Association of Clinical and Demographic Factors With the Severity of Palmoplantar Pustulosis

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IMPORTANCE Although palmoplantar pustulosis (PPP) can significantly impact quality of life, the factors underlying disease severity have not been studied.

OBJECTIVE To examine the factors associated with PPP severity.

DESIGN, SETTING, AND PARTICIPANTS An observational, cross-sectional study of 2 cohorts was conducted. A UK data set including 203 patients was obtained through the Anakinra in Pustular Psoriasis, Response in a Controlled Trial (2016-2019) and its sister research study Pustular Psoriasis, Elucidating Underlying Mechanisms (2016-2020). A Northern European cohort including 193 patients was independently ascertained by the European Rare and Severe Psoriasis Expert Network (2014-2017). Patients had been recruited in secondary or tertiary dermatology referral centers. All patients were of European descent. The PPP diagnosis was established by dermatologists, based on clinical examination and/or published consensus criteria. The present study was conducted from October 1, 2014, to March 15, 2020.

MAIN OUTCOMES AND MEASURES Demographic characteristics, comorbidities, smoking status, Palmoplantar Pustulosis Psoriasis Area Severity Index (PPPASI), measuring severity from 0 (no sign of disease) to 72 (very severe disease), or Physician Global Assessment (PGA), measuring severity as 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), and 4 (severe).

RESULTS Among the 203 UK patients (43 men [21%], 160 women [79%]); median age at onset, 48 (interquartile range [IQR], 38-59) years, the PPPASI was inversely correlated with age of onset ($r = -0.18, P = .01$). Similarly, in the 159 Northern European patients who were eligible for inclusion in this analysis (25 men [16%], 134 women [84%]); median age at onset, 45 (IQR, 34-53.3) years, the median age at onset was lower in individuals with a moderate to severe PGA score (41 years [IQR, 30.5-52 years]) compared with those with a clear to mild PGA score (46.5 years [IQR, 35-55 years]) ($P = .04$). In the UK sample, the median PPPASI score was higher in women (9.6 [IQR, 3.0-16.2]) vs men (4.0 [IQR, 1.0-11.7]) ($P = .01$). Likewise, moderate to severe PPP was more prevalent among Northern European women (57 of 134 [43%]) compared with men (5 of 25 [20%]) ($P = .03$). In the UK cohort, the median PPPASI score was increased in current smokers (10.7 [IQR, 4.2-17.5]) compared with former smokers (7 [IQR, 2.0-14.4]) and nonsmokers (2.2 [IQR, 1.6]) ($P = .003$). Comparable differences were observed in the Northern European data set, as the prevalence of moderate to severe PPP was higher in former and current smokers (51 of 130 [39%]) compared with nonsmokers (6 of 24 [25%]) ($P = .14$).

CONCLUSIONS AND RELEVANCE The findings of this study suggest that PPP severity is associated with early-onset disease, female sex, and smoking status. Thus, smoking cessation intervention might be beneficial.

Published online September 16, 2020.

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Palmoplantar pustulosis (PPP) is an uncommon pustular eruption affecting the palms and/or soles. It is observed in approximately 1:2000 individuals of European descent and 1:800 individuals of East Asian descent. The disease typically manifests in adulthood, with a median age of onset older than 45 years reported in most studies. Palmoplantar pustulosis shows a marked sex bias, with women accounting for 60% to 90% of affected individuals. The disease is also characterized by an association with cigarette smoking, with up to 90% of patients self-identifying as smokers at the time of diagnosis.

The disease manifests with the eruption of sterile, neutrophil-filled pustules on the palms and soles. The lesions, which can occur on a background of normal or inflamed skin, are persistent (>3 months), painful, and disabling, and can be accompanied by fissures, pruritus, and a burning sensation. Comorbidities are also common, as affected individuals are at increased risk of psoriasis vulgaris, psoriatic arthritis, and autoimmune thyroid disease.

While PPP can profoundly impact quality of life, the factors underlying variable disease severity have not been investigated. The rarity of the condition has hindered the ascertainment and characterization of adequately powered data sets. In this context, the objective of our study was 2-fold: to evaluate the features of PPP in 2 independent patient cohorts and to examine whether PPP severity is influenced by sex and smoking status—the 2 most well-established risk factors for the disease. Given that symptoms typically manifest in adulthood, we also sought to examine whether the presentation of PPP is more severe in early-onset cases.

Methods

Patients

This study was carried out in accordance with the principles of the Declaration of Helsinki and with the approval of the participating institutions’ ethics committees. The present study was approved by London Bridge Research ethics committee (London, UK) and Kantonale Ethikkommission (Zurich, Switzerland). All patients granted their informed consent in writing; participants did not receive financial compensation. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cross-sectional studies. The present study was conducted from October 1, 2014, to March 15, 2020.

The UK resource included 203 unrelated and prospectively ascertained patients. Forty-two patients were recruited between 2016 and 2019 through Anakira in Pustular Psoriasis, Response in a Controlled Trial (APRICOT). The remaining 161 patients were enrolled between 2016 and 2020 through the sister research study Pustular Psoriasis, Elucidating Underlying Mechanisms (PLUM). A total of 23 dermatology centers located across the UK were involved in the recruitment.

The Northern Europe resource included 193 unrelated patients. Affected individuals were mostly enrolled between 2014 and 2017 through 3 centers affiliated with the European Rare Disease and Severe Psoriasis Expert Network (ERASPEN). These centers were in the dermatology departments of the Medical University of Vienna, Austria (n = 100), Tartu University, Estonia (n = 57), and University Medical Centre Schleswig-Holstein, Campus Kiel, Germany (n = 31). The remaining 5 patients were recruited outside the main reference centers by clinicians who provided individual cases to the ERASPEN Consortium.

Pustular psoriasis was always diagnosed by a dermatologist, based on clinical examination and/or the ERASPEN consensus criteria. The observation of sterile, macroscopically visible pustules on palms or soles was the main inclusion criterion. Conversely, the presence of pustules restricted to the edges of psoriatic plaques represented an exclusion criterion. Individuals with concomitant generalized pustular psoriasis or concomitant acrodermatitis continua of Hallopeau were also excluded from the study, given that lesions affecting nails or nonacral skin are deemed incompatible with a diagnosis of PPP.

Clinical information and key demographics were collated using a standardized case report form, shared by all centers. In the UK cohort, disease severity was measured using the Palmoplantar Pustulosis Area Severity Index (PPASAI) and the Dermatology Life Quality Index (DLQI). Both the PPPASI measures severity of the disease with scores from 0 (no sign of disease) to 72 (very severe disease). The DLQI measures quality of life with scores ranging from 0 to 30, with higher scores indicating greater impairment. In the Northern European cohort, patients were assessed with the Physician Global Assessment (PGA), which has been shown to correlate with the PPASAI. The individuals who recorded clinical data and measured disease severity (reporting dermatologists or trained research nurses) were blinded to the study objectives.

Statistical Analysis

Given that different scoring systems were used in the UK and Northern European cohorts, the 2 data sets were analyzed separately. The quantitative PPPASI and DLQI measures obtained in the UK cohort were analyzed using the Mann-Whitney test for binary variables, such as sex, or the Kruskal-Wallis test for categorical variables, such as smoking status. The correlation

Key Points

Question Are clinical and demographic factors associated with the severity of palmoplantar pustulosis?

Findings In a cross-sectional study of 203 patients in the UK, the Palmoplantar Pustulosis Psoriasis Area Severity Index score was significantly higher in women compared with men and in current smokers vs former and never smokers. Both of these findings were replicated in an independently ascertained, Northern European cohort including 159 patients.

Meaning The findings of this study suggest that smoking cessation interventions may be beneficial in patients with palmoplantar pustulosis and should be investigated in clinical studies.
between PPPASI or DLQI findings and age at onset was assessed using the Spearman rank correlation coefficient. To account for the confounding effects of therapeutic intervention, statistical significance was confirmed by regression analysis. The PPPASI and DLQI values were normalized (square root transformation) and analyzed vs sex, age of onset, or smoking status, using treatment as a covariate.

To maximize statistical power, the categorical PGA scores recorded in the Northern European data set were dichotomized into clear to mild (including PGA-0 [clear], PGA-1 [almost clear], and PGA-2 [mild]) and moderate to severe (including PGA-3 [moderate] and PGA-4 [severe]). The 2 groups were then compared using the Fisher exact test. Given that the purpose of the PGA analysis was to replicate results showing statistical significance in the UK cohort, P values were computed based on a 1-tailed distribution. As the number of individuals receiving systemic treatment was relatively small (n = 25 from the Medical University of Vienna and 9 from Tartu University), the confounding effect of therapeutic intervention was addressed by excluding these cases from downstream analyses.

Individuals for whom information on smoking status or age at onset was missing (Table) were excluded from the relevant analyses. All statistical tests were implemented in R, version 3.6.1 (R Project for Statistical Computing). P values < .05 were considered statistically significant.

## Results

### Patient Cohorts

The features of the UK and Northern European cohorts are summarized in the Table. Among the 203 UK patients (43 men [21%]; 160 women [79%]; median age at onset, 48 [interquartile range (IQR), 38-59] years). The Northern European cohort comprised 193 patients (32 men [17%]; 161 women [83%]; median age at onset, 45 [IQR, 33-54] years). Of these, 159 patients were available for analysis (25 men [16%]; 134 women [84%]; median age at onset, 45 [IQR, 34-53.3] years). All patients were of European descent. The percentage of women (>75%), median age of onset (>45 years), and prevalence of current and former smokers (>80%) were comparable in the 2 data sets. Prominent nail involvement was observed in both study populations, with more than 30% of patients presenting with at least 1 of the following: pustules involving the nail apparatus, subungual hyperkeratosis, permanent nail loss, and non-nutritional nail dystrophy.

Concurrent psoriasis vulgaris was observed in substantial numbers of study participants (66/203 [33%] UK patients and 22/193 [11%] Northern European cases), while psoriatic arthritis was reported in fewer patients from both cohorts (20/203 [10%] UK cases and 17/193 [9%] Northern European individuals).

Autoimmune thyroid disease was reported in several affected individuals from both data sets (14 of 203 [7%] of UK cases and 25 of 193 [13%] of Northern European patients). The prevalence of obesity (60 of 150 [40%] in the UK data set and 51 of 193 [26%] in the Northern European sample) was comparable to that observed among the overall population of British (36%), German (25%), and Estonian (21%) adults. In keeping with this observation, no correlation between the body
mass index of patients with PPP and their PPPASI was noted (Spearman $r = 0.03$, $P = .61$).

While different scoring systems were used in the 2 cohorts, both included a substantial proportion of individuals with severe PPP, reflecting ascertainment in hospital settings. Specifically, 84 of 203 UK patients (41%) had a PPPASI score greater than 10 and 73 of 193 of their Northern European counterparts (38%) had a PGA score greater than or equal to 3 (Table).

### Disease Severity

Among UK patients, age at onset was inversely correlated with the PPPASI score ($r = -0.18$, $P = .01$) (Figure 1A), although not with DLQI score ($r = -0.08$, $P = .21$). The association with the PPPASI score remained significant when the confounding effect of systemic treatment was taken into account by linear regression ($P = .04$) (eTable in the Supplement). In keeping with these findings, the analysis of the Northern European cohort revealed that the median age at onset was lower in patients with moderate-to-severe disease. Data are presented as median (interquartile range). $P < .05$ per Mann-Whitney test. PPPASI measures severity with scores from 0 (no sign of disease) to 72 (very severe disease).

In the UK sample, the median PPPASI score was higher in women (9.6 [IQR, 3.0-16.2]) compared with men (4.0 [IQR, 1.0-11.7]) ($P = .01$) (Figure 2A). The same applied to the median DLQI (women: 10.5 [IQR, 4.3-17] vs men: 4 [IQR, 1-9]; $P = 8.2 \times 10^{-8}$) (eFigure 2 in the Supplement). Both associations were confirmed when systemic treatment was included in a linear regression model ($P = .03$ for PPPASI, $P < .001$ for DLQI) (eTable in the Supplement). In agreement with these observations, analysis of the Northern European data set revealed that moderate to severe PPP was more prevalent among women (57 of 134 [43%]) compared with men (5 of 25 [20%]) ($P = .03$) (Figure 2B). Thus, PPP severity appeared to be associated with the sex of the patients in both the UK and Northern European study populations.

Among the UK patients, the median PPPASI score was highest in current smokers (10.7 [IQR, 4.2-17.5]), intermediate in former smokers (7 [IQR, 2.0-14.4]), and lowest among non-smokers (2.2 [IQR, 1-6]) ($P = .003$) (Figure 3A). Comparable findings were obtained when the median DLQI scores were analyzed (current smokers: 10 [IQR, 4.8-16.3] vs former smokers: 2.5 [IQR, 1-7]).

A, In the UK cohort, the Palmoplantar Pustulosis Psoriasis Area Severity Index (PPPASI) score was inversely correlated with age of onset ($r = -0.18$, $P = .01$). Regression lines are plotted with their 95% CIs (gray areas). B, In the Northern European sample, age of onset was significantly lower among patients with moderate-to-severe disease. Data are presented as median (interquartile range). $P < .05$ per Mann-Whitney test. PPPASI measures severity with scores from 0 (no sign of disease) to 72 (very severe disease).

A, In the UK cohort, Palmoplantar Pustulosis Psoriasis Area Severity Index (PPPASI) scores were significantly higher in women than men. Data are presented as median (interquartile range). $P < .01$ per Mann-Whitney test. B, In the Northern European sample, the proportion of individuals with moderate to severe disease was significantly elevated in women compared with men. $P < .05$ per Fisher exact test. Physician Global Assessment (PGA) measures severity as 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), and 4 (severe). PPPASI measures severity with scores from 0 (no sign of disease) to 72 (very severe disease). PPP indicates palmoplantar pustulosis.
Moderate to severe PPP was more frequent among current and former smokers (51 of 130 [39%]) than nonsmokers (6 of 24 [9%]) (eTable in the Supplement). The percentage of current smokers, intermediate in former smokers, and lowest in never smokers. Data are presented as median (interquartile range). P < .01 per Kruskal-Wallis test. B, In the Northern European sample, the proportion of individuals with moderate to severe disease was elevated in current and former smokers compared with never smokers. Physician Global Assessment (PGA) measures severity as 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), and 4 (severe). PPPASI measures severity with scores from 0 (no sign of disease) to 72 (very severe disease). PPP indicates palmoplantar pustulosis.

While the analysis of the smaller Northern European data set did not yield statistically significant results, we observed a similar trend toward increased disease severity in smokers. Moderate to severe PPP was more frequent among current and former smokers (51 of 130 [39%]) than nonsmokers (6 of 24 [25%]) (P = .14) (Figure 3B).

**Discussion**

To our knowledge, this is the first systematic study of the factors associated with PPP severity. This study builds on previous work from our network, which enabled the definition of consensus diagnostic criteria for PPP and suggested that the disease is genetically different from other forms of pustular psoriasis.

Our investigation noted key epidemiologic features of PPP, such as the late age of onset and sex bias (male-female ratios were >1:3.5 in both cohorts). Psoriasis vulgaris concurrence, which is frequently reported in PPP, was also observed in the 2 data sets. While the prevalence of psoriasis vulgaris in the 2 cohorts was consistent with published estimates (14%-61%),

the number of individuals with both PPP and psoriasis vulgaris was too small for subgroup analyses, and the use of different scoring systems prevented us from merging the UK and Northern European data sets. Conversely, the study of the entire resource highlighted aspects of PPP that, to our knowledge, had not been systematically investigated before.

We observed nail involvement in approximately one-third of affected individuals. Subungual pustulation was reported in a similar fraction of cases in a small UK study,

suggesting that nail abnormalities are a consistent feature of PPP.

We also report substantial comorbidity with psoriatic arthritis, which was present in both cohorts at a frequency greater than 9%. This percentage exceeds the prevalence of the disease in the general population (0.1%-0.3%).

Obesity was relatively uncommon, affecting only one-third of all study participants. This level contrasts with findings obtained in psoriasis vulgaris studies, where the association with obesity is well established and up to 42% of individuals with severe disease have a body mass index greater than 30.

Overall, these findings suggest that PPP is part of the psoriasis spectrum because the substantial comorbidity with psoriasis vulgaris and psoriatic arthritis points to shared pathogenic pathways. At the same time, the distinctive demographics of PPP suggest the involvement of risk factors that are specific to this disease. For example, the female bias that characterizes PPP is not observed in palmoplantar psoriasis. Likewise, psoriasis vulgaris affects both sexes equally and occurred with comparable frequency in the male (15/28 [35%]) and female (51/160 [32%]) patients examined in this study (P = .72).

Our analysis of PPPASI and PGA scores suggests that PPP severity is higher in women vs men. Further experimental studies will be required to dissect the causes of this phenomenon. These sources may involve genetic modifiers or hormonal imbalances that could be targeted for disease treatment.

Our study also noted an association between cigarette smoking and disease severity that was statistically significant in the UK cohort (P < .01), where PPPASI values were highest in smokers, intermediate in former smokers, and lowest in nonsmokers. This observation suggests a clinically relevant dosage effect that may be validated and refined by analyzing pack-year data in further patient resources.

Smoking cessation is sometimes applied to the management of PPP and was found to be beneficial in a pilot study. In this context, our findings suggest that smoking cessation should be systematically investigated in adequately powered trials.

**Limitations**

This study has limitations. The setting was exclusively based in secondary and tertiary referral centers, where the proportion of patients with severe PPP and the burden of comorbid disease may be higher than in other settings. Thus, the poten-
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Conclusions

The findings from this cross-sectional study note the benefits of multicenter collaboration and standardized data collection in the analysis of rare skin diseases. The study also suggests that PPP symptoms are particularly severe in patients with early-onset disease, women, and current smokers. The association between the severity of the disease and smoking will need to be replicated in further data sets; however, the increased severity suggests that smoking cessation interventions may benefit the treatment of PPP.

ARTICLE INFORMATION

Accepted for Publication: June 19, 2020.
Published Online: September 16, 2020.

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Conflict of Interest Disclosures: Dr Borroni reported receiving grants from Celgene Research Award and personal fees from AbbVie outside the submitted work. Dr Burden reported receiving personal fees from Boehringer Ingeheim, Novartis, Celgene, Janssen, AbbVie, and Almiral outside the submitted work. Dr Cro reported receiving grants from the National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation during the conduct of the study. Dr Griffiths reported receiving grants from the Medical Research Council (MRC) NIHR during the conduct of the study. Dr Koks reported receiving grants from Estonian Research Council and grants from H2020 ERAChair during the conduct of the study and Prion Ltd, a member of the board and shareholder of the company. Dr McAteer reported receiving grants from AbbVie, Almiral, Amgen, Celgene, Eli Lilly, Janssen, LEO Pharma, UCB, and Thornton and Ross Derma outside the submitted work. Dr Patel reported receiving grants from Efficacy and Mechanism Evaluation (EME) Programme during the conduct of the study. Dr Pink reported receiving personal fees from AbbVie, Lilly, Sanofi, Leo Pharma, Novartis, Almiral, UCB, Janssen, and La Roche-Posay outside the submitted work. Dr Reynolds reported receiving lecture fees from AbbVie (to Newcastle University), payment for medical advisory board meeting and lectures fees from Almiral (to Newcastle University), contributing to a clinical trial from Anaptyxis (to Newcastle upon Tyne Hospital), lecture fees from Celgene to Newcastle University), lecture fees from Janssen (to Newcastle University), grants and serving as a paid member of a medical advisory board from Novartis, and lecture fees from UCB Pharma Ltd (to Newcastle University) outside the submitted work. Dr Wahie reported receiving nonfinancial support from Janssen, AbbVie, Novartis, and Almiral outside the submitted work. Dr Navarinii reported receiving grants from EADV during the conduct of the study; grants and personal fees from AbbVie; personal fees from Almiral, Amgen, Eli Lilly, Galderma, Leo Pharma, Novartis, Sanofi, UCB, and Biomed; grants and personal fees from Boehringer Ingeheim; and nonfinancial support from Janssen-Cilag outside the submitted work. Dr Smith reported receiving grants from National Institute for Health Research and nonfinancial support from SOBI during the conduct of the study; grants from Medical Research Council, grants from Boehringer Ingeheim GmbH, grants from Innovative Medicines Initiative Horizon 2020, and grants from Medical Research Council outside the submitted work; and serving as an unpaid guideline committee member for UK and European guidelines for psoriasis, including pustular psoriasis. Dr Capon reported receiving grants from the European Academy of Dermatology and Venereology and MRC/NIHR during the conduct of the study; and grants from Boehringer Ingeheim and personal fees from Anaptyxis outside the submitted work. No other disclosures were reported.

Funding/Support: Support for the study was received from the Department of Health via the NIHR BioResource Clinical Research Facility and comprehensive Biomedical Research Centre awards.
to Guy’s and St Thomas’ NHS Foundation Trust in partnership with King’s College London and King’s College Hospital NHS Foundation Trust (gyo1bcr2012-1). Support was also received from the Newcastle NIHR Biomedical Research Centre. The APRICOT trial and the PLUM study were funded by the EME Programme, an MRC and NIHR partnership (grant EME 13/50/17 to Drs Smith, Capon, Barker, and Griffiths). This work was supported by the European Academy of Dermatology and Venereology (grant PPRC-2018-25 to Drs Barker, Capon, and Navarini, and grant PPRC-2012-11 to Drs Navarini and Barker). Ms Benzian-Ölsson was funded by an NIHR predoctoral fellowship (grant NR300473). Dr Dan was funded by Health Data Research UK (MR/SD03126/1). Dr Griffiths was funded in part by the NIHR Manchester Biomedical Research Centre and is an NIHR Emeritus Senior Investigator. Dr Reynolds is an NIHR Senior Investigator and receives support from the Newcastle MRC/EPSRC Molecular Pathology Node and the Newcastle NIHR MedTech and In Vitro Diagnostic Co-operative. Dr Warren is supported by the Manchester NIHR Biomedical Research Centre.

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication.

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Disclaimer: The views expressed in this publication are those of the authors and not necessarily those of the MRC, NHS, NIHR, or the Department of Health.

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