Dermatology Practical & Conceptual

Impact of Pemphigus on Sleep Quality: A Prospective Observational Single-Center Case-Control Study

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ABSTRACT

Introduction: Pemphigus, an autoimmune disorder, significantly impacts the quality of life for those affected.

Objective: This study examined the sleep quality in patients with pemphigus, a domain for which the existing literature provides limited data without a focused analysis.

Methods: A total of 156 individuals, 52 in the case and 104 in the control group, completed several questionnaires (Pittsburgh Sleep Quality Index [PSQI], General Health Questionnaire-12 [GHQ-12], and ABQOL [Autoimmune Bullous Disease Quality of Life]). Disease severity was evaluated using the Pemphigus disease area index (PDAI index).

Results: The case group exhibited significantly higher levels of psychological distress, reflected in GHQ-12 scores (P = 0.00), and notably poorer sleep quality compared to controls across various parameters (sleep latency [SL], disturbances [SDi], medication [SM], daytime sleep dysfunction [DSD]), and the global PSQI score (GS)] (P = 0.00)). Significant correlations were observed between PDAI scores and sleep duration (SDu) (P = 0.01), SM (P=0.03), SL (P =0.03), and GS (P=0.00). An association was found between the equivalent steroid intake and SDu (P=0.00) as well as GS (P=0.02). No statistically significant correlation emerged between disease duration and PSQI scores. Our findings indicated a correlation between poor sleep quality and cutaneous rather than mucosal manifestations (p=0.01). Pemphigus affects sleep quality. Severe disease showed heightened SDi, correlating with higher steroid doses, and in the chronic phase, the impact seems to have been more influenced by the pro-inflammatory stage of the disease. Patients with cutaneous pemphigus exhibited reduced sleep quality compared to those with oral pemphigus.

Conclusion: Understanding that pemphigus worsens sleep quality can be beneficial for the holistic management of individuals with this condition.

Introduction

The quality of sleep in autoimmune diseases is a growing area of interest in medical research with sleep disturbances being prevalent among patients with autoimmune disorders. As example, patients with multiple sclerosis often experience sleep disturbances like insomnia and restless legs syndrome which may be linked to neurological damage and inflammation significantly impacting the patient's quality of life [1]. In lupus patients, sleep deprivation can exacerbate disease symptoms; sleep fragmentation and altered sleep-stage transitions are common, contributing to increased fatigue and health deterioration [2].

Finally, rheumatoid arthritis is associated with a higher incidence of sleep apnea, where chronic inflammation and pain interfere with sleep, further aggravating daytime fatigue [3].

In dermatology, most studies on sleep quality have been dedicated to psoriasis and atopic dermatitis, and the literature provides very limited data on the relationship between sleep quality and autoimmune blistering diseases [4].

In particular, pemphigus is the autoimmune blistering disease with the greatest clinical impact and, consequently, the most significant influence on patients' quality of life (QoL). This is due to various factors, such as the chronic nature of the disease, its severe impact on sensitive areas like mucous membranes, and the necessity for long-term management Several tools have been developed to standardize the evaluation of disease severity and its influence on QoL. However, there is limited literature available on the sleep quality of individuals affected by pemphigus.

Our primary objective in conducting a prospective observational single-center case-control study was to investigate the impact of pemphigus on this topic.

Methods

The study, conducted between March 2019 and November 2021, recruited participants from the outpatient clinic of the Dermatology Department at the University Hospital of Brescia, Italy. This hospital is a designated European Reference Network (ERN) for pemphigus. Patients with a confirmed diagnosis of pemphigus through histological examination plus serology (or serology plus positive DIF) were included in the case group, while the control group consisted of healthy individuals with no history of pemphigus or other systemic diseases or medications that could bias the study results. Both groups had to be aged between 18 and 75 years and possess the cognitive ability to complete the questionnaires provided. The case group was purposely selected, while the control group was chosen based on convenience. During the visit, demographic and clinical information such as age, sex, and comorbidities were recorded. For the case group, the age at which pemphigus was diagnosed, disease duration, type of pemphigus, and affected sites were documented through questionnaires, along with the concomitant and previous treatments administered over time for both groups.

Data were collected through self-administered questionnaires designed to evaluate the impact of pemphigus on patients' quality of life and sleep quality. Both groups completed the same questionnaires.

Pittsburgh Sleep Quality Index Questionnaire (PSQI)

The Pittsburgh Sleep Quality Index (PSQI) [5] is a self-rated tool used to evaluate various dimensions of sleep, such as sleep quality (SQ), sleep duration (SDu), sleep latency (SL), sleep disturbances (SDi), sleep efficiency (SE), daytime sleep dysfunction (DSD), sleep medications (SM), and global score (GS) over a 1-month period. It includes a cutoff score of 5 to differentiate between good and poor sleep quality.

General Health Questionnaire-12 (GHQ-12)

The level of mental well-being was evaluated in both the case and control groups through the GHQ-12 questionnaire [6]. The scores obtained from the questionnaire were utilized to distinguish between individuals experiencing psychological distress and those who were not. Scores exceeding 14 indicated the presence of psychological distress. Furthermore, the scores were categorized into mild (15-18) and moderate-severe (19-36) ranges.

Autoimmune Bullous Disease Quality of Life Questionnaire (ABQOL)

The ABQOL questionnaire, used to evaluate the quality of life of patients with autoimmune bullous diseases like pemphigus, was completed only by patients diagnosed with pemphigus. The questionnaire comprises 17 items that assess different aspects of the patient's life, such as physical symptoms, psychological well-being, social functioning, and treatment-related factors [7].

During the study, the participants were provided with clear instructions on how to fill out the questionnaires. They were also given the opportunity to request further clarification if needed.

Pemphigus Disease Area Index (PDAI)

In the case of patients with pemphigus, an expert dermatologist was responsible for assessing their Pemphigus Disease Area Index (PDAI) scores. The scores were categorized as follows: scores below 15 indicated mild pemphigus, scores between 15-45 indicated mild disease, and scores above 45 indicated extensive disease [8].

The study was approved by the local ethics committee, and all participants provided written informed consent. We conducted the study following the principles of the

Declaration of Helsinki, ensuring the confidentiality of all participants' data, and their right to withdraw from the study at any time was guaranteed.

The encoded and anonymous database was formatted using Microsoft-Excel TM software and subsequently imported from IBM-SPSS TM ver. 27.1.

Epi-Info StatCalc® software ver. 7.2 was used to calculate the sample size, sampling tests was calculated at the power level 1-beta = 80%, alpha = 5% two-tailed. The ratio of controls to cases is equal to 2, and the percentage of controls exposed is equal to 40%. Assuming an odds-ratio of 3 are calculated 42 cases and 83 controls with Kelsey test.

Descriptive statistics such as mean, standard deviation, median, and range were calculated for continuous variables. The Kolmogorov-Smirnov test was used to assess the normality of the distributions. The Mann-Whitney U test and Kruskal-Wallis H test were used to compare non-normally distributed continuous variables between groups, while the independent samples t-test was used to compare normally distributed continuous variables. Categorical variables are presented as frequency counts, percentages and analyzed using the Chi-square test or Fisher's exact test, when appropriate. The Chi-square test for 2x2 tables was used to calculate the odds ratio. A p-value of less than 0.05 was considered statistically significant for all analyses.

Results

The study involved 156 participants: 52 in the case group (21 males, 31 females, average age 57.96 ± 15.78 years) and 104 in the control group (46 males, 58 females, average age 51.98 ± 14.01 years). The pemphigus patients were diagnosed at an average age of 52.92 ± 15.13 years and followed up for a median of 2.5 years (range: 0-22). Most patients in the case group (86.54%) had pemphigus vulgaris, while 13.46% had the foliaceous form. The majority had cutaneous involvement (69.23%), followed by mucosal involvement (26.92%), and concurrent skin and mucous membrane involvement (3.85%). The median methylprednisolone equivalent dose was 0.75 (range: 0–16). All but one patient received steroid therapy, either alone or with steroid-sparing agents. Azathioprine was prescribed to 23 patients, 17 received plasma exchange, one received intravenous immunoglobulins, six were treated with rituximab, 18 with mycophenolate, and 18 with dapsone.

The analysis revealed that cases had significantly poorer sleep quality than did controls, indicated by the global score (GS) and most individual domains, including sleep latency (SL), sleep disturbance index (SDi), sleep medication (SM), and daytime sleep dysfunction (DSD) (Figure 1). A Pearson chi-squared test on GHQ-12 scores, stratified by

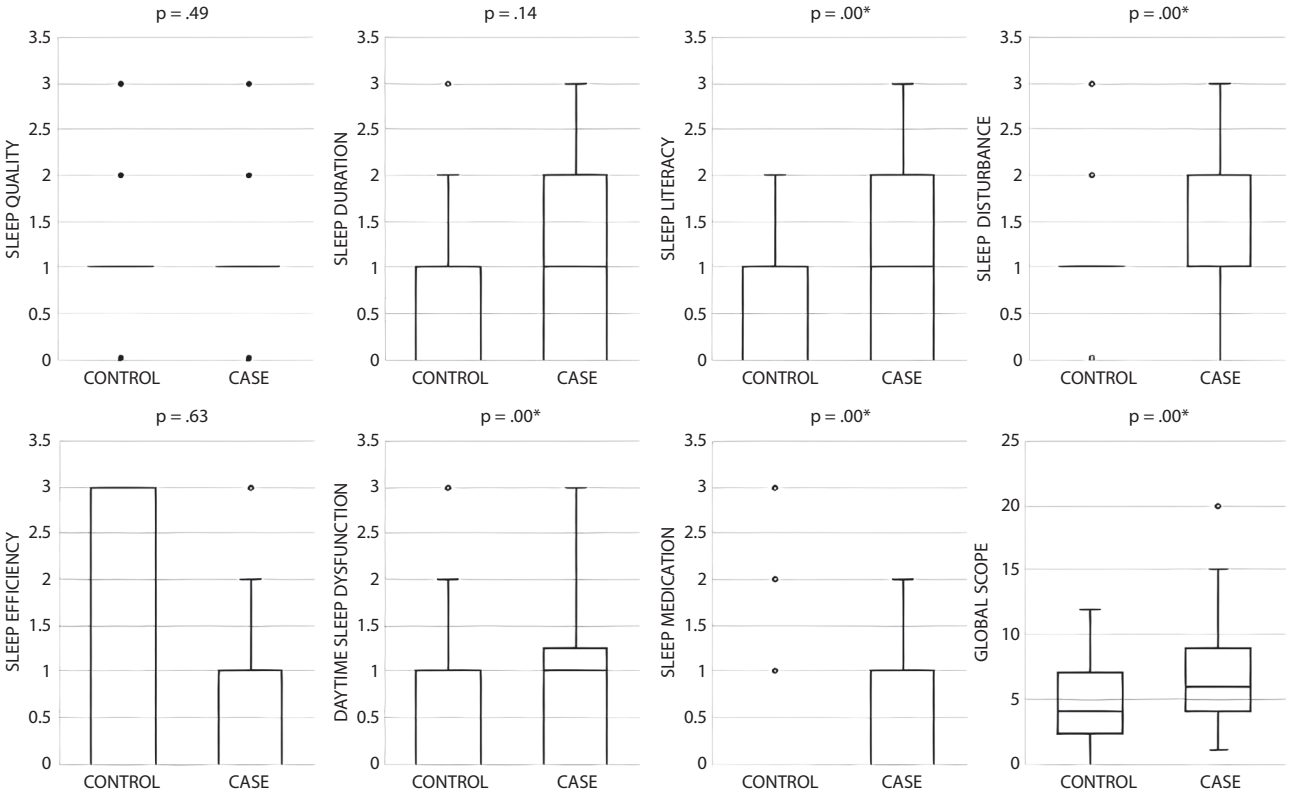

Figure 1. Boxplot of PSQI for each domain examined in the study between cases and controls. The box plot lines correspond from bottom of box to top: 25th percentile, median percentile, 75th percentile. Whiskers extend from both ends of the box to the data points located within the lower quartile minus 1.5 times the interquartile range (IQR) or the upper quartile plus 1.5 times the IQR. Data points beyond these whiskers are plotted individually as points and are considered outliers. p-values presented as from a Mann–Whitney test of differences across the case/control groups. *Statistically significant difference in medians between cases and controls.

Table 1. Baseline and Demographic Characteristics.

Variables	Case Group (N=52)	Control Group (N=104)
Sex, *n (%)*		
Male	21	46
Female	31	58
Age (y), *mean (DS)*	57.96 (15.78)	51.98 (14.01)
Age at diagnosis (y), *mean (DS)*	52.92 (15.13)	
Follow-up time (y), *median (range)*	2.5 (0-22)	
Subtype, *n (%)*		
Vulgaris	42 (86.54)	
Foliaceous	7 (13.46)	
Involvement at the visit, *n (%)*		
Cutaneous	36 (69.23)	
Mucosal	14 (26.92)	
Both	2 (3.85)	
Concomitant methylprednisolone equivalent dose, *median (range)*	0.75 (0-16)	
Previous therapies, *n (%)*		
Corticosteroids	51 (98)	
Azathioprine	23 (44)	
Mycophenolate mofetil	18 (34)	
Dapsone	18 (34)	
Plasmapheresis	17 (32)	
Rituximab	6 (11)	
Intravenous immunoglobulin	1 (2)	

psychological distress severity, showed significant differences between the groups ($P = 0.001$), indicating higher psychological distress among cases (Table 2).

Table 3 demonstrated a significant correlation between PDAI scores and parameters such as SDu, SL, SM, and GS. Additionally, ABQOL scores were significantly correlated with various PSQI domains, including sleep quality (SQ), SL, SDi, DSD, and GS.

We investigated the relationship between PSQI-measured sleep quality and daily steroid doses, considering known side effects. Spearman's correlation showed significant links between corticosteroid dosage and sleep quality, particularly GS (P=0.02) and SDu (P=0.00) (Table 3). The dosage also correlated significantly with disease severity (PDAI score, P=0.00).

Despite aiming to assess the impact of cumulative corticosteroid therapy on sleep quality, determining the total dose was challenging. Disease duration was used as an indirect indicator, but no significant correlation with PSQI was found. Further analysis indicated a significant impact of cutaneous symptoms on sleep quality (p=0.01), with no significant impact from mucosal symptoms (P=0.22). No trends were observed across PSQI subdomains regarding the localization of pemphigus symptoms.

Discussion

Sleep is a fundamental component of personal well-being and plays a pivotal role in the degradation of the quality of life in chronic conditions [9]. Although bullous diseases are rare, they often progress to chronic states, leading to a deterioration in various aspects of patients' quality of life [10]. Our study sought to offer a more precise understanding of the influence of pemphigus on the sleep quality of these patients. The literature on the relationship between sleep and pemphigus is notably limited. Probable causes for this scarcity may be attributed to the rarity of the pathology and the age of patients affected by pemphigus, often younger than others affected by other chronic diseases, where the impact on sleep could be more evident.

In a study by Hsu and colleagues [11] involving 130 cases, a correlation between pemphigus and insomnia was highlighted, linked to steroid intake. However, it is important to note that due to the study's structure, additional

Table 2. Quality of Life Comparisons Between Case and Control Groups.

PSQI	Case group *(n=52)*		Control group *(n=104)*		*p-value*
	mean	*(min-max)*	*mean*	*(min-max)*	
Sleep quality (SQ)	1.06	(0-3)	0.96	(0-3)	.49
Sleep duration (SDu)	0.86	(0-3)	0.59	(0-3)	.14
Sleep latency (SL)	1.18	(0-3)	0.61	(0-2)	.00*
Sleep disturbances (SDi)	1.40	(0-3)	1,00	(0.3)	.00*
Sleep efficiency (SE)	0.78	(0-3)	0.98	(0-3)	.63
Daytime sleep dysfunction (DSD)	0.68	(0-3)	0.22	(0-3)	.00*
Sleep medication (SM)	0.94	(0-3)	0.39	(0-3)	.00*
Global score (GS)	6.90	(1-20)	4.75	(0-12)	.00*
Sleep quality, *n (%)*					
Good	20 (38)		64 (62)		
Poor	32 (62)		40 (38)		
GHQ-12	**Case group *(n=52)***		**Control group *(n=104)***		***P-value***
	n	**%**	***n***	**%**	**.00***
None	11	21	48	46	
Mild	26	50	46	44	
Moderate-severe	15	29	9	9	

Abbreviations: GHQ-12: General Health Questionnaire-12.

Table 3. Correlation Analysis Between PSQI And Disease Severity Scores and Steroid Intake.

	PDAI *(n=52)*		ABQOL *(n=52)*		Equivalent Steroid Intake	
	r	*p-value*	*r*	*p-value*	*r*	*P-value*
PSQI						
Sleep quality (SQ)	.28	.05	.37	.00*	.25	.08
Sleep duration (SDu)	.35	.01*	.05	.76	.38	.00*
Sleep latency (SL)	.31	.03*	.31	.03*	.18	.22
Sleep disturbances (SDi)	.16	.27	.33	.02*	.03	.85
Sleep efficiency (SE)	.05	.72	-.01	.94	.13	.38
Daytime sleep dysfunction (DSD)	.19	.18	.35	.01*	.29	.10
Sleep medication (SM)	.30	.03*	.11	.47	.05	.75
Global score (GS)	.46	.00*	.39	.00*	.33	.02*

Abbreviations: ABQOL: Autoimmune Bullous Disease Quality of Life questionnaire; PDAI: Pemphigis Disease Area Index; PSQI: Pittsburgh Sleep Quality Index questionnaire.

information from the sample, such as standardized extent of pemphigus, steroid dosages used, and the duration of treatment, is not obtainable. In our study, we confirm the relationship between pemphigus and sleep. Patients with more severe manifestations, and consequently a higher PDAI score, exhibit a significant deterioration in various domains of the PSQI. This finding becomes even more crucial considering the overall worsening reported by patients, evaluated through specific questionnaires dedicated to the condition.

It should be emphasized that in our study, steroid dosage was higher in more severe patients, potentially correlating with the deterioration of the PSQI. However, when considering the duration of steroid treatment and, consequently, the cumulative role of such therapy, a direct correlation with the worsening of sleep quality is not evident. Likely, while in the acute phase of the disease, high steroid dosage may compromise the normal sleep quality, in patients with long-standing disease, the pro-inflammatory state associated with

the pathology continues to play a more significant role. This observation is supported by various studies indicating that the disruptive effect of corticosteroids on sleep appears to be dose-related and not time-related [12-13]. A more intriguing hypothesis, proposed by other authors [14], revolves around the role of bidirectional immunological interplay between pemphigus and sleep. Pemphigus is characterized by an increase in cytokines such as IL-6 and TNF-alpha [15], which seem to influence brain activity during the NREM and REM phases of sleep [16-17]. On the other hand, consequent sleep deprivation could potentially enhance the production of these cytokines, thereby impacting the course of the pathology and hamper the patient's recovery. However, it should be emphasized that beyond the immunological context, in our sample of pemphigus patients, there was evident psychological distress that could have played a role in the deterioration of sleep quality. Furthermore, as our data do not allow us to date the onset of psychological distress, we cannot exclude its occurrence before pemphigus and, consequently, assess its subsequent impact.

An additional aspect of our study aimed to evaluate the impact of oral lesions on the quality of sleep of pemphigus patients. In a study on oropharyngeal pemphigus, Calabria and colleagues [18] reported a lower quality of sleep in patients with oropharyngeal pemphigus compared to a healthy control group. Moreover, there was no statistically significant difference in the case group when comparing patients' presence or absence of steroid therapy, or in consideration of the cumulative time of the disease duration. These data appear interesting; however, their further analysis seems limited due to the absence of a group of patients with cutaneous lesions. Differently, our data reveal that individuals with a predominant mucosal involvement experience a lesser impact on sleep compared to those with a predominant cutaneous manifestation. This result could be interpreted in light of a higher expression of certain cytokines, such as IL-6, in cutaneous lesions of pemphigus compared to oral lesions, consequently leading to a greater impact on the quality of sleep in patients with skin involvement [19].

Conclusion

This study underscores the imperative to investigate the quality of sleep in individuals with pemphigus, considering the enduring and substantial impact of the disease on this fundamental aspect of well-being. However, it is crucial to acknowledge the limitations inherent in this study, such as the relatively small sample size and the single-center nature of the research design. Another factor that could have influenced the study's outcome was the absence of patients with pemphigus in complete remission without steroid therapy or the inclusion of an additional control group of autoimmune diseases typically treated with steroids. Further investigations in this domain are warranted to validate the identified findings.

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