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Impact of severity of CSU on sleep, anxiety and depressive symptoms in adults

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Abstract:

Background and aim: *Chronic Spontaneous urticaria (CSU) impairs the quality of life of patients and causes many psychiatric comorbidities, the affection of sleep quality and other sleep parameters were not previously investigated thoroughly .The aim of this study was to assess the impact of severity of CSU on sleep, anxiety and depression in adult patients.*

Patients and methods: *64 cases of CSU and 50 healthy control were enrolled; Urticaria severity was assessed by using Urticaria Activity score 7 (UAS-7), sleep assessment by Pittsburgh Sleep Quality Index (PSQI), anxiety by using the Generalized Anxiety Disorder 7 (GAD-7) and depressing by using the Patient Health Questionnaire 9 (PHQ-9).*

Results: *the study found a significant increase in PSQI, GAD-7 and PHQ-9 in patients with CSU then the control subjects, with significant increase in the prevalence of poor sleep, anxiety diagnosis and depression diagnosis in CSU than the control group. With a significant positive correlation between UAS-7 and all PSQI, GAD-7 and PHQ-9.*

Conclusion: *a significant increase in poor sleep, anxiety and depression in patients with CSU were proved, this study recommend the screening of psychiatric illnesses in examining patients with CSU, also the need of controlling the aspects of psychiatric disorders during the management of CSU through multidisciplinary approaches.*

Key words: Chronic Spontaneous urticaria, sleep disorders, anxiety, depression, Urticaria Activity score 7, Pittsburgh Sleep Quality Index, Generalized Anxiety Disorder 7 and Patient Health Questionnaire 9.

INTRODUCTION:

Chronic Spontaneous urticaria (CSU) known to impair the quality of life of the patients in many parameters including psychiatric health affections[1]-[2].

The itching itself increase the psychiatric symptoms especially depression[3], and the depression on the other hand increase the perception of pruritus in skin disorders as psoriasis, atopic dermatitis, and CSU[4].

Although a few studies have investigated the relations between CSU, anxiety and depression; no study had devoted to examine the direct relation between the CSU and sleep disorders and its variable aspects.

Aim of this study: to assess the effect of CSU severity on sleep disorder, anxiety and depressive symptoms in adults (16-65 y)

METHODS:

The design of the study was case-control, performed on the patients attended the outpatient clinic of Allergy and clinical

[1] Staubach P, Eckhardt-Henn A, Dechene M, Vonend A, Metz M, Magerl M, Breuer P, Maurer M. Quality of life in patients with chronic urticaria is differentially impaired and determined by psychiatric comorbidity. British Journal of Dermatology. 2006 Feb 1;154(2):294-8.

[2] O'donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. British Journal of Dermatology. 1997 Feb 1;136(2):197-201.

[3] Lsheehan-dare RA, Henderson MJ, A COTTERILL J. Anxiety and depression in patients with chronic urticaria and generalized pruritus. British journal of dermatology. 1990 Dec 1;123(6):769-74.

[4] Gupta MA, Gupta AK. Depression modulates pruritus perception: a study of pruritus in psoriasis, atopic dermatitis and chronic idiopathic urticaria. Annals of the New York Academy of Sciences. 1999 Oct 1;885(1):394-5.

immunology, Ain Shams University Hospital in the period from September to December 2016.

Patients with CSU; diagnose by the occurrence of spontaneous wheals +/- angioedema for more than 6 weeks after exclusion of other systemic diseases (e.g. Cardiac disease, hypertension, thyroid disorders, renal diseases, liver impairment or chronic viral hepatitis, smoking, other dermatological Diseases, etc...), also patients reported using antihistaminic drugs or other drugs to control the symptoms of urticaria in the last month were excluded.

Assessment of Urticaria severity:

By the Urticaria Activity score 7 (UAS-7) which record the score of urticaria over the last 7 days for number of hives each day (if no hives so score= 0, if hives <20/24 hours score = 1, hives 20 to 50/24 hours score =2 and if hives >50 or large confluent area score =3),and the score of itching as following (no itching so score=0, mild not annoying score=1 , mild annoying but not interfere with daily activity score=2 ,and if sever interfering with daily activity score=3).

With daily score ranging from 0 to 6 and the weekly score (UAS-7) ranging for 0-42[5].

Assessment of sleep disorders:

Subjective sleep measures obtained by The Pittsburgh Sleep Quality Index (PSQI),which measures sleep duration (score from 0 to 3 ,o is better and 3 is worst), sleep disturbance (score from 0 to 3 ,o is better and 3 is worst), sleep latency (score from 0 to 3 ,o is better and 3 is worst), day dysfunction due to sleepiness (score from 0 to 3 ,o is better and 3 is worst), sleep efficiency (score from 0 to 3 ,o is better and 3 is worst), overall

[5] Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, Church MK, Ensina LF, Giménez-Arnau A, Godse K, Goncalo M. The EAACI/GA2LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy. 2014 Jul 1;69(7):868-87.

sleep quality (score from 0 to 3 ,o is better and 3 is worst), need medication to sleep (score from 0 to 3 ,o is better and 3 is worst) calculating the total score of by summation of those 7 items to get score ranging from 0 which is better and 21 is the worst ; the overall score of 5 or less associated with good sleep quality and the score of more than 5 associated with poor sleep quality[6].

Assessment of anxiety:

Using the Generalized Anxiety Disorder 7 (GAD-7); which assess over the last 2 weeks, how often has the patient been bothered by any of the following problems.1) Feeling nervous, anxious or on edge,2) Not being able to stop or control worrying,3) Worrying too much about different things,4) Trouble relaxing,5) Being so restless that it is hard to sit still,6) Becoming easily annoyed or irritable,7) Feeling afraid as if something awful might happen. Each item get a score from 0 to 3 (0= not at all,1=several days,2= more than half the days and 3 = nearly all the days);the summation of all items will give each patient a score from 0 to 21.[7]

GAD-7 is a self-assessment score developed by Spitzer et al.[7] To be used in the primary care facilities as screening method and to evaluate the severity of Generalize Anxiety Disorder (GAD) with cut off value of 10 with 89% sensitivity and 82% specificity[8].

Assessment of Depression:

By using the Patient Health Questionnaire 9 (PHQ-9); witch is a self-reported tool to diagnose and asses the severity of

[6] Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry research. 1989 May 31;28(2):193-213.

[7] Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Archives of internal medicine. 2006 May 22;166(10):1092-7.

[8] Rutter LA, Brown TA. Psychometric Properties of the Generalized Anxiety Disorder Scale-7 (GAD-7) in Outpatients with Anxiety and Mood Disorders. Journal of Psychopathology and Behavioral Assessment. 2016:1-7.

depression in primary care settings; the English form was confirmed to be feasible [9]and also an Arabic form was used with good validation[10].

This include 9 questions to be rated by the patients as following (0= not at all,1=several days,2= more than half the days and 3 = nearly all the days); the questions was based on the criteria from the Diagnostic and Statistical Manual of Mental disorders, Fourth Edition Text Revision (DSM-IV-TR)[11], the items were 1) Little interest or pleasure in doing things,2) Feeling down, depressed, or hopeless ,3) Trouble falling or staying asleep, or sleeping too much ,4) Feeling tired or having little energy ,5) Poor appetite or overeating ,6) Feeling bad about yourself, or that you are a failure or have let yourself or your family down ,7) Trouble concentrating on things, such as reading the newspaper or watching television ,8) Moving or speaking so slowly that other people could have noticed, or the opposite, being so fidgety or restless that you have been moving around a lot more than usual ,9) (Thoughts that you would be better off dead or hurting yourself in some way. The items questioned about the last 2 weeks and the total score ranging from 0 to 27 after the summation of the scores of the 9 items[9].

A control of healthy individuals matching the study group sociodemographically were screened for GAD-7, PHQ-9 and PSIQ.

Statistical methods:

Parametric data were expressed as means ±SDs and non-parametric data were expressed as number and percentage or mean and interquartile range. Data were compared by

[9] Spitzer RL, Kroenke K, Williams JB, Patient Health Questionnaire Primary Care Study Group. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Jama. 1999 Nov 10;282(18):1737-44.

[10] Becker S, Al Zaid K, Al Faris E. Screening for somatization and depression in Saudi Arabia: a validation study of the PHQ in primary care. The International Journal of Psychiatry in Medicine. 2002 Sep;32(3):271-83.

[11] Association AP. Diagnostic and statistical manual of mental disorders. text rev.). 2000.

Student's t-test for parametric data, chi-square test and Mann-Whitney T test for non-parametric data, Pearson correlation coefficient for correlation between two variables.

RESULTS:

This case-control study included 64 cases of CSU and 50 healthy control, the case and control subjects were matched for age and sex as described in **Table 1**.

Table 1: the age and gender of both case and control subjects

	CSU	CONTROL	Significance
Age: mean (SD)	32.4 (12.6)	31.8 (12)	P 0.81 §
Gender: male/female	27 / 38	21 /29	X^2= 0.0025. p= 0.960317 §

§ = non-significant statistical difference
Comparing the age by student t-test
Comparing the gender by Chi-square test

The median of UAS-7 of the cases was 16.5 with Inter-Quartile Range (IQR) of (3-18).

Table 2 demonstrates that: the total scores of PSQI for CSU patients were higher than that of the control (P=0.00022) and the prevalence of poor sleep quality (total PSQI more than 5) in CSU patients was 48.8% versus 18% for the control subjects with in-between difference of 30.8% (P=0 .001271).

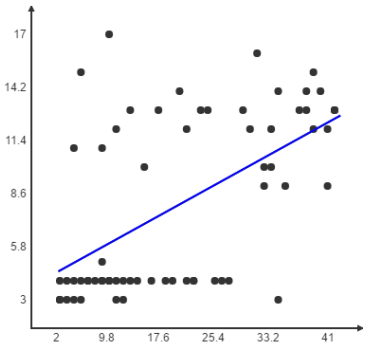
Table 2: Comparison between CSU and healthy control regard: values of total PSQI and number of patients diagnosed to have poor sleep quality.

	CSU	Control	Significance
PSQI total score : Median (IQR)	4.5(4-13)	4(3-4)	The Z-Score is 3.69463¶ P=0.00022 *
Poor sleep quality =total PSQI more than 5: no. (%)	31 (48.4%)	9 (18%)	X^2= 7.2589 ¶¶ P=0 .001271*

*statistically significant difference
¶ Comparison by Mann-Whitney.
¶¶ Comparison by chi square test

Furthermore there was a significant positive correlation between UAS-7 and total scores of PSQI (Pearson correlation coefficient; r= 0.564 and p =0.00001), the linear regression is shown in **Figure 1**.

Figure 1: Simple Linear regression between UAS-7 and total scores of PSQI.



UAS-7 presented as X axis, PSQI presented at Y axis

The author found a significant differences in-between cases and control as regards sleep duration (PSQIDURAT), sleep disturbance (PSQIDISTB), sleep latency (PSQILATEN) and day dysfunction due to sleepiness (PSQIDAYDYS) p value (< .00001, 0.00152, 0.00452 and 0 .04136 respectively) . However a higher scores but non-significant differences were found in comparing sleep efficiency (PSQIHSE), over all sleep quality (PSQISLPQUAL) and need medication to sleep (PSQIMEDS); **Table 3** .

Table 3: Comparison between CSU patients and control regarding individual PSQI parameters:

	CU median (IQR)	Control median (IQR)	value of U	The Z-Score	The p-value
PSQIDURAT	2(2-2)	1(1-2)	713.5	5.05942.	< .00001*
PSQIDISTB	1(1-2)	1(0-1)	1044	3.17213	0.00152*
PSQILATEN	0(0-2)	0(0-0)	1102.5	2.83807	0.00452*
PSQIDAYDYS	1(0-2)	0(0-1)	1242	2.04147	0 .04136*
PSQIHSE	1(0-2)	1(0-1)	1403	1.12209	0.26272¶
PSQISLPQUA	1(1-2.75)	1(1-1)	1313.5	1.63318	0.1031¶
PSQIMEDS	0(0-0)	0(0-00	1517	0.47111	0.63836¶

*=significant difference, ¶ =non-significant difference
The comparison performed via Mann-Whitney T test.

There were a significant differences between the cases and control subjects regarding the total GAD-7 score (p=0.02088), and the percentage of individuals diagnosed to have anxiety (GAD-7 score of 10 or more) 39.06% for CSU patients and 8% for healthy control individuals (p= P=0.007); **Table 4**.

Table 4: Comparison between CSU and healthy control regard: values of total GAD-7 and number of patients diagnosed to have diagnosis of Anxiety.

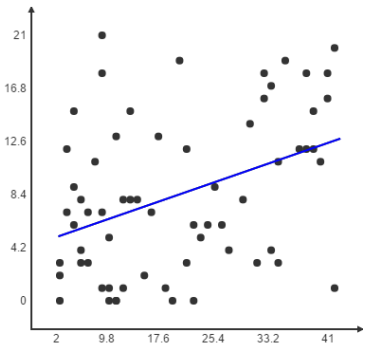
	CSU	Control	Significance
GAD -7 total score	7.5(3-13)	4(1-8)	The Z-Score is 2.307¶ P=0.02088*
Anxiety identified by GAD-7 score of 10 or more	25(39.06%)	8(16%)	X^2= 7.2589¶¶ P=0.007055*
PHQ -9 total score	6(2-11.5)	3.5(1.75-7.25)	The Z-Score is 1.52182¶ The p-value is 0.12852§
Depression identified by PHQ -9 score of 10 or more	18(28.125%)	6(16%)	X^2= 10.3837¶¶ P=0 .001271

*statistically significant difference.
§ Non- significant difference.
¶ Comparison by Mann-Whitney.
¶¶ Comparison by chi square test

Moreover there was a significant positive correlation between UAS-7 and total scores of GAD-7 (Pearson correlation

coefficient; r= 0.3931and p =0.0013), the linear regression is shown in **Figure 2**.

Figure 2: Simple Linear regression between UAS-7 and total scores of GAD-7.

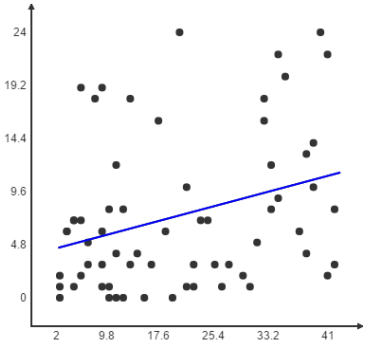


UAS-7 presented as X axis, GAD-7 presented at Y axis

As regarding PHQ-9 total score there was a difference between the CSU patients and the control which was not statistically different (p=0.12852), however when comparing the number of individuals who identified to have depression (PHQ -9 score of 10 or more); the significance was demonstrated 18 of the CSU patients (28.125%) versus 6 individuals in the control (16%) with p= 0 .001271; **Table 4**.

Also the correlation between the UAS-7 and PHQ-9 was significant (Pearson correlation coefficient; r= 0.012and p =0.0013), the linear regression is shown in **Figure 3**.

Figure 3: Simple Linear regression between UAS-7 and total scores of PHQ-9.



UAS-7 presented as X axis, PHQ-9 presented at Y axis

DISCUSSION:

Sleep and skin diseases interacting in many ways; skin itself has a role in thermoregulation during sleep and the circadian rhythm affects the levels of anti-inflammatory hormones as cortisone during sleep which exacerbate the pruritus and other skin manifestations[12].

Although an observation suggested that the control of CSU symptoms significantly improves sleep; there was no investigations to evaluate directly the effect of CSU severity and its impact on individual different sleep parameters and overall poor sleep quality[13].

The current study found a significant higher overall score of PSQI in CSU patients than the healthy control and a significant increase in the prevalence of poor sleep quality in

[12] Gupta MA, Gupta AK. Sleep-wake disorders and dermatology. Clinics in dermatology. 2013 Feb 28;31(1):118-26.

[13] Gimenéz-Arnau AM, Spector S, Antonova E, Trzaskoma B, Rosén K, Omachi TA, Stull D, Balp MM, Murphy T. Improvement of sleep in patients with chronic idiopathic/spontaneous urticaria treated with omalizumab: results of three randomized, double-blind, placebo-controlled studies. Clinical and Translational Allergy. 2016 Aug 18;6(1):32.

the CSU group, a similar finding was observed during the assessment of the overall quality of life in CSU patients using a questioner of primarily a 37 items from which 4 items were assessing the sleep parameters; Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL). Although there were no healthy control on this study, a significant impact of CSU on sleep through the four questions dedicated to sleep was also detected, with increase in difficulty in falling to sleep, wakening during night and interference with day activity due to lake of sleep[14] which are consistent with the current study.

More ever the current study found a significant positive correlation between urticaria score (UAS-7) and the overall PSQI score denoting that with increasing the symptoms of urticaria there is a corresponding increase in poor sleep; on the other hand Finn et al found the revers correlation indirectly by noticing a linear improvement of sleep with increasing the dose of Fexofenadine in treating CSU patients, in the same study there were significant linear trend in reduction in pruritus score and wheals score also with increasing the dose of Fexofenadine[15].

When comparing the anxiety parameters using GAD-7 score in this study the total GAD-7 score was significantly higher in patients with CSU than the healthy control; Engin et al. also found a similar results by using another anxiety score (Beck Anxiety Inventory) they found the Beck Anxiety Inventory score for the CSU patients 14.28 ± 11.58 compared to score of 3.82 ± 3.11 in the healthy subject ($p = 0.001$)[16].

[14] Baiardini I, Pasquali M, Braido F, Fumagalli F, Guerra L, Compalati E, Braga M, Lombardi C, Fassio O, Canonica GW. A new tool to evaluate the impact of chronic urticaria on quality of life: chronic urticaria quality of life questionnaire (CU-Q2oL). Allergy. 2005 Aug 1;60(8):1073-8.

[15] Finn AF, Kaplan AP, Fretwell R, Qu R, Long J. A double-blind, placebo-controlled trial of fexofenadine HCl in the treatment of chronic idiopathic urticaria. Journal of allergy and clinical immunology. 1999 Nov 30;104(5):1071-8.

[16] Engin B, Uguz F, Yilmaz E, Özdemir M, Mevlitoglu I. The levels of depression, anxiety and quality of life in patients with chronic idiopathic urticaria. Journal of the European Academy of Dermatology and Venereology. 2008 Jan 1;22(1):36-40.

In this study performed on adults the percent of CSU patients diagnosed to have Anxiety by GAD-7 score was higher than the healthy control 39.06 versus 16%; a related finding was observed by Hergüner et al. in children with CSU when they found 48% of children with CSU had anxiety versus 15% only in healthy control (p=0.004)[17].

Although in Engin et al. study there was no significant correlation between the UAS score and the Beck Anxiety Inventory score[16]; in the current study there was a significant correlation between UAS-7 and GAD-7 score it may be contributed to a different methods to measure the Anxiety symptoms, the fact that when Hergüner et al used a third anxiety score (State Trait

Anxiety Inventory for Children) they found a significant correlation between the UAS-7 score and the State Trait Anxiety Inventory for Children (r=0.36, p=0.06)[17].

The current study confirmed a significant increase in both PHQ-9 score and the prevalence of patients who established to have depression in CSU patients than the healthy control, a similar results were also found in several studies on CSU patients[16]-[17]-[18] . It is also found in a data base study that even the occurrence of acute urticaria raise the odds to develop depression in the future[19].

In this study there was a significant correlation between UAS-7 score and PHQ-9 score; in contemporary Hergüner et al found no correlation between UAS-7 and the depression score used in that study (Children's Depression Inventory)[17],also no correlation were found in adults between UAS-7 and the Beck

[17] Hergüner S, Kılıç G, Karakoç S, Tamay Z, Tüzün Ü, Güler N. Levels of depression, anxiety and behavioural problems and frequency of psychiatric disorders in children with chronic idiopathic urticaria. British Journal of Dermatology. 2011 Jun 1;164(6):1342-7.

[18] Hashiro M, Okumura M. Anxiety, depression, psychosomatic symptoms and autonomic nervous function in patients with chronic urticaria. Journal of dermatological science. 1994 Oct 1;8(2):129-35.

[19] Hsieh PY, Chang CY, Chou CC, Lin YR, Chen CY. Urticaria in adolescence increases the risk of developing new-onset depression: A database study. Journal of Acute Medicine. 2014 Sep 30;4(3):120-6.

Depression Inventory score[16]. However our results may be explained by the fact that the using of different scores of depression gives a different correlation results especially that both the two mentioned studies found a significant increase in prevalence of depression in CSU patients than control.

CONCLUSION:

CSU increases sleep disorders and other psychiatric health aspects such as Anxiety and depression, the severity of the CSU symptoms directly related to the psychiatric disorders levels. So this study recommend the screening of psychiatric illnesses in examining patients with CSU, also the need of controlling the aspects of psychiatric disorders during the management of CSU through multidisciplinary approaches.