09
	unchanged and deteriorated	18 (15)	7y 3m ± 2y 8m	0.44 ± 1.25	12.48 ± 14.39	56.39 ± 8.62
	p value	0.58	0.44	0.09	0.58	0.004
Attention Problems	improved	18 (14)	7y 1m ± 1y 5m	0.27 ± 1.50	12.03 ± 13.92	67.89 ± 8.46
	unchanged and deteriorated	12 (10)	8y 2m ± 3y 5m	−0.11 ± 0.85	10.81 ± 9.57	63.08 ± 9.58
	p value	0.71	0.31	0.38	0.78	0.17
Delinquent Behavior	improved	10 (7)	6y 10m ± 1y 2m	0.39 ± 1.57	14.82 ± 17.81	66.00 ± 7.20
	unchanged and deteriorated	20 (17)	7y 10m ± 2y 10m	−0.02 ± 1.13	9.90 ± 8.26	56.70 ± 6.75
	p value	0.33	0.17	0.48	0.42	0.003
Aggressive Behavior	improved	18 (15)	7y 5m ± 2y 0m	0.19 ± 1.47	12.15 ± 13.94	67.11 ± 9.81
	unchanged and deteriorated	12 (9)	7y 7m ± 3y 0m	0.01 ± 0.96	10.62 ± 9.52	58.08 ± 9.47
	p value	0.58	0.89	0.68	0.72	0.02

Abbreviations: OSA, obstructive sleep apnea; ASD, autism spectrum disorder; AT, adenotonsillectomy; AHI, apnea-hypopnea index; 3% ODI, 3% oxygen desaturation index; CBCL, Child Behavior Checklist; y, year; m, month.
Values are expressed as mean ± standard deviation.

deprivation also causes alterations in cognitive performance and functional alteration of the frontal and parietal cortices (Chee & Choo, 2004). Consequently, diminished sleep quality due to OSA might worsen frontal lobe functioning and lead to the observed social difficulties. After AT, improvement of sleep quality might lead to improvements in this brain functioning, and thus result in behavioral improvements. To determine whether this is the case, further investigation is necessary.

Daytime problematic behaviors were significantly ameliorated by AT, even in cases of mild OSA (AHI/3% ODI < 5). This finding highlights the importance of the detection and treatment of even mild OSA from a developmental point of view.

The prevalence of sleep problems ranges from 50% to 80% in children with ASD (Johnson, Giannotti, & Cortesi, 2009; Sivertsen et al., 2012). In these children, sleep problems include chronic insomnia, sleep-onset delay, or parasomnia (including night waking). Recently, we reported that the prevalence of OSA is higher in children with ASD than in the general population (Hirata et al., 2016). However, OSA may be overlooked because of several other behavioral problems that may have to be intervened with, and other sleep problems that may exhaust patients or caregivers. Furthermore, difficulties in the evaluation of OSA in uncooperative ASD children due to their hypersensitivity might impede the diagnosis of OSA. The pathology underpinning the high prevalence of OSA in ASD children remains unclear, but immune deregulation and/or inflammation might be an etiology common to both ASD and OSA (Bhattacharjee et al., 2012; Gozal et al., 2012; Morgan et al., 2012; Suzuki et al., 2013). Alternatively, Guilleminault and Ramar

(2009) proposed that OSA is a neurological impairment, stating that patients with OSA show a sleep-related blunted cortical response to inspiratory occlusion that is accompanied by a brainstem defect. ASD is a neurodevelopmental disorder and is now understood as a "connectivity disorder" (Minshew & Williams, 2007). These neurological impairments might also represent the shared etiology of ASD and OSA.

4.2. Demographical characteristics of OSA children with ASD

Regarding the sex ratio of the prevalence of OSA, previous studies have reported that the prevalence of childhood OSA is equal between boys and girls (Lumeng & Chervin, 2008). In the present study, however, the number of boys affected was greater than that of girls. This is because the frequency of ASD occurrence is higher in men than in women (Howe et al., 2015).

The contribution of obesity to OSA may be different between Japanese children and those in western countries. Several reports have focused on obesity in children with OSA; 83% of participants were obese or overweight in the CHAT study (Marcus et al., 2013), and the mean body mass index was close to the threshold of obesity in two OSA reports from Taiwan (Huang et al., 2007; Li et al., 2006). In the present study, the mean Kaup Index/Rorer Index z-score was 0.1 (SD = 1.3), and obese children comprised only 13.3% of the OSA group. These values were approximately the same for TD children with OSA (the mean Kaup Index/Rorer Index z-score was 0.1 (SD = 0.9), and obese children comprised only 15.8% of the population; Appendix A). One explanation for this discrepancy between Japan and other countries, including other Asian countries, is that most Japanese individuals are leptosomes, and craniofacial factors may contribute more to the occurrence of OSA in Japanese children.

4.3. Characteristics associated with behavioral improvement following treatment of OSA

Few previous studies have examined the characteristics associated with improvement in behavior following treatment of OSA in ASD children with OSA. Mitchell and Boss (2009) reported that the presence of obesity was not an influential factor affecting improvement in behavioral impairment. Consistent with this finding, obesity was not identified as a characteristic of behavioral improvement after AT in the present study.

The severity of OSA as measured based on AHI/3% ODI was also unrelated to postoperative behavioral improvement (Chervin et al., 2005). Consistent with this finding, the severity of OSA was not identified as a characteristic of behavioral improvement after AT in the present study. And we showed that the number of behavioral problems was significantly decreased in ASD children with mild OSA. This finding is also consistent with previous reports. However, the CHAT study reported that only small and selective effects of AT were observed on cognitive tests in children with OSA without prolonged desaturation (Taylor et al., 2016). It might be possible that patients with ASD are particularly susceptible to the effects of sleep deprivation. Further investigation is required to test this theory in ASD children with OSA.

Furthermore, there were no significant differences in sex and AT age between the improved group and unchanged/deteriorated group. Thus, sex, AT age, obesity, and the severity of OSA may not influence improvement of cognitive and behavioral functioning in ASD children with OSA after AT.

We revealed that the improved group shown significantly higher scores on the CBCL at pre-AT than the unchanged/deteriorated group in ASD children with OSA after OSA treatment. Our data indicate that OSA of ASD children should be treated regardless of obesity and age, and even in children with mild OSA, especially when they have more severe behavioral problems. Further investigation is required to test this.

Overall, these data may indicate that cerebral function of ASD is more vulnerable to sleep deprivation. Further investigation is required to clarify this hypothesis.

Recently, it was reported that sleep restriction may change neural morphology (de Vivo et al., 2016) and brain connectivity (Billeh et al., 2016). Overall, children need good quality sleep for the proper development of the brain. Further investigation must be conducted to detect if "inadequate sleep" is a detriment to brain development.

4.4. Limitations and future directions

This study has several limitations. The first limitation is that this study was not designed as a case-control study. A proper control group (OSA untreated group) was not possible due to ethical considerations (i.e., to withhold treatment of OSA is not permissible). To partially answer the question of whether behavioral improvement is due to treatment or natural developmental course, we analyzed behavior over time in children with ASD but without OSA.

The second limitation is that PSG not performed on all participants. PSG is required to make a definite diagnosis of OSA, but it is difficult for many ASD children because they have a hypersensitivity and strong anxiety of unfamiliar places and events. Instead of PSG, 3% ODI measured using pulse oximetry was used as an approximate value of AHI (Oeverland et al., 2002). In addition, improvement of OSA was confirmed by conducting a clinical assessment, but not by repeated PSG or other objective measures in all cases after AT.

The third limitation is that the CBCL is susceptible to a caregiver-related bias in the behavioral assessment, as a parent-rated

questionnaire was the only measure of behavior in this study. We evaluated the behavior twice at approximately 6 months' interval because the longer interval would incorporate many additional factors, such as medication and special education.

The fourth limitation is with the timing of the second evaluation. Evaluations conducted after too long an interval are at risk of being affected by several environmental conditions. In the current study, we usually scheduled to see the patient once or twice within six months after AT, and the time of the second evaluation depended on the consultation day. The optimal interval for evaluation is still unknown, however, and could be the subject of future research.

Finally, the diagnosis of ASD was made using DSM criteria, and a structured diagnostic interview or observational assessment of ASD was not performed for all children.

5. Conclusion

Behavioral problems are expected to decrease after AT in ASD children with OSA. When caring for ASD children, clinicians must check for OSA in addition to sleep problems such as insomnia and circadian rhythm disorders. Contrary to the case among adults, many non-obese children suffer from OSA, especially in Japan. To ensure adequate quality of sleep and support their mental development, we clinicians must be aware of OSA in ASD children.

Author contributions

Emi Murata: Ms. Murata conceptualized and designed the study, conducted statistical analysis, drafted the initial manuscript, and revised the manuscript.

Ikuko Mohri: Dr. Mohri conceptualized and designed the study, diagnosed and treated the patients, collected data, participated in the interpretation of data, reviewed the manuscript, coordinated and supervised data, and approved the final manuscript.

Kumi Kato-Nishimura: Dr. Kato-Nishimura conceptualized and designed the study, diagnosed and treated the patients, collected data, reviewed the manuscript, coordinated and supervised data collection, and approved the final manuscript.

Jiro Iimura: Dr. Iimura performed the adenotonsillectomy on the patients and collected data, reviewed the manuscript, and approved the final manuscript.

Makoto Ogawa: Dr. Ogawa performed the adenotonsillectomy on the patients and collected data, critically reviewed the manuscript, and approved the final manuscript.

Masaya Tachibana: Dr. Tachibana coordinated and supervised data collection, reviewed the manuscript, and approved the final manuscript.

Yuko Ohno: Professor Ohno instructed statistical analysis, reviewed the manuscript, and approved the final manuscript.

Masako Taniike: Professor Taniike conceptualized and designed the study, diagnosed and treated the patients, collected the data, and participated in the interpretation of data, reviewed the manuscript, coordinated and supervised data, and approved the final manuscript. All authors approved the manuscript as submitted and agree to be accountable for all aspects of the work.

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Conflict of interest

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Appendix A

Table A1
The Change of the Scores on the Child Behavior Checklist of children with typical development and OSA.

		Underwent AT (n = 57)	
boy [n (%)]		38 (66.7)	
age		6y 10m ± 1y 5m	
AT age		7y 0m ± 1y 4m	
Kaup Index / Rohrer Index z-score		0.1 ± 0.9	
obesity [n (%)]		9 (15.8)	
AHI/3% ODI		12.8 ± 13.9	
Interval from AT to second CBCL (m)		2.1 ± 1.3	
Interval from baseline to second CBCL (m)		4.1 ± 1.7	
T-score	Total Scale		
	Pre-AT / Baseline	58.63 ± 9.11	] ***
	Post-AT / Second	52.67 ± 9.04	
	Internalizing		
	Pre-AT / Baseline	56.95 ± 9.32	] **
	Post-AT / Second	53.54 ± 7.91	
	Externalizing		
	Pre-AT / Baseline	55.70 ± 9.33	] ***
	Post-AT / Second	51.72 ± 9.23	
	Withdrawn		
	Pre-AT / Baseline	57.14 ± 7.21	] *
	Post-AT / Second	55.23 ± 5.80	
	Somatic Complaints		
	Pre-AT / Baseline	53.79 ± 5.71	] **
	Post-AT / Second	51.70 ± 4.22	
	Anxious / Depressed		
	Pre-AT / Baseline	57.02 ± 7.60	] **
	Post-AT/ Second	54.40 ± 5.67	
	Social Problems		
	Pre-AT / Baseline	56.26 ± 6.00	] ***
	Post-AT / Second	53.35 ± 4.25	
	Thought Problems		
	Pre-AT / Baseline	55.18 ± 7.57	] **
	Post-AT / Second	52.51 ± 4.83	
	Attention Problems		
	Pre-AT / Baseline	57.84 ± 6.65	] ***
	Post-AT / Second	53.54 ± 4.63	
	Delinquent Behavior		
	Pre-AT / Baseline	56.28 ± 6.70	] **
	Post-AT / Second	53.86 ± 5.62	
	Aggressive Behavior		
	Pre-AT / Baseline	57.14 ± 6.93	] ***
	Post-AT / Second	54.77 ± 6.32	

Abbreviations: OSA, obstructive sleep apnea; AT, adenotonsillectomy; AHI, apnea-hypopnea index; 3% ODI, 3% oxygen desaturation index; CBCL, Child Behavior Checklist.
Values are expressed as mean ± standard deviation and n (%). *p < 0.05, **p < 0.01, ***p < 0.001.

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