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Original Article

Association between the severity of chronic spontaneous urticaria and sleep-disordered breathing

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AHI, Apnea-hypopnea index; CSU, Chronic spontaneous urticaria; ESS, Epworth sleepiness scale; OCS, oral corticosteroid; OCST, Out-of-center sleep testing; ODI, Oxygen desaturation index; OOC, Out-of-center; PAT, Peripheral arterial tonometry; PSQI, Pittsburgh Sleep Quality Index; SDB, Sleep-disordered breathing; UAS7, Urticaria activity score 7

ABSTRACT

Background: Chronic spontaneous urticaria (CSU) is a common mast cell-driven disease, presenting with wheals, angioedema, or both. Sleep-disordered breathing (SDB) is also a common condition and contributes to various diseases by causing chronic inflammation. Recent studies have suggested an association between CSU and SDB.

Methods: To determine the association between the severity of SDB and that of CSU, we studied consecutive patients with CSU who visited the Sagamihara National Hospital allergy department or dermatology department between April 1 and October 31, 2018. The severity of CSU and SDB was evaluated based on the urticaria activity score 7 (UAS7) and peripheral arterial tone apnea-hypopnea index (pAHI) derived from out-of-center sleep testing (OCST) findings, respectively; their correlation was examined.

Results: Of the 37 patients studied, 19 had symptom-free-to-mild CSU (UAS7 $\leq$15) and 18 had moderate-to-severe CSU (UAS7 $\geq$16). The pAHI in the latter group was significantly higher than that in the former group (18 vs. 4.2, $p = 0.001$). In multivariate logistic analysis, moderate-to-severe SDB (pAHI $\geq$15) was significantly associated with moderate-to-severe CSU even after adjusting for the BMI (adjusted odds ratio 22 [95% confidence interval, 1.7–285]).

Conclusions: The severity of SDB is correlated with that of CSU independently of the BMI. Physicians should consider comorbid SDB when treating patients with CSU.

Introduction

Chronic spontaneous urticaria (CSU) is a common disease involving the spontaneous appearance of wheals, angioedema, or both and lasting for more than 6 weeks without a specific eliciting factor.[1] Sleep-disordered breathing (SDB) is also a common condition presenting as disorder of sleep and wakefulness.[2] In addition to interfering with daily life, SDB contributes to various diseases, such as hypertension, diabetes mellitus, and hyperlipidemia.[3–5] Because SDB has a high prevalence worldwide[6] and severe SDB is related to high mortality,[7] early detection and treatment are considered major public health concerns.

Recent studies have focused on the possible association between CSU and SDB. A nationwide observational study in Taiwan revealed a higher incidence of CSU in patients with SDB than in those without SDB.[8] Overnight polysomnography (PSG) of asymptomatic or oligosymptomatic patients with CSU showed that 25% had SDB.[9] Although these studies revealed a high rate of concordance between SDB and CSU, a high BMI has been documented in patients with CSU[10,11] and those with SDB,[12] adjustment for BMI, a

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potentially important confounding factor between CSU and SDB, was not performed when analyzing the association between these diseases.[8,9] Furthermore, the number of studies on this association is limited.

Therefore, we focused on the possible association between the severity of CSU and that of SDB after adjusting for BMI. CSU severity was evaluated using a scoring scale known as the urticaria activity score 7 (UAS7), and SDB severity was assessed by the apnea-hypopnea index (AHI) score calculated using an out-of-center sleep testing (OCST).

Methods

Study design and patients

We studied consecutive 42 outpatients with CSU who visited the Sagamihara National Hospital allergy department or dermatology department between April 1 and October 31, 2018. The following patients were included: (1) patients aged at least 16 years, (2) patients with persistent urticaria for more than 6 weeks without an eliciting factor, and (3) patients with an inadequate response to histamine H1 receptor antagonist. All recruited patients were carefully interviewed and examined to ensure that they had no eliciting factors for their urticaria. Supplementary Figure 1 shows a flowchart of the study design. After excluding 5 patients who refused to participate in the study, 37 patients were evaluated. All patients were asked to answer a structured questionnaire regarding their demographics, comorbidity, CSU symptoms, and sleep condition at the time of entry. OCST was performed within 2 weeks of entry. We obtained written informed consent from all participants. The Ethics Committee of Sagamihara National Hospital approved the study protocol (No.12-2018, UMIN000032435).

Urticaria activity score 7 (UAS7)

The current EAACI/GA2LEN/EDF guidelines state that the urticaria activity score (UAS) can help define the effects and impact of urticaria.[1] In this study, we used UAS7 to evaluate one-week activity. UAS7 shows the correlation with CSU patients' QOL scores[13] and is recommend for use when evaluating patients with CSU.[14] Patients were asked to score the number of wheals and intensity of itch each from 0 to 3, with higher scores indicating greater disease severity.[1] For each number of wheals, 0 corresponded to no wheals, 1 indicated less than 20 wheals/24 h, 2 indicated 20–50 wheals/24 h, and 3 indicated more than 50 wheals/24 h or large confluent areas of wheals. For the intensity of itching, 0 corresponded to no itching, 1 indicated itching that was not annoying or troublesome, 2 indicated troublesome itching that did not interfere with normal daily activity or sleep, and 3 indicated severe pruritus, which was sufficiently troublesome that it interfered with normal daily activity or sleep. The daily score was calculated as the sum of the wheals score and itch score (score 0–6), and UAS7 was determined as the sum over 7 consecutive days (score 0–42). The final UAS7 score evaluation was as follows: 0, symptom-free; 1–6, well-controlled; 7–15, mild; 16–27, moderate; 28–42, severe.[13] UAS7 translated to Japanese was used in this study[15] and was answered at the time of entry. In this study, patients with UAS7 $\leq$15 were assigned to the symptom-free-to-mild CSU group (n = 19), whereas patients with UAS7 $\geq$16 were assigned to the moderate-to-severe CSU group (n = 18).

Out-of-center sleep testing (OCST) and apnea-hypopnea index (AHI)

All patients wore an out-of-center sleep testing device (WatchPAT®, Philips, Amsterdam, Netherlands) overnight at home and data were collected later. Although AHI is a sum of the number of apneas and hypopneas events per hour of sleep, the OCST cannot measure accurate sleep time. However, the OCST used in this study utilizes the peripheral arterial tonometry (PAT) signal, and the result is reported to highly correlate with the PSG result (r = 0.91).[16,17] AHI measured by WatchPat® was expressed as PAT AHI (pAHI), and patients with pAHI $\geq$5 were defined as having SDB regardless of their subjective symptoms.[18] The severity of SDB was evaluated based on pAHI as mild (5$\leq$ pAHI <15), moderate (15$\leq$ pAHI <30), and severe (30$\leq$ pAHI).[19] Patients were classified into 3 groups based on SDB severity (pAHI <5 to none, 5–15 as mild, $\geq$15 as moderate-to-severe).

Daytime sleepiness and disordered sleep

Daytime sleepiness and disordered sleep were evaluated using the Japanese translated version of the Epworth sleepiness scale (ESS)[20] and Pittsburgh Sleep Questionnaire (PSQI),[21] respectively, which were answered at the time of study entry.[22–24] An ESS score $\geq$11 indicated strong daytime drowsiness and a PSQI score $\geq$6 indicated sleep disturbance.[20,21]

Clinical observation of patients with pAHI $\geq$5

The current Japanese guidelines for SDB recommend that all patients with pAHI $\geq$5 and/or sleep-related symptoms should undergo additional PSG to evaluate SDB more accurately.[25,26] Therefore, we also advised all patients with pAHI $\geq$5 (n = 23) to undergo additional PSG and receive treatment for SDB if needed. As a result, 6 of 23 patients underwent PSG; depending on the results, a mouthpiece was given to patients with 5$\leq$ AHI <20, and CPAP treatment was used for patients with AHI $\geq$20 according to Japanese guidelines.[26] Finally, 4 patients started treatment for their SDB not as a study intervention, but as a guideline-based treatment within public health insurance coverage. One month after starting treatment, the UAS7 was re-examined and compared to the baseline UAS7.

Statistical analysis

The BMI was calculated using the height and weight on the structured questionnaire provided at the time of entry. The Fisher's exact test was used to determine whether the distributions of categorical variables exhibited significant differences. The Mann–Whitney U test was used to compare differences between the two groups. The correlation between AHI and UAS7 was evaluated by Spearman rank correlation coefficient. Logistic regression analysis was used to evaluate the association between the severity of SDB and moderate-to-severe CSU. Adjusted OR and 95% CIs were calculated after adjusting for sex and BMI. Tests for trends were evaluated by assigning consecutive integers to each severity group of CSU and SDB. The UAS7 scores before and after SDB treatment were compared by the paired-*t* test, as differences in UAS7 scores followed a normal distribution. A p-value <0.05 was considered as statistically significant. The collected data were analyzed using SPSS V.25.0 software (SPSS, Chicago, IL, USA).

Results

Patient characteristics

The clinical characteristics of the patients are shown in Table 1. Of the 37 patients, 19 patients were in the symptom-free-to-mild CSU group (UAS7 $\leq$15) and 18 patients were in the moderate-to-severe CSU group (UAS7 $\geq$16). Patients in the moderate-to-severe CSU

Table 1
Patient characteristics and OCST findings classified by the severity of chronic spontaneous urticaria.

	Total	Symptom		p-value
		free-to-mild (UAS7 ≤15)	moderate-to-severe (UAS7 ≥16)	
Patient characteristics				
n (%)	37	19 (51)	18 (49)	
Age (years)	46 (36–58)	45 (32–58)	49 (40–57)	0.316
Female, n (%)	22 (59)	8 (42)	14 (78)	0.045
BMI (kg/m^2)	23 (21–28)	21 (20–24)	27 (23–28)	0.016
Use of doublets or quantitas duplex with histamine H1 receptor antagonist (yes), n (%)	18 (49)	9 (47)	9 (50)	1.000
Use of OCS (yes), n (%)	4 (11)	1 (5)	3 (17)	0.340
Use of Omalizumab (300 mg/4w) (yes), n (%)	4 (11)	0 (0)	4 (22)	0.046
Smoking habit, n (%) current/past/never	7/8/22	4/3/12	3/5/10	0.734
Past surgical history around the head and neck (yes), n (%)	4 (11)	1 (5)	3 (17)	0.340
Use of hypnotic drugs (yes), n (%)	9 (24)	3 (16)	6 (33)	0.269
PSQI	8 (5–11)	6 (4.5–10.5)	10 (6–11)	0.121
ESS	5 (3–9.3)	5 (3–9)	5.5 (2.5–9.8)	0.855
OCST finding				
SDB, n (%)	23 (62)	7 (37)	16 (89)	0.002
pAHI	7.8 (3.7–21)	4.2 (2.8–8)	18 (8.4–29)	0.001
pAHI <5/5–15/15≥, n	14/11/12	12/5/2	2/6/10	0.002
Sleep time (min)	317 (282–395)	306 (267–321)	342 (297–462)	0.037
ODI	3.6 (0.8–8.5)	0.8 (0.4–3.1)	7.1 (3.8–16)	<0.001
SpO_2 (%) during sleep				
Mean value	96 (95–97)	96 (96–97)	95 (94–96)	0.024
Lowest value	91 (86–92)	92 (91–94)	88 (84–90)	0.002
T90 (%)	0 (0–0.2)	0 (0–0)	0.1 (0–0.7)	0.129
Snoring rate > threshold (%)[†]	18 (3.6–31)	5.1 (2.9–21)	24.8 (13–36)	0.008

Data are presented as the median.
UAS7, urticaria activity score 7; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; SDB, sleep-disordered breathing; pAHI, peripheral arterial tone apnea-hypopnea index; OCS, oral corticoid steroid; OCST, out-of-center sleep testing; ODI, Oxygen Desaturation Index; SpO_2, peripheral oxygen saturation.
[†] Set a threshold at 45 dB.

group were more likely to be female (78% vs. 42%, p = 0.045) and had a significantly higher BMI (BMI = 27 vs. 21 kg/m^2, p = 0.016) than those in the symptom-free-to-mild CSU group. There were no significant differences between the two groups regarding their age, use of doublets or quantitas duplex with histamine H1 receptor antagonist and use of hypnotic drugs. The number of the patients treated with Omalizumab (300 mg/4w) was significantly high in the moderate-to-severe CSU group (22% vs. 0%, p = 0.046), on the other hand, the number of the patients treated with OCS (oral corticosteroid) did not show any significance between the two groups. Based on the ESS, 8 (22%) patients had daytime drowsiness and 26 (70%) patients had sleep disturbances based on the PSQI. There were no significant differences in the PSQI and ESS between the two groups. The comorbidity and past medical history of the two groups are shown in Table 2. None of them showed any significant differences between the two groups. The two patients with chronic thyroiditis were asymptomatic and did not require any treatment and were under careful observation. The presence of anti-TPO antibody or anti-thyroglobulin antibody was unknown.

Out-of-center sleep testing (OCST) findings

The detailed results of OCST are shown in Table 1. Of the 37 patients, 23 (62%) had SDB (pAHI ≥5). Specifically, 16 (89%) patients had SDB in the moderate-to-severe CSU group (UAS7 ≥16), whereas 7 (37%) had SDB in the symptom-free-to-mild CSU group (UAS7 ≤15). The median value of pAHI and ODI was significantly higher in the moderate-to-severe CSU group (pAHI 18 vs 4.2, p = 0.001, ODI 7.1 vs 0.8, p < 0.001), indicating more severe SDB. Figure 1 shows the distribution of pAHI by CSU severity. As shown in Table 1, the mean value and lowest value of peripheral oxygen saturation during sleep were lower in the moderate-to-severe CSU group, suggesting more severe hypoxia (p = 0.024, p = 0.002 respectively). The percentage of time at which the peripheral oxygen saturation during sleep was below 90% (T90) did not differ significantly between the groups. The snoring rate exceeding the threshold (45 dB) was significantly greater in the moderate-to-severe CSU group. There were no significant differences in the heart rate or rate of supine position during sleep between groups (data not shown).

Association between clinical parameters and severity of CSU

Next, we analyzed the association between the clinical parameters and severity of CSU by logistic regression analysis (Table 3). In

Table 2
Comorbidity and past medical history classified by the severity of chronic spontaneous urticaria.

	Total	Symptom		p-value
		free-to-mild (UAS7 ≤15)	moderate-to-severe (UAS7 ≥16)	
Bronchial asthma	10 (27)	5 (26)	5 (28)	1.000
Allergic rhinitis	6 (16)	4 (21)	2 (11)	0.660
Atopic dermatitis	4 (11)	4 (21)	0 (0)	0.105
Sinusitis	4 (11)	2 (10)	2 (11)	1.000
Tonsillar hypertrophy	1 (3)	1 (5)	0 (0)	1.000
Diabetes mellitus	1 (3)	0 (0)	1 (6)	0.486
Hyperlipidemia	3 (8)	2 (10)	1 (6)	1.000
Hypertension	5 (14)	2 (10)	3 (17)	0.660
Arrhythmia	0 (0)	0 (0)	0 (0)	–
Congestive heart failure	0 (0)	0 (0)	0 (0)	–
Coronary artery disease	0 (0)	0 (0)	0 (0)	–
Stroke	1 (3)	1 (5)	0 (0)	1.000
Graves' disease	0 (0)	0 (0)	0 (0)	–
Chronic thyroiditis	2 (6)	1 (5)	1 (6)	1.000
Mood disorder	0 (0)	0 (0)	0 (0)	–
Cognitive impairment	0 (0)	0 (0)	0 (0)	–

Data are presented as n (%).

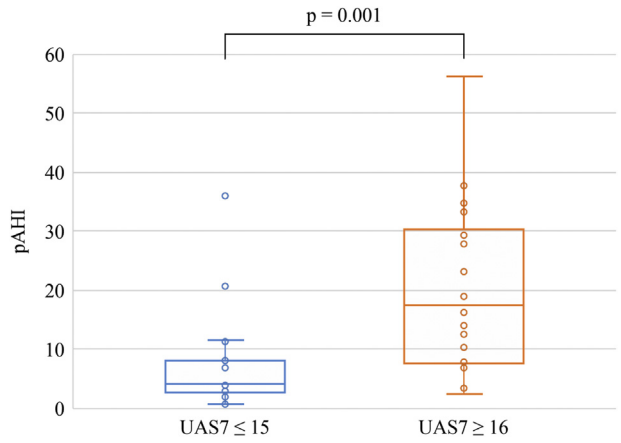

Fig. 1. Distribution of pAHI by CSU severity (symptom-free-to-mild CSU [UAS7 ≤ 15] and moderate-to-severe CSU [UAS7 ≥ 16]).
CSU, chronic spontaneous urticaria; pAHI, peripheral arterial tone apnea-hypopnea index; UAS7, urticaria activity score 7.

Table 3
Association between clinical parameters and moderate-to-severe chronic spontaneous urticaria (ref free-to-mild CSU).

Variables	Crude OR (95% CI)	Adjusted† OR (95% CI)		
		Model 1	Model 2	Model 3
Sex (female)	4.8 (1.1–20)	5.0 (0.9–29)	–	5.2 (0.9–29)
Age (year)	1.0 (1.0–1.1)	–	–	–
BMI (kg/m^2)	1.2 (1.0–1.5)	–	1.1 (0.8–1.3)	1.1 (0.8–1.4)
Severity of SDB				
pAHI <5 (n = 14)	1	1	1	1
5 to 15 (n = 11)	7.2 (1.1–49)	8.6 (1.1–67)	6.6 (0.4–46)	7.7 (0.9–62)
≥15 (n = 12)	30 (3.6–253)	30 (3.1–282)	22 (1.7–285)	19 (1.2–282)
P for trend	<0.001	0.003	0.022	0.028

SDB, sleep-disordered breathing; pAHI, peripheral arterial tone apnea-hypopnea index.
† Variables in model 1 are adjusted for sex. Model 2 is adjusted for BMI. Model 3 is adjusted for sex and BMI.

univariate analysis, female sex, BMI, mild SDB group (5≤ pAHI <15), and moderate-to-severe SDB group (pAHI ≥15) were associated with moderate-to-severe CSU (crude OR [95% CI]: 4.8 [1.1–20], 1.2 [1.0–1.5], 7.2 [1.1–49], 30 [3.6–253], respectively). In multivariate logistic regression analysis, the association between moderate-to-severe SDB (pAHI ≥15) and moderate-to-severe CSU remained significant even after adjusting for sex (model 1), BMI (model 2), and both (model 3) (adjusted OR [95%CI] in model 1: 30 [3.1–282], model 2: 22 [1.7–285], and model 3: 19 [1.2–282], respectively). Moreover, in all models, as SDB became more severe, the association with the severity of CSU became stronger (p for trend in model 1: 0.003, model 2: 0.022, and model 3: 0.028, respectively).

Change in UAS7 before and after treatment for SDB

After OCST, 6 patients additionally underwent PSG. According to the PSG results, two patients had started oral appliance treatment and the other two patients had started CPAP (another two patients declined oral appliance treatment). The characteristics of patients who started treatment for SDB are shown in Supplementary Table 3. The UAS7 was re-examined one month after starting SDB treatment and a significant decrease in UAS7 was observed, suggesting an improvement in the urticaria symptoms (p = 0.023) (Fig. 2, Supplementary Table 3). During this one month, unintentionally, CSU treatment of all four patients did not change.

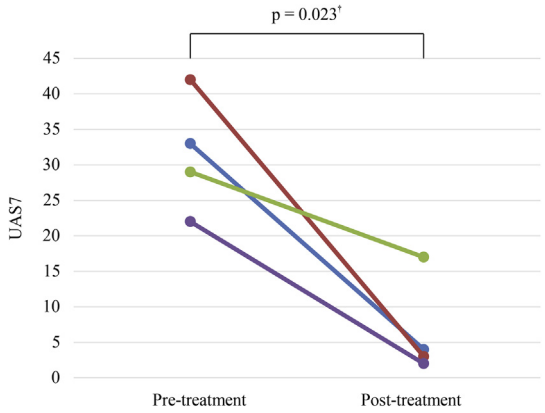

Fig. 2. Change in UAS7 before and 1 month after SDB treatment.
SDB, sleep-disordered breathing; UAS7, urticaria activity score 7.
†Paired-*t* test.

Discussion

Our findings indicate that there is a positive correlation between the severity of CSU and that of SDB, even after adjusting for BMI. Additionally, clinical observation of patients whose SDB was treated by oral appliance or CPAP suggested that CSU symptoms improve after treatment for SDB. These findings indicate that comorbid SDB worsens the disease activity of CSU and that treating comorbid SDB is a new option for CSU treatment.

We found that 62% of enrolled patients had SDB among patients with CSU. Considering that the prevalence of SDB among Japanese people aged 30–69 years is 32.7–43.2%,[6,27] the prevalence of comorbid SDB among patients with CSU in our study was relatively high. The prevalence of SDB was even higher in patients with CSU with moderate-to-severe diseases than in those with free-to-mild diseases (Table 1, 3). We also found significant difference in pAHI between symptom-free-to-mild CSU group and the moderate-to-severe CSU group (Table 1, Fig. 1). These data suggest a close association of SDB with the presence and worsening of CSU.

These correlations between SDB and CSU can be explained by some common features of these disease entities, such as increased oxidative stress[28,29] and acceleration of the coagulation system.[30,31] SDB involves oxygen depletion and rapid improvement during sleep, resulting in chronic sleep fragmentation and intermittent hypoxia.[28] These factors lead to oxidative stress.[28] A case control study showed that children with CSU have a higher serum level of total oxidants than children without CSU and that these levels are correlated with disease severity.[29] These studies suggest the involvement of oxidative stress in the pathogenesis of both SDB and CSU.

In addition, increased production of thrombin and D-dimer was reported to be correlated with the severity of urticaria.[28] Tissue factor expression has also been observed in wheals,[30] indicating mast cell activation via activation of the extrinsic clotting system.[28] It has also been shown that the levels of fibrinogen/fibrin degradation products and D-dimers are elevated in patients with SDB because of inhibition of tissue plasminogen activator, making patients more thrombogenic.[28,31,32] Thus, the mechanisms of the coagulation system are common to both diseases.

Obesity is an important confounding factor for the association between CSU and SDB. Previous studies showed a high rate of concordance between CSU and obesity[10,11] as well as between SDB and obesity.[12] However, in our multivariate logistic regression

analysis, the association between moderate-to-severe SDB and moderate-to-severe CSU remained significant, even after adjusting for BMI. Additionally, the association between BMI and moderate-to-severe SDB did not reach significance in this multivariate model (model 2 in Table 3). These results suggest that SDB is a more important factor for CSU than obesity.

Furthermore, 4 patients who started SDB treatment showed significant improvement in their CSU symptoms. This finding indicates that treating SDB can improve CSU symptoms and is a choice for CSU treatment in the future. All 4 patients who started SDB treatment had had moderate-to-severe CSU symptoms lasting more than one year. They had difficulty in improving their CSU symptoms even under OCS and/or Omalizumab treatment (Supplementary Table 3). During the one-month period from start of the SDB treatment to re-evaluation of UAS7, unintentionally, CSU treatment of all four patients did not change. Thus, SDB treatment appeared to significantly impact the improvement of CSU. It is generally known that the burden on patients with CSU is substantial, and some patients do not respond to any treatment. Therefore, it may be important to evaluate the presence of SDB in patients with uncontrolled CSU, although we could not demonstrate that the improvement in CSU symptoms was due to SDB treatment because we did not include a control group.

All patients in our study used histamine H1 receptor antagonist for CSU treatment, which was shown to cause cognitive and psychomotor impairment.[32] However, the prevalence of the use of doublets or quantitas duplex with histamine H1 receptor antagonist was not significantly different between the symptom-free-to-mild-CSU group and moderate-to-severe CSU group (Table 1). Thus, the dose of histamine H1 receptor antagonist was not associated with the high prevalence of SDB. Though the Japanese guideline recommend up to 2 folds of histamine H1 receptor antagonist dose, the frequency of the patients who used doublets or quantitas duplex with histamine H1 receptor antagonist in moderate-to-severe CSU group in our study were relatively low (only 50%) (Table 1). This may be because of financial burden, lack of mention in the Japanese drug package insert, and adverse effects. Moreover, there were 4 patients who used OCS for their CSU symptom in our study. Although OCS is one of the treatment options for refractory urticaria, OCS is also known to cause obesity as a side effect. Thus, the findings of our study suggest a possibility that OCS should had been avoided for obese CSU patients, because it can result in further weight gain and accompanying worsening of SDB and CSU. Comorbid diseases, such as allergic rhinitis, sinusitis, tonsillar hypertrophy, and bronchial asthma, are also known to affect SDB.[12,33] However, the rate of these comorbid diseases did not significantly differ between the symptom-free-to-mild-CSU group and moderate-to-severe CSU group (Table 2).

There were some limitations to this study. The first limitation is the risk of missing patients with SDB. We used an OCST to evaluate all recruited patients, although PSG is essential for accurate SDB diagnosis. The OCST cannot accurately measure sleep time because it does not contain an electroencephalogram. Therefore, the pAHI calculated in this study may underestimate the AHI value, resulted in missing patients with SDB. Second, we did not measure biomarkers, such as oxidant status, thrombin, and D-dimers. Various pathways, such as the oxidative stress and coagulation system pathways, are thought to affect both SDB and CSU. Therefore, biomarker evaluation in a randomized controlled study is needed to confirm our results.

Conclusion

In conclusion, SDB severity is correlated with CSU severity independently of BMI. Moreover, CSU symptoms could be improved by the treatment of SDB. Physicians may have to pay more attention to comorbid SDB when treating patients with CSU. Further studies are required to confirm these results.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2021.08.001.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

KN, KW, and YF designed the study, wrote the manuscript, and performed statistical analysis. KS, MI, YH, YN, AM, KR, HH, and HO contributed to data collection. KS, YK, and MT supervised the study. All authors read and approved the final manuscript.

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