Impact of Itch on Sleep Disturbance in Patients with Prurigo Nodularis

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Chronic pruritus is associated with sleep disturbance and negatively impacts on patients' quality of life (QoL) (1). Pruritus is often worse in the evening (2), and the severity of nocturnal pruritus (NP) correlates significantly with the severity of sleep disturbance (3). NP is present in numerous pruritic conditions, including atopic dermatitis (AD), psoriasis, and prurigo nodularis (PN) (3). However, there are conflicting reports on the impact of pruritus on sleep in patients with PN (4–7). A prospective case-control study of patients with endogenous eczema, with ($n=36$) and without ($n=47$) prurigo nodules, found no significant difference in the degree each group scratched at night (8); however, the impact of scratching on sleep was not reported directly, as it was combined with the impact on eating and sleep.

The aim of the current study was to determine the impact of itch, specifically NP, on sleep in patients with PN, compared with another severely itchy dermatosis with well-established sleep abnormalities, AD. Validated questionnaires were used to explore itch timing, frequency, and sleep disturbance over multiple time-points (9, 10).

MATERIALS AND METHODS

Data obtained from an itch questionnaire bank that has enrolled subjects since April 2015 (3) were analysed. All participants completed validated questionnaires (9, 10), as outlined in a previous report (3). All participants were examined and diagnosed by an attending dermatologist. Briefly, overall severity of itch was quantified using an 11-point numerical rating scale (NRS), itch characteristics were measured on a scale from 0 to 4 (0=not at all, 1=minimal, 2=mild, 3=moderate, 4=great), and ItchyQol items were measured on a scale from 0 to 5 (1=never, 2=rarely, 3=sometimes, 4=often, 5=all the time) (10).

All data were analysed using the licensed statistical package JMP Pro (version 15.0, SAS Institute Inc. 2019) with significance set at $p<0.05$. Descriptive statistics for quantitative variables are reported as mean ± standard deviation (SD), median and range values. Qualitative variables are reported as percentages. Differences in quantitative outcomes were assessed using non-parametric tests, as normality and homogeneity assumptions were not satisfied. Correlations were assessed using the non-parametric measure Spearman's rank correlation.

RESULTS

Overall, 39 patients with PN (29 females; 74.4%) and 81 with AD (48 females; 59.3%) completed the questionnaires, with a mean ± SD age for patients with PN of 62.8 ± 11.8 years, and for patients with AD 44.2 ± 19.6 years. Additional demographic data are shown in Table SI[1]. Pruritus history (mean ± SD) of patients with PN (8.75 ± 8.9 years) and AD (13.8 ± 16.6 years) was not significantly different, nor was the current severity of pruritus (7.7 ± 2.3 vs 7.2 ± 2.5, respectively). Ratings for evening pruritus and NP were not significantly different between patients with PN and AD, and pruritus usually occurred most of the time to constantly for both groups (**Fig. 1**C, Table SII[1]). Further comparison of patients with PN and AD pruritus characteristics, timing, frequency, severity over different recall periods, severity of sleep disturbance, and other qualitative sleep-related variables, were not significantly different (Table SII[1]). The majority of patients with PN ($n=24$; 61.5%) and AD ($n=48$; 64.0%) reported that pruritus disturbed sleep to a great extent (Fig. 1A and B).

For patients with PN, evening pruritus and NP significantly correlated with sleep disturbance ($r_s=0.32$, $p=0.0449$; $r_s=0.33$, $p=0.0439$) and, specifically, sleep disturbance in the past week ($r_s=0.46$, $p=0.0031$;

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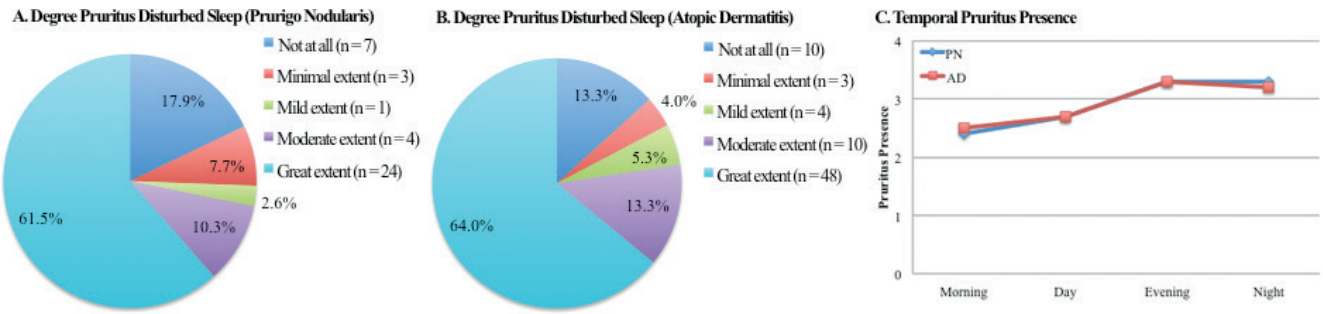

Fig. 1. Impact of itch on sleep disturbance in patients with prurigo nodularis (PN) and atopic dermatitis (AD). (A) Sleep disturbance reported by patients with PN. (B) Sleep disturbance reported by patients with AD. (C) Presence of pruritus over time; frequency defined as 0 (never), 1 (rarely), 2 (sometimes), 3 (most of the time), or 4 (constantly).

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$r_s = 0.58$, $p = 0.0001$). However, qualitative pruritus-related factors, including "tiresome" and "tiring", did not correlate with sleep disturbance (Table SIII[1]). NP correlated significantly with the pruritus-related factor "tiresome" ($r_s = 0.37$, $p = 0.0252$). "Depression/sadness" and "anger/irritability" did not significantly correlate with NP or sleep disturbance. Other correlations are shown in Table SIII[1].

DISCUSSION

A recent systematic review, summarizing all PN studies prior to 12 May 2019 investigating sleep disturbance, found very little evidence on the effect of PN pruritus on sleep (11). In fact, there are conflicting reports on how the severity of pruritus impacts on sleep quality (4–7). One of the largest studies, comprising 39 patients with PN and 39 healthy controls, found that there was no significant correlation between severity of pruritus and sleep quality (5). Furthermore, a pan-European multicentre cross-sectional study reported that only 4% of those surveyed ($n = 304$) regarded sleep disturbance as their greatest burden; however, sleep was affected in 66.5% of patients (sometimes, often, or always; ($n = 405$) (12).

More recently, studies have measured the effect PN treatments have on improving sleep disturbance. A retrospective analysis of patients with PN-like phenotype in AD ($n = 11$) found, through measuring the quality of sleep using the Non-Restorative Sleep Scale (NRSS), that dupilumab improved sleep quality (13). A larger retrospective study of 27 patients with chronic nodular prurigo found that dupilumab improved NRS values for sleeplessness as early as 4 weeks after the start of treatment, and sleep continued to improve through 36 weeks (14). A well-designed 12-week randomized controlled trial (RCT) of nemolizumab involving 70 patients also used a NRS (values from 0 to 10) and found numerical improvements in sleep quality starting at week 1 after the first treatment and at week 4 (15).

The current study shows that sleep disturbance occurs in a large proportion of patients with PN, with the majority reporting sleep to be disturbed to a great extent (Fig. 1A). In addition, sleep disturbance correlates significantly with pruritus timing in the evening and night (Table SIII[1]). It is notable that, by reporting the frequency at which patients with PN have disturbed sleep over multiple recall periods, e.g. historical and over the past week, variations can be seen in related factors (Tables SII and SIII[1]), including how the severity of historical sleep disturbance correlated significantly with severity of pruritus in the past 6 weeks and 1 year, but not the severity of current pruritus, while sleep disturbance in the last week showed significant correlation for all recall periods of pruritus severity rating (Table SIII[1]). This study provides further analysis of the impact of itch, and how sleep disturbance in patients with PN is present and correlates with pruritus in the evening and night.

When comparing sleep measures in patients with PN and AD, they were not significantly different, indicating that both populations experience NP and sleep disturbance to a similar degree (Fig. 1 and Table SII[1]). However, compared with patients with AD, little is known about sleep disturbances and related impacts in patients with PN, and multiple gaps remain with respect to the measurement of severity of PN pruritus and related sleep impairment, sex differences, as well as the influence cross-cultural factors have on these measures.

The current study included fewer patients with PN than with AD, and the mean age was significantly higher for patients with PN than for patients with AD, which could affect the comparative analysis. Further limitations include the difficulty encountered with studies of sleep disturbance, and how recall bias is present when collecting subjective patient-reported outcomes. Discrepancies between subjective data and objective sleep quality/quantity data need to be considered.

Future research, that investigates multiple recall periods, severity scores, sex differences and cross-cultural factors in comparison with objective sleep data, is necessary to further develop our understanding of sleep disturbance in PN, and to improve the assessment techniques used to define pruritus, sleep disturbance and related impacts in patients with PN.

In conclusion, this study demonstrates that PN has a significant effect on sleep and that evening pruritus and NP have a major impact on sleep in patients with PN.

Conflicts of interest: GY conducted clinical trials or received honoraria for serving as a member of the Scientific Advisory Board and consultant of: Pfizer, TREVI, Kinksa, Sanofi Regeneron, Galderma, Novartis, Eli Lilly, LEO, Bellus and received research funds from: Pfizer, Kiniksa, Sanofi Regeneron and Leo.

REFERENCES

1. Silverberg JI, Kantor RW, Dalal P, Hickey C, Shaunfield S, Kaiser K, et al. A comprehensive conceptual model of the experience of chronic itch in adults. Am J Clin Dermatol 2018; 19: 759–769.
2. Steinke S, Zeidler C, Riepe C, Bruland P, Soto-Rey I, Storck M, et al. Humanistic burden of chronic pruritus in patients with inflammatory dermatoses: results of the European Academy of Dermatology and Venereology Network on Assessment of Severity and Burden of Pruritus (PruNet) cross-sectional trial. J Am Acad Dermatol 2018; 79: 457–463.
3. Lavery MJ, Stull C, Nattkemper LA, Sanders KM, Lee H, Sahu S, et al. Nocturnal pruritus: prevalence, characteristics, and impact on ItchyQoL in a chronic itch population. Acta Derm Venereol 2017; 97: 513–515.
4. Todberg T, Zachariae C, Skov L. Treatment and burden of disease in a cohort of patients with prurigo nodularis: a survey-based study. Acta Derm Venereol 2020; 100: adv00119.
5. Konda D, Chandrashekar L, Rajappa M. Kattimani S, Thappa DM, Ananthanarayanan PH. Serotonin and interleukin-6: association with pruritus severity, sleep quality and depression severity in prurigo nodularis. Asian J Psychiatr 2015; 17: 24–28.
6. Spring P, Gschwind I, Gilliet M. Prurigo nodularis: retrospective study of 13 cases managed with methotrexate. Clin Exp Dermatol 2014; 39: 468–473.
7. Sharma AD. Oral ketotifen and topical antibiotic therapy in the management of pruritus in prurigo nodularis: a randomized, controlled, single-blind, parallel study. Indian J Dermatol 2013; 58: 355–359.

8. Oh CC, Li H, Lee W, Tey HL. Biopsychosocial factors associated with prurigo nodularis in endogenous eczema. Indian J Dermatol 2015; 60: 525.
9. Dawn A, Papoiu AD, Chan YH, Rapp SR, Rassette N, Yosipovitch G. Itch characteristics in atopic dermatitis: results of a web-based questionnaire. Br J Dermatol 2009; 160: 642–644.
10. Desai NS, Poindexter GB, Monthrope YM, Bendeck SE, Swerlick RA, Chen SC. A pilot quality-of-life instrument for pruritus. J Am Acad Dermatol 2008; 59: 234–244.
11. Gwillim EC, Janmohamed SR, Yousaf M, Patel KR, Silverberg JI. The impact of prurigo nodularis on sleep disturbance and related impact: a systematic review. J Eur Acad Dermatol Venereol 2020; 34: e815–e817.
12. Pereira MP, Hoffmann V, Weisshaar E, Wallengren J, Halvorsen JA, Garcovich S, et al. Chronic nodular prurigo: clinical profile and burden. A European cross-sectional study. J Eur Acad Dermatol Venereol 2020; 34: 2373–2383.
13. Ferrucci S, Tavecchio S, Berti E, Angileri L. Dupilumab and prurigo nodularis-like phenotype in atopic dermatitis: our experience of efficacy. J Dermatolog Treat 2019 Sep 2 [Epub ahead of print].
14. Chiricozzi A, Maurelli M, Gori N, Argenziano G, De Simone C, Calabrese G, et al. Dupilumab improves clinical manifestations, symptoms, and quality of life in adult patients with chronic nodular prurigo. J Am Acad Dermatol 2020; 83: 39–45.
15. Ständer S, Yosipovitch G, Legat FJ, Lacour JP, Paul C, Narbutt J, et al. Trial of nemolizumab in moderate-to-severe prurigo nodularis. N Engl J Med 2020; 382: 706–716.