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Published in:
World Allergy Organization Journal

DOI:
10.1016/j.waojou.2021.100577

Publication date:
2021

Document version
Publisher's PDF, also known as Version of record

Cherrez-Ojeda et al. World Allergy Organization Journal (2021) 14:100577
http://doi.org/10.1016/j.waojou.2021.100577

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

"Chronic urticaria and obstructive sleep apnea: Is there a significant association?"

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ABSTRACT

Background: Few studies have explored the association between obstructive sleep apnea (OSA) and chronic urticaria (CU). Our study aims to fill this gap by determining the frequency of the risk categories for OSA and how they might correlate with the specific CU patient reported outcome measures urticaria activity score (UAS7), urticaria control test (UCT) and CU quality of life questionnaire (CU-Q2oL).

Methods: We conducted a cross-sectional study involving a cohort of 171 Latin American CU patients. Descriptive statistics were used to determine frequency and proportions for demographic and clinical variables, while a chi-squared test for association between STOP-Bang OSA questionnaire categories and both UAS7 and UCT categories was performed to analyze how such variables interact. To further assess the strength of the correlation a Cramer's V coefficient was reported. Finally, a Kendall-Tau b correlation coefficient was performed to measure the correlation between the STOP-Bang score and other independent continuous variables.

Results: The average STOP-Bang score was 2.5, with 24% and 21% of patients falling into the intermediate and high-risk category for moderate-to-severe OSA, respectively. There was a strong statistically significant association (Cramer's $V = 0.263$; $p = .000$) between UAS-7 categories and STOP-Bang risk categories. A similar pattern of strong significant association (Cramer's $V = .269$; $p = .002$) was observed between UCT categories and STOP-Bang risk categories. A weak positive correlation between the STOP-Bang score and the CU-Q2oL average score ($\tau_b = 0.188$, $p = .001$) was identified. Overall, 72.5% patients reported limitations with respect to sleep in a varied degree according to the CU-Q2oL.

Conclusions: Our results suggest that a considerable proportion of patients with CU are at intermediate to high risk for OSA. Higher disease activity, poor CU control, and worse quality of life were all found to be associated with an increased risk. Additional studies are needed to determine the exact link between these conditions, and to determine whether screening and treatment for OSA might benefit patients with CU.

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Full list of author information is available at the end of the article https://doi.org/10.1016/j.waojou.2021.100577

http://doi.org/10.1016/j.waojou.2021.100577

Received 5 April 2021; Received in revised from 7 June 2021; Accepted 3 August 2021
Online publication date 24 August 2021

Keywords: Chronic urticaria, Quality of life, Sleep apnea

INTRODUCTION

Chronic urticaria (CU) is a common and recurrent skin disorder characterized by the development of hives, angioedema or both. It has been divided into 2 types: chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU).[1,2] Chronic urticaria commonly affects individuals between 20 and 40 years old and can highly impact their quality of life (QOL), mental health, and ability to perform daily tasks.[3,4] These limitations can severely hinder the productivity of CU patients at work that combined with direct health care costs to manage this condition, represents a significant individualized and societal economic burden.[5]

Physical signs and symptoms of CU highly affect a patient's QOL, in particular the sleep cycle, which ultimately may reduce their energy levels.[6,7] Among the sleep disorders that patients frequently report are nocturnal awakenings and difficulty with sleep initiation.[7] Although patients may describe pruritus as one of the most bothersome symptoms, particularly during nighttime, some studies have found that urticarial itching may not be solely responsible for the sleep disturbances observed, and other physiologic mechanisms such as disruption of the skin thermoregulatory function might be involved.[8–10] Despite the negative impact that sleep disorders might have on QOL, a previous internet-based survey found that roughly half of respondents considered the sleep disturbances caused by CU remained inadequately addressed.[11] Another study by Perkowska and colleagues reported that around 25% of participants with CSU had sleep related breathing disorders, a higher rate compared to the general population.[12] Interestingly, when compared to another dermatologic disease, a higher proportion of CU patients reported sleep difficulties compared to psoriasis patients.[3]

Despite the wide-ranging spectrum that sleep-related breathing disorders represent, few studies have explored the association between obstructive sleep apnea (OSA) and CU.[12,13] For instance, a previous study found that 40% of CU patients had OSA assessed through polysomnography, a rate which appears higher than reported for the general population.[14] It is still unclear whether CU increases the risk for developing OSA, or the latter increases the risk for CU.[13] There are many unanswered questions including what the risk is for OSA among CU patients and its influence on CU disease severity and control. Thus, this study aims to expand the current knowledge on OSA and CU by determining in a sample cohort of Latin American CU patients, the frequency of risk categories for undiagnosed OSA and how they might correlate with CU clinical and patient reported outcomes.

METHODS

Study design and conduct

This is a cross-sectional study involving 171 Latin American patients diagnosed with CU according to the International guidelines that were serially enrolled.[2] Patient demographics and clinical characteristics were reported. Validated patient reported outcome measurements (PROM) for CU were used to assess disease activity over seven days (UAS7), control (UCT) and QOL (CUQoL). The risk for moderate-to-severe OSA was assessed using the STOP-Bang validated questionnaire. To be included in this study patients were required to be at least 18 years old and have an accurate CU diagnosis (development of wheals, angioedema, or both for more than 6 weeks). Patients with psychiatric conditions, language impairment, intellectual disability, or those who had difficulty in completing the questionnaires were excluded.

Ethical considerations

This study was approved by the ethics committee Comité de ética e Investigación en Seres Humanos (HCK-CEISH-19-0059). All patients were

informed of the study aims and completed an informed consent.

Procedure

Screening of patients for obstructive sleep apnea (OSA)

Patients were screened for OSA by use of the STOP-Bang questionnaire. This instrument was originally designed to screen surgical patients preoperatively for OSA. It has since been used in non-surgical patients.[15,16] The "STOP" portion of the questionnaire assesses with 4 questions, a) snoring, b) tiredness during daytime, c) observed apnea, and d) high blood pressure. The "Bang" part screens for a) a BMI $\geq$35, b) age $\geq$50, c) neck circumference $>$40 cm and d) male gender.[15]

The STOP-Bang questionnaire is a useful and highly sensitive screening tool for OSA of all levels of severity. In contrast, its specificity is 56%, 43%, and 37% for predicting mild, moderate-severe, and severe OSA, respectively, thus producing in many cases false-positives.[15–17] Given that this study did not confirm OSA diagnosis through polysomnography, we used the two-step approach proposed by Chung and coworkers to increase the STOP-Bang questionnaire specificity.[18] To this end, we first used the standard method, which sets 3 risk categories: low risk (STOP-Bang = 0–2), intermediate risk (STOP-Bang = 3–4) and high risk (STOP-Bang = 5–8). We then reclassified intermediate risk patients as high-risk patients, if they had 2 positive items from the 4 STOP questions plus being male or having a BMI $>$35 kg/m2.

Description of chronic urticaria patient reported outcome measurement questionnaires

The UAS7 categorizes CSU patients for disease activity based on wheal (maximum daily score of 3) and pruritus (maximum daily score of 3) severity each day (maximum daily score 6) over seven days (maximum weekly score 42). Chronic urticaria severity is divided[2] into 5 groups: Itch/hive-free urticaria (0), well-controlled (1–6), mild (7–15), moderate (16–27) and severe (28–42).[19]

The UCT asks 4 questions where each answer is rated on a four-point scale,[20,21] with a total score ranging from 0 (poor control) to 16 (well controlled). The total UCT score was categorized into poorly controlled urticaria (0–11) and well-controlled urticaria (12–16) for the purpose of this study.

The chronic urticaria QOL questionnaire (CU-Q2oL) is a disease specific QOL instrument that asks 23 questions each answered on a scale of 1–5 grouped into 6 categories: itch (2 questions), swelling (2 questions), activities (6 questions), sleep (5 questions), limitations (3 questions), and looks (5 questions).[22] The total score ranges from 0 (good QOL) to 100 (worst QOL).

Statistical analyses

This study applied descriptive statistics to determine frequency and proportions for demographic (gender) and clinical variables (urticaria type, presence/absence of angioedema, comorbidities), as well as mean and SD for age, years with CU, years undergoing CU treatment, and scores for each questionnaire (UAS7, UCT, CU-Q2oL and STOP-Bang).

A Chi-square test for association between STOP-Bang categories and both UAS7 and UCT categories was performed to determine the statistical significance of their interaction. To further determine how strongly 2 categorical variables were associated, a Cramer'sV coefficient (ϕ_c) was reported.

Furthermore, to measure the correlation between the STOP-Bang score and other independent continuous variables such as UAS7, CU-Q2oL and UCT scores, as well as years with CU and years undergoing CU treatment, a Kendall-Tau b correlation coefficient was reported. All data were analyzed using SPSS, version 24.0 software (SPSS Inc., Chicago, IL, USA). For all tests, a p-value $<$ .05 was considered statistically significant.

RESULTS

Patient population

The studied population comprised a cohort of 171 patients from Latin America (Argentina, Brazil, Mexico, Colombia, Peru, and Ecuador) with a gender distribution of 68.4% female and 31.6%

Characteristics	Patients (n = 171) n (%)
Gender	
Male	31.6 (54)
Female	68.4 (117)
Country	
Argentina	31.0 (53)
Brazil	11.1 (19)
Colombia	7.6 (13)
Ecuador	14.0 (24)
Mexico	28.7 (49)
Peru	7.6 (13)
Urticaria type	
CSU	76.0 (130)
CIndU	11.7 (20)
Both (CSU & CIndU)	12.3 (21)
Angioedema	52.0 (89)
Comorbidities	
Cardiovascular disease	22.8 (39)
Autoimmune disease	20.5 (35)
Malignant disease	4.1 (7)
Allergic disease	53.2 (91)
Mental disorder	37.4 (64)
UAS-7 category	
Itch/hive-free urticaria	5.3 (9)
Well-controlled urticaria	3.5 (6)
Mild urticaria	14.0 (24)
Moderate urticaria	19.9 (34)
Severe urticaria	35.1 (60)
UCT category	
Controlled urticaria	19.9 (34)
Non-controlled urticaria	80.1 (137)
Risk of moderate-severe OSA	
Low risk	55.6 (95)
Intermediate risk	24.0 (41)
High risk	20.5 (35)

Table 1. Demographic and clinical information of surveyed population *Notes: CSU, chronic spontaneous urticaria; CIndU, chronic inducible urticaria; UAS-7, urticaria activity score over 7 days; UCT, urticaria control test; OSA, obstructive sleep apnea.*

male, whose mean age and years with CU were 41.9 and 3.8 years, respectively. Among all patients, 76.0% had CSU, 11.7% had CIndU, and 12.3% had an overlap of both (Table 1). As assessed by the UCT, only 19.9% of patients had well-controlled CU with a mean score of 7.9 (Table 2). With respect to QOL, the total mean CU-Q2oL score was 31.2, with "itching/embarrassment" (37.9) and "sleep" (37.2) being the domains most frequently affected followed closely by "mental status" (33.7).

Characteristics	Mean (SD)
Age	41.9 (14.4)
Years with urticaria	3.8 (3.9)
Years under urticaria treatment	3.0 (2.9)
UAS-7 score	22.8 (13.1)
UCT score	7.9 (4.0)
CU-Q2oL mean score	31.2 (23.6)
Functioning	25.2 (22.8)
Sleep	37.2 (28.7)
Itching/Embarrassment	37.9 (26.0)
Mental status	33.7 (31.7)
Swelling/eating	29.2 (41.0)
Limits looks	24.0 (27.0)
STOP-BANG	2.46 (1.7)

Table 2. Mean UAS-7, UCT, CU-Q2oL axes and STOP-BANG scores of surveyed population *Notes: UAS-7, urticaria activity score over 7 days; UCT, urticaria control test; CU-Q2oL, chronic urticaria quality of life.*

Four of ten patients with CU have a high or intermediate risk of OSA

The average STOP-Bang score was 2.5, with 24% and 21% of patients falling into the intermediate and high-risk category for moderate-to-severe OSA. The proportion of patients in each STOP-Bang score category with CU that is poorly or well controlled, is summarized in Fig. 1.

Increased risk for OSA, in patients with CSU, is linked to high urticaria activity and poor disease control

There was a strong statistically significant association (Cramer's V = 0.263; p = .000) between UAS-7 categories and STOP-Bang risk categories. More than half of the subjects within the "moderate-severe" CU category presented with an intermediate or high risk for moderate-to-severe OSA compared to less than 20% who were "itch-free/well-controlled" or in the "mild" urticaria group with an intermediate or high risk for OSA (Fig. 2; Table 3). A similar pattern of a strong significant

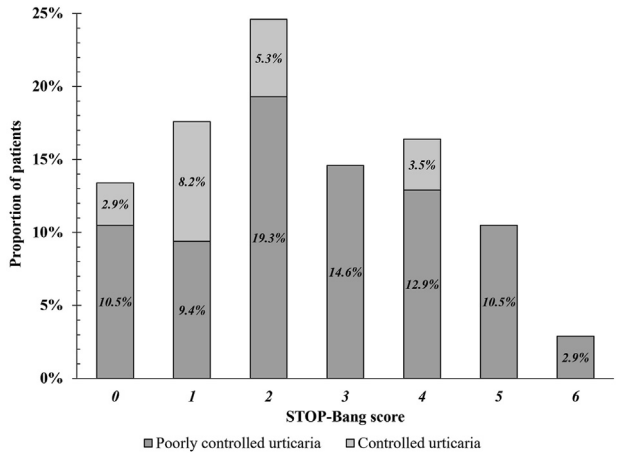

Fig. 1 Proportion of patients according to the STOP-Bang score group given their UCT category

association (Cramer's V = 0.269; p = .002) was observed between UCT categories and STOP-Bang risk categories, with most controlled CU patients (82.4%) having a low risk for moderate-to-severe OSA whereas most participants in the non-controlled CU group were categorized into the intermediate (27.7) and high (23.4) risk categories (Table 3).

A worsening quality of life is correlated with a higher STOP-Bang score

A weak positive correlation between the STOP-Bang score and the CU-Q2oL average score ($\tau_b = 0.188$, p = .001) was identified (Table 4). This was also observed for "mental status" ($\tau_b = 0.210$, p = .000), "swelling/eating" ($\tau_b = 0.201$, p = .001), "sleep" ($\tau_b = 0.178$, p = .002) and "functioning" ($\tau_b = 0.160$, p = .005).

Seven out of ten patients report having sleep problems according to the CU-Q2oL

From the total cohort, 72.5% of patients reported sleep limitations to a variable degree (Q7-CU-Q2oL). Specifically, 67.3% reported having problems falling sleep (Q11-CU-Q2oL), 73.3% reported awakening from sleep (Q12-CU-Q2oL), and 72.5% described feeling fatigued during the daytime due to poor quality of sleep (Q13-CU-Q2oL). As a result, 6 of 10 patients reported difficulty concentrating (59.1%; Q14-CU-Q2oL), which might affect their productivity at work (63.2%; Q5-CU-Q2oL), as well as contributing to physical activity (59.6%; Q6-CU-Q2oL) limitations and social interactions (56.1%; Q9-CU-Q2oL).

DISCUSSION

Impaired sleep in CU patients is commonly attributed to the level of their disease control with itch-related insomnia causing difficulty in falling or remaining asleep.[23] However, recent studies suggest that CU patients are at an increased risk for developing sleep-related breathing disorders compared to the general population, including OSA.[12-14] For example, a previous article found that 41.9% of CU patients had OSA confirmed by polysomnography that was mostly considered mild. In our study, we found that roughly 4 out of 10 CU patients had a high to intermediate risk for OSA based on screening with the STOP-Bang questionnaire. This observation is consistent with the existing literature and underscores the importance of screening CU patients for sleep-related breathing disorders.

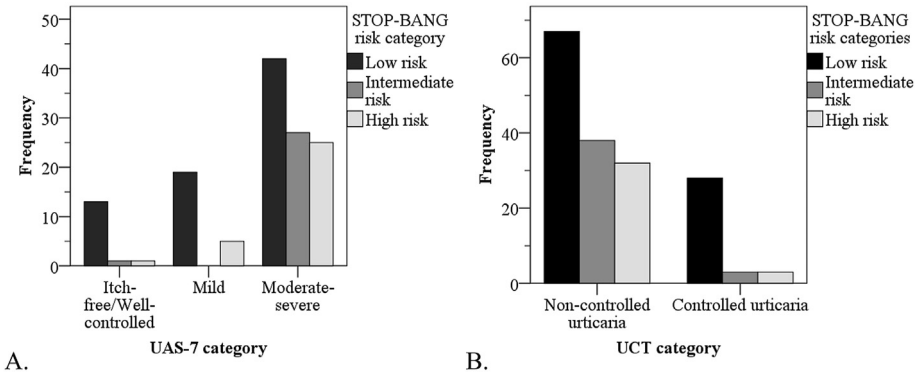

Fig. 2 (A) Proportion of participants that belong to each STOP-Bang risk category by UAS-7 category group. (B) Proportion of participants that belong to each STOP-Bang risk category by UCT category group. UAS-7, urticaria activity score over 7 days; UCT, urticaria control test

	Low risk (n = 95)	Intermediate risk (n = 41)	High risk (n = 35)	Cramer's V	p value	Total
UAS-7						
Itch-free/Well-controlled urticaria	86.7 (13)	6.7 (1)	6.7 (1)	.263	.000[a]	11.3 (15)
Mild urticaria	79.2 (19)	0.0 (0)	20.8 (5)			18 (24)
Moderate-severe urticaria	44.7 (42)	28.7 (27)	26.6 (25)			70.7 (94)
UCT						
Controlled urticaria	82.4 (28)	8.8 (3)	8.8 (3)	.269	.002	19.9 (34)
Non-controlled urticaria	48.9 (67)	27.7 (38)	23.4 (32)			80.1 (137)

Table-3. Associations between UAS-7 and UCT categories versus STOP-BANG risk categories of the surveyed population [a] *Fisher exact test performed. Chi-squared results might have been invalid due to assumption violation (more than 20% of cells on this subtable have expected cell counts less than 5)*

Problems with quality of sleep, even transient sleep loss, can impair cognitive performance and judgement, and lead to an increased risk for other comorbidities including cardiovascular disease.[24] Patients with CU commonly report pruritus as one of the most bothersome symptoms, especially at night when it intensifies, making falling asleep challenging and causing night-time awakenings.[8,25] In our study, we found a statistically significant association between the UCT and STOP-Bang risk categories, in which patients with uncontrolled CU had an increased risk for OSA. Previous studies have found that the level of control of the patient's CSU disease state has a direct and significant impact on their sleep interference score, which in turn leads to chronic fatigue in daily life.[23] In fact, disturbed sleep in CU has been found to be a predictor of fatigue (OR: 8.35; $p = .001$).[26] Although currently the significance of this relationship is not completely understood, worse disease control of other chronic disease like asthma has also been associated with to an increased risk for OSA.[27]

	t_b	p value
Age	.223	.000
Years with urticaria	.017	.767
Years under urticaria treatment	.043	.442
UAS-7 score	.223	.000
UCT score	-.186	.001
CU-Q2oL mean score	.188	.001
Functioning	.160	.005
Sleep	.178	.002
Itching/Embarrassment	.093	.104
Mental status	.210	.000
Swelling/eating	.201	.001
Limits looks	.091	.131

Table-4. Correlations between the selected variables and STOP-BANG scores of the surveyed population *Notes: t_b, Kendall's tau b correlation coefficient; UAS-7, urticaria activity score over 7 days; UCT, urticaria control test; CU-Q2oL, chronic urticaria quality of life.*

Previous studies have found a link between sleep impairment and urticaria activity scores (UAS7), where impairment was increased during times of higher disease activity.[9,22] Our results found a strong association between UAS7 and STOP-Bang risk categories with patients in the "moderate to severe" CU groups having an intermediate to high risk for OSA. This interesting finding is consistent with a previous study that found a positive correlation between the apnea/hypopnea index and UAS7 scores ($r = 0.537$, $P = .002$).[14]

Chronic urticaria can significantly affect QOL, with the degree of impairment comparable to coronary artery disease and significantly greater than other dermatological diseases.[25] In our study, we found that a worse QOL correlated with higher STOP-Bang scores. Furthermore, 7 out of 10

patients reported having sleep problems according to the QOL questionnaire. This latter finding has also been described in a previous study, where roughly 50% of patients with CU complained of sleeping problems and 80% reported significant fatigue and lack of concentration in the daytime according based on the CU-Q2oL.[12] The pruritus that CU patients experience is caused by excessive release of histamine from mast cells and basophils, leading to a decreased QOL that may be in part responsible for many of the sleep-related abnormalities seen in these patients. Histamine has a pleiotropic role as a neurotransmitter and in patients with CU it stimulates venular endothelial cell H-1 receptors leading to vasodilation, increased vascular permeability and stimulation of type C sensory fibers to mediate pruritus and secrete substance P.[28] Whether histamine release in CU contributes to the dysregulation and maintenance of wakefulness, and this in turn is associated to an increased risk for OSA remains to be determined.

The results of a recent population-based study suggests that sleep apnea may contribute to the development of CSU. This retrospective matched-cohort study included more than 100,000 patients with new-onset sleeping disorders including sleep apnea as well as more than 100,000 randomly selected controls. Each patient was monitored for 10 years for the onset of CSU. The risk of CSU was significantly higher in the patients with sleep apnea.[13] However, this study design was not able to determine whether CU or OSA were causative of the other and the authors concluded that there is a need for additional studies as insufficient sleep has a significant consequence on both physical and mental health and increases the risk for chronic diseases.[29] Furthermore, sleep loss dramatically affects work performance, daily functioning, leisure activities which causes or aggravates downstream chronic diseases and lowers life expectancy.[30,31]

Strengths and limitations

Although we included participants of different age, gender, and from different geographical regions in Latin America, there are several limitations worth mentioning. The study design was cross-sectional; therefore, cause-and-effect relationships could not be detected. Additionally, participants were knowledgeable about the purpose of this study in advance which might have biased some of their answers. Since we used the validated version of the STOP-Bang questionnaire, which is a screening tool, a diagnosis of OSA could not be confirmed as performing an overnight laboratory polysomnography was not possible due to cost limitations. Despite these potential limitations, this study is among the first to investigate the risk of OSA in CU patients from Latin American countries using validated PROM instruments.

Conclusion

Our results suggest that a considerable proportion of CU patients are at intermediate to high risk for having OSA according to the STOP-Bang screening tool. Higher disease activity, poor CU control, and worse QOL were all associated with a statistically significant increased risk for OSA. In addition, most patients also reported sleep problems in their QOL questionnaire responses. Additional studies are needed to further investigate the observed relationship between CU and OSA, the underlying pathomechanism(s) of this interaction and whether routine screening and treatment of CU patients for OSA might improve clinical outcomes.

Abbreviations

Obstructive sleep apnea (OSA); chronic urticaria (CU); urticaria activity score (UAS7); urticaria control test (UCT); chronic urticaria quality of life questionnaire (CU-Q2oL); chronic spontaneous urticaria (CSU); chronic inducible urticaria (CIndU); quality of life (QOL); patient reported outcome measurements (PROM).

Funding statement

This study was partially supported by an unrestricted grant from Universidad Espíritu Santo. The sponsor had no role in the design of the study or in the collection, analysis, and interpretation of data.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

All authors declare that they have made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; drafted the article or reviewed it critically for important intellectual

content; and given final approval of the version to be published.

Ethics statement

This study was approved by the ethics committee Comité de ética e Investigación en Seres Humanos (HCK-CEISH-19-0059). All patients were informed of the study aims and completed an informed consent.

Declaration of competing interest

Authors declare no conflicts of interest in relation to this work.

Acknowledgements

The authors acknowledge the guidance and knowledge imparted by the MECOR Program for this study, especially from Sonia Buist MD, Ana Menezes MD, and Juliana Ferreira M.D. Special thanks to all members of Respiralab Research Group. Finally, we want to express our gratitude to Universidad Espiritu Santo for their continuous support.

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