Palmoplantar pustulosis – a cross-sectional analysis in Germany

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Abstract

Background: Palmoplantar pustulosis (PPP) is a recalcitrant chronic inflammatory skin disease. Data relevant for the medical care of patients with PPP are scarce. Thus, the aim of this work was to investigate the disease burden, clinical characteristics, and comorbidity of PPP patients in Germany. Patients and Methods: PPP patients were examined in a cross-sectional study at seven specialized psoriasis centers in Germany. Results: Of the 172 included patients with PPP, 79.1% were female and 69.8% were smokers. In addition, 25.0% suffered from psoriasis vulgaris, 28.2% had documented psoriatic arthritis, and 30.2% had a family history of psoriasis. In 77 patients the mean Dermatology Life Quality Index (DLQI) was 12.2 ± 7.7 (mean ± SD). The mean Psoriasis Palmoplantar Pustulosis Area and Severity Index (PPPASI) was 12.6 ± 8.6. Mean body mass index was above average at 27.1 ± 5.5. The PPP patients had previously received an average of 2.6 ± 2.1 different anti-psoriatic systemic drugs or UV-therapies. The systemic drugs that had been used most frequently were corticosteroids in 40.1% of patients, followed by acitretin (37.8%), and methotrexate (27.9%). The PPPASI was 13.4 ± 8.9 in patients without current systemic therapy and 10.4 ± 7.9 in patients with systemic therapy. Conclusion: Many PPP patients had a concomitant diagnosis of psoriasis vulgaris and/or psoriatic arthritis or had a family history of psoriasis. Despite the fact that many of the patients were using anti-psoriatic therapies, there was still a high burden of disease within this PPP cohort. This insufficient control of symptoms demonstrates the urgent need for new PPP treatments.

Keywords: palmoplantar pustulosis, pustular palmoplantar psoriasis, therapy, psoriasis comorbidity, psoriasis arthritis, psoriasis vulgaris

Introduction

Palmoplantar pustulosis (PPP), also known as psoriasis pustulosa palmoplantaris, is a chronic inflammatory skin disease with an estimated prevalence of 0.01 to 0.05% [1]. So far, few investigations on disease characteristics, disease burden, and comorbidity in PPP have been performed. The discussion as to whether PPP is a subtype of psoriasis or if it constitutes a separate disease has been ongoing for decades. Presently, the concept that PPP constitutes a separate disorder is favored by many authors because of the genetic differences between psoriasis vulgaris (PV) and PPP [2, 3].

The standard therapies for PPP are potent to super potent topical corticosteroids, oral retinoids, and UV therapy [4]. In the present prospective cross-sectional study we analyze the disease burden, characteristics, and comorbidity as well as the treatment of PPP patients at seven German psoriasis centers. These data will contribute to better ongoing healthcare for PPP patients.

Methods

From July 2011 until May 2014, 172 patients with a clear diagnosis of PPP were included in this prospective study in six dermatological university hospital departments and in one clinic for rehabilitation with a focus on psoriasis in Germany. Patients with PPP

as a paradoxical reaction to a biologic treatment were excluded from participation in this study. Detailed clinical and historical data regarding body weight, height, nicotine and alcohol consumption, clinical characteristics, and therapy of PPP, as well as onset and duration, comorbidity, and family history (atopic, arterial hypertension, hyperlipidemia, diabetes mellitus) were collected by a physician-administered questionnaire. Psoriatic arthritis (PsA) was considered present when the diagnosis was confirmed by a rheumatology specialist. Pustules were counted on the most affected location (e.g. left palm) and categorized into one of five levels (0, 1-10, 11-25, 25-60, > 60 pustules). In addition, the Dermatology Life Quality Index (DLQI, n = 77) and the Psoriasis Palmoplantar Pustulosis Area Severity Index (PPPASI, n = 91) were collected in subgroups of patients. Systemic therapies with anti-psoriatic drugs and ultraviolet (UV) light therapies (including systemic or topical psoralen (P)UVA therapy) were documented. UV-therapy was counted as one, irrespective of the number of different UV-therapies the patient had received. The approval from each of the responsible ethics committees was obtained prior to the beginning of the study. Patients provided written consent to take part in the study in respect with GCP guidelines according to the declaration of Helsinki.

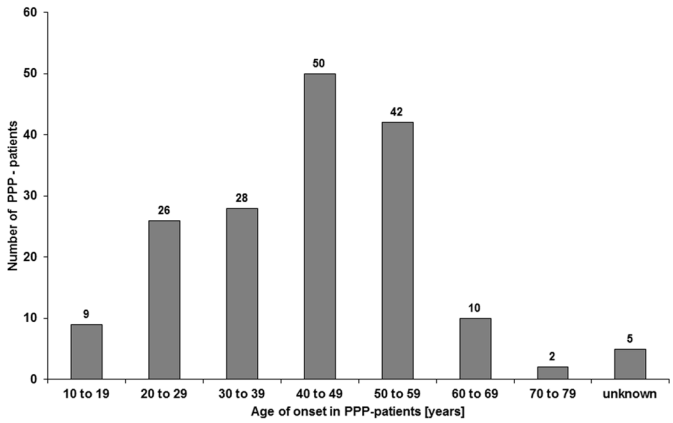

Figure 1. *Age at PPP onset.*

For statistical analysis Mann-Whitney U tests were performed to compare two different categories. Pearson test for correlation analysis and post hoc Tukey test were used for the analysis of variance (SPSS version 22).

Results

In our cross-sectional study 172 PPP patients were included. Females made up 79.6% of the patients and the mean age at study inclusion was 51.1 years with an SD of ± 12.9 years (**Table 1**). The mean age of PPP onset was 41.6 ± 13.3 years. Initial manifestation of PPP occurred most frequently between the ages

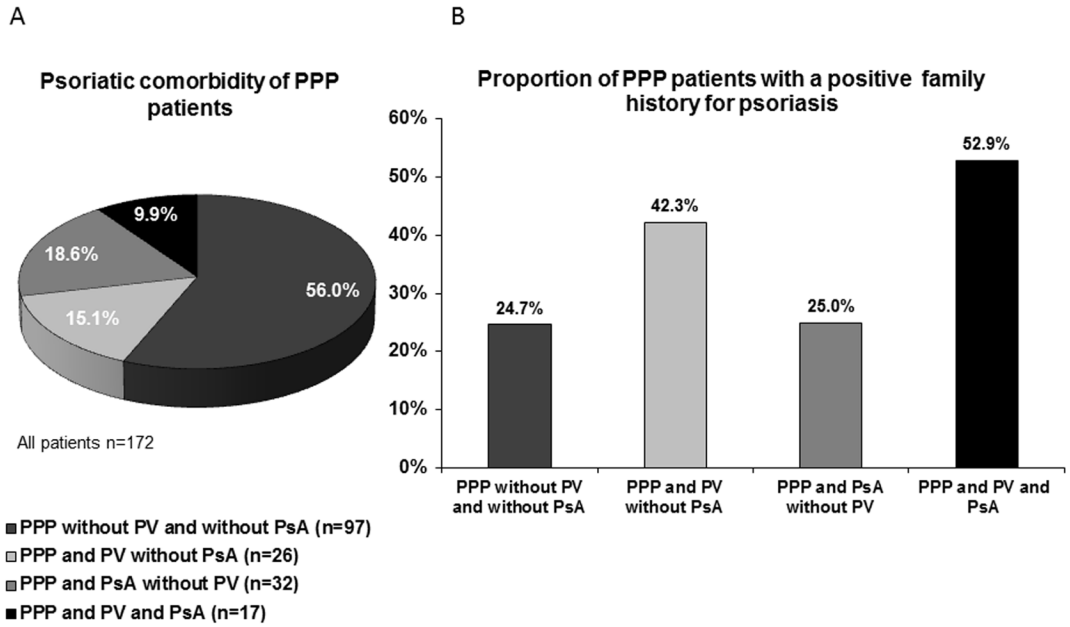

Figure 2. *(A) Prevalence of different psoriatic manifestations in patients with PPP. (B) Positive family history of psoriasis in different groups.*

Table 1. *Clinical characteristics of PPP patients (n=172)*

Disease duration of PPP (in years, mean ±SD)	**9.2 ± 11.8**
Age at time of study inclusion (in years, mean ±SD)	51.1 ± 12.9
Age of onset of PPP (in years, mean ±SD)	41.6 ± 13.3
Age of onset of PV (in years, mean ±SD)	35.0 ± 14.8
Age of onset of PsA * (in years, mean ±SD)	48.7 ± 13.0
female	79.7%
Smoker at time of study inclusion	69.8%
Smoker or former smoker	95.4%
Passive smoker** among the 7 never-smokers	57.1%
Smoker at time of first manifestation of PPP	77.3%
Positive family history for psoriasis	30.2%
Positive family history for PsA or rheumatism	16.5%
Additional PV	25.0%
Additional PsA*	28.5%
Distribution of PPP	
palmar and plantar	77.3%
only palmar	5.2%
only plantar	16.9%
Number of Pustules on time of studyinclusion	
0	11.1%
1-10	22.7%
11-25	20.2%
26-60	19.8%
>60	11.6%
no information	4.7%
PPPASI (n=91, mean ±SD)	12.6 ± 8.6
DLQI (n=77, mean ±SD)	12.2 ± 7.7
* 26 PsA patients were not able to declare the age of onset of PsA ** passive smoker: defined as exposition of at least 1 hour/day for at least 1 year	

of 40 and 49 years, followed by the age range of 50 to 59 years. The lowest age of disease onset was 10 years in two female patients (**Figure 1**). The mean time from the start of PPP to induction into this study was 9.2 ± 11.8 years. PPP alone was documented in 56.4% of patients, whereas 15.1% were affected by concomitant PV, 18.6% by PsA, and 9.9% by both PV and PsA (**Figure 2**A).

Overall, 28.5% of patients had been diagnosed with PsA. The age of PsA onset was noted in 23 patients with a mean age of 48.7 ± 13.0 years. A family history

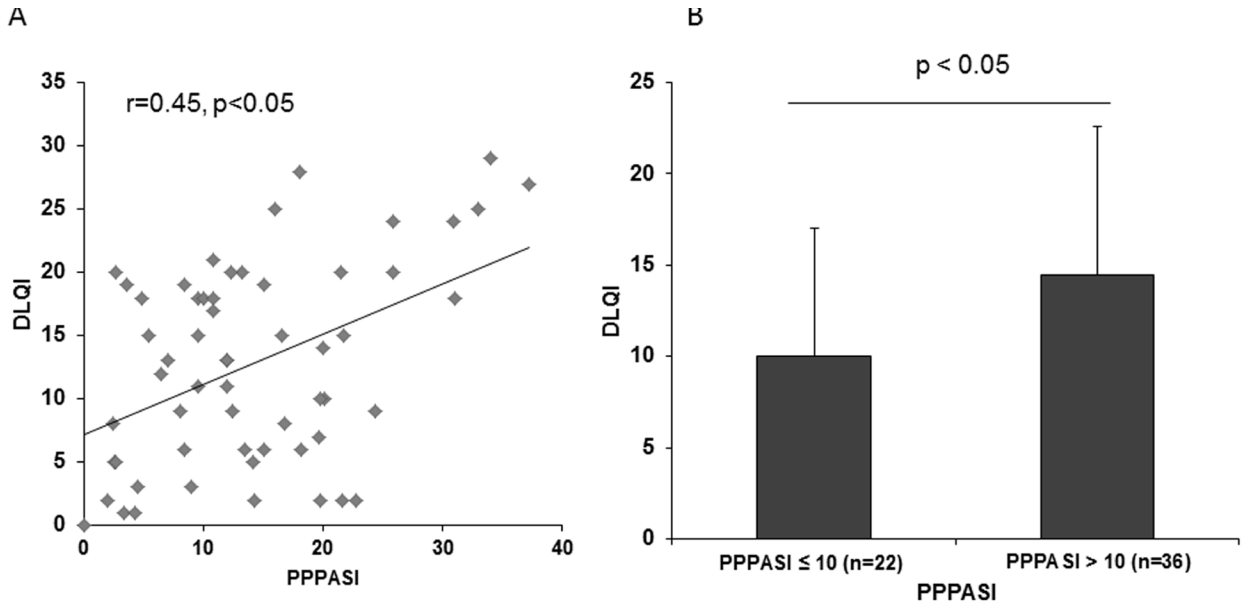

Figure 3. *(A) Correlation of DLQI (Dermatology Life Quality Index) with PPPASI (Palmoplantar Pustulosis Area Severity Index) in patients with PPP (n=58). (B) DLQI and PPPASI in two subgroups of patients with a PPPASI of ≤ 10 or a PPPASI of >* **10.**

of PsA or rheumatoid arthritis was noted in 16.5% of patients.

Among the 172 patients, 25.0% also suffered from concomitant PV. In 39/43 patients the age of onset of PV was recorded. The mean age at the start of disease was 35.0 ± 14.8 years. In most cases (21/39 patients, 53.8%), PV manifested at the same time as PPP (defined as manifestation in the same year of life); in 28.2% PV preceded PPP; and in 15.4% PV manifested after PPP. In one patient the order of manifestation was unknown.

Positive family history of psoriasis was documented in 30.2% of PPP patients. PV within the family was least common in the patient group with PPP only (24.7%). Conversely, 52.9% of the PPP patients with concomitant PV and PsA reported a family history of PV (**Figure 2**B).

PPP and clinical characteristics

In 163 patients, the number of pustules at the time of entry into the study was documented (**Table 1**). During the course of disease, in 68.6% of patients both palms and both soles had been involved (**Table 1**). The PPPASI score was deterimined in 91 patients with an average of 12.6 ± 8.6. The correlation coefficient of PPPASI and number of pustules was r=0.47 (p<0.05, data not shown). In 77 patients the DLQI was obtained and was 12.2 ± 7.7. 41 of 77 patients (53.2%) had a DLQI > 10. Palmoplantar pustulosis - only patients had the lowest DLQI of 10.8 ± 6.7, compared to the patient groups also affected by psoriasis (14.2 ± 9.3), PsA (12.6 ± 9.5), or both (14.9 ± 7.2). However, the difference was not significant. There was a significant positive correlation between PPPASI and DLQI (r=0.45, p<0.05) (**Figure 3**A). For 58 patients both PPPASI and DLQI were recorded. Of these, in 22 patients with a PPPASI ≤ 10 the average DLQI was 10.0 ± 6.9, whereas in the remaining 36 patients with a PPPASI > 10 the mean DLQI was 14.4 ± 8.1 (**Figure 3**B). Nail involvement was present in 36.0% of patients.

Comorbidity

Allergic rhinits, atopic dermatitis, and asthma bronchiale (not restricted to allergic asthma) were reported as comorbidity by 15.1%, 7.0%, and 11.6% of patients, respectively (**Table 1**). Diabetes was reported in 9.9% of patients. Hypertension and dyslipidemia were reported in 28.5% and 18.0%, respectively (**Figure 4**A).

Body Mass Index (BMI)

The BMI of PPP patients was 27.1 ± 5.5. Within the group, 63 patients (36.7%) had a BMI < 25, 69 patients (40.1%) had a BMI between 25 and 29.9, and 38 patients (22.1%) had a BMI ≥ 30 (**Figure 4**B). In patients with a family history of psoriasis, BMI was 27.6 ± 5.5 and in patients with no family history of

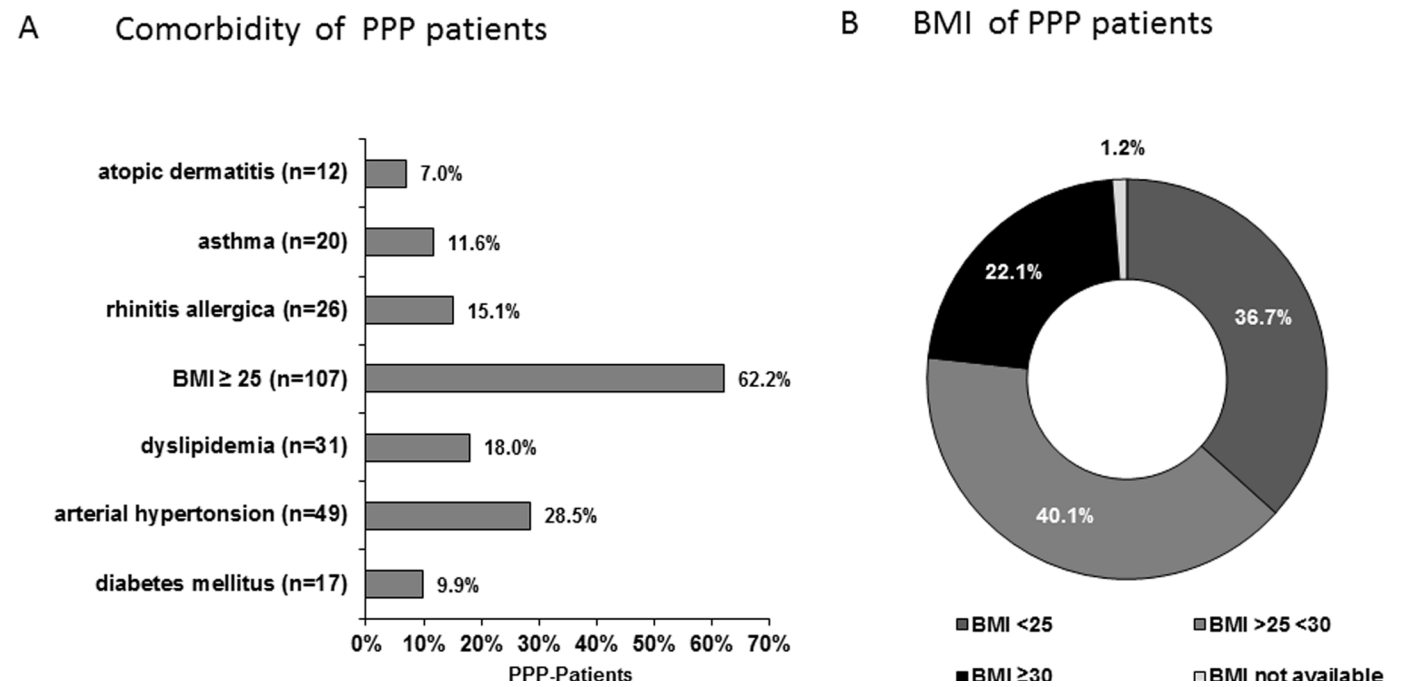

Figure 4. *(A) Prevalence of comorbidity in patients with PPP. (B) Different BMI categories in patients with PPP.*

psoriasis the BMI was 26.9 ± 3.9.

In the general population, BMI is known to differ between men and women and to increase with age. Therefore, in our PPP patients, BMI was calculated for different age groups and for men and women separately (**Table 2**).

In the age group of patients under 40 years of age (n=30), age at manifestation of PPP was 25.5 ± 6.7 years and BMI measured 27.7 ± 5.6; in the female patients of this group (n=26) BMI measured 27.6 ± 5.6. The age at manifestation in this young' female group was 24.8 ± 6.5 years. In the PPP-patients aged between 40 and 64 years with an average age of onset of PPP of 44.6 ± 10.1 years, BMI measured 27.4 ± 5.9; in the female patients of this age group (n=93) BMI was 27.4 ± 6.0. In PPP-patients with an age at inclusion of 65 years or more (n=20), age of PPP onset was 49.5 ± 19.6 years and BMI measured 24.5 ± 4.5; in the female patients of this age group (n=18) BMI was 24.1 ± 4.8.

Smoking

Smoking history was noted in 69.8% of PPP patients at the time of induction into this study. On average, smokers in this study consumed 8.1 ± 8.3 cigarettes per day. An additional 25.6% of patients were former smokers who had stopped smoking at a mean age of 50.1 years. Only 4.1% of PPP patients had never smoked and 77.3% of patients were smokers at the time of PPP manifestation. Smokers and former smokers had started smoking at the age of 18.8 ± 6.0 years. In one patient, smoking history was missing. In 60 patients who smoked at the time of study inclusion, PPPASI was 14.1 ± 9.2. The former smokers had a PPPASI of 9.5 ± 5.4 (23 patients) and the 5 never-smokers had a PPPASI of 9.0 ± 10.3 (**Figure 5**).

Additional potential trigger or aggravating factors of PPP

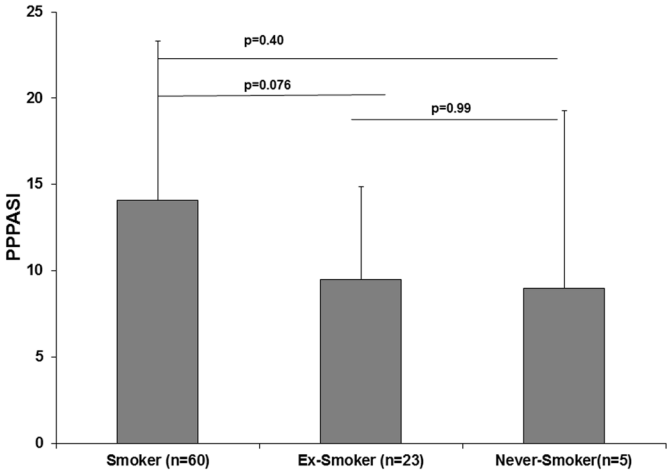

Figure 5. *PPPASI compared between smokers, ex-smokers and never-smokers in PPP patients.*

Table 2. *BMI of PPP patients divided by age and sex. Data from German patients with psoriasis only (Psohealth 3) and the general population of Germany are include for comparison [22].*

BMI					
		all age groups	18-39 years	40-64 years	≥ 65 years
PPP	All	27.1	27.7	27.4	24.5
	Male	27.6	29.3	27.5	26.5
	Female	27.0	27.6	27.4	24.1
Psohealth 3	All	28.0	27.0	28.3	28.0
	Male	28.4	27.6	28.8	28.1
	Female	27.4	26.1	27.6	27.9
General population in Germany	All	25.9	24.3	26.4	26.7
	Male	26.5	25.1	27.2	27.2
	Female	25.0	23.2	25.3	26.3

Mechanical stress at work was reported in 31.4% of patients and 56.4% reported psychosocial stress itself as a trigger factor or as an aggravating factor of their PPP. Infections were perceived by 16.3% of PPP patients as a trigger or aggravating factor.

Of 21 patients in whom a tonsillectomy had been performed in the past, one patient reported an improvement that had lasted for one year, whereas 2 patients had not experienced any improvement. The other patients could not answer the question of the effect of a tonsillectomy upon the course of PPP. Past antibiotic therapy was reported to have been beneficial on the course of PPP by 12 patients, but 46 had not seen such an effect and the remaining patients could not answer this question.

Antipsoriatic systemic therapies including UV-therapies

All drug and UV therapies used by PPP patients, not only at the start of the study but also at any point during the course of their disease, are listed in Table 3. At the time of study, 85 PPP patients (49.4%) were using a systemic drug or UV-therapy. Systemic therapies only were used by 63 of these patients, whereas 22 patients were only treated with UV-therapy. Fifteen patients received a combination of a systemic drug and UV-therapy. With respect to systemic medications, most of these patients received mono-therapy (n=54, 13 in combination with UV-therapy). Eight patients had a combination of two systemic drugs (one patient with additional UV-therapy) and one patient had triple drug therapy plus UV therapy.

The majority of patients had been given systemic drug therapies (in 73.3% of patients) or UV-therapies (72.1%) during their disease course, whereas 9.9% of patients had neither obtained a systemic drug therapy nor a UV-therapy (**Table 3**). Of the drugs used, corticosteroids were used most frequently (40.1% of patients), followed by acitretin (37.8%), and methotrexate (27.9%) (**Table 3**). Among the patients who were receiving MTX at the time of entry into this study or had MTX previously, 51.9% also suffered from PsA, whereas among patients with a history of systemic glucocorticosteroids, 18.9% suffered from additional PsA (**Figure 6**). The average number of different systemic drug therapies per patient was 1.9 ± 2.0 and the number of different systemic therapies including UV-therapies was 2.6 ± 2.1. Palmoplantar pustulosis patients without an additional psoriatic

Table 3. *Systemic therapies of PPP patients*

Therapy	Ever Used	Currently
Acitretin	37.8 % (n=65)	11.0% (n=19)
Adalimumab	10.5 % (n=18)	1.2 % (n=2)
Alitretinoin	1.7 % (n=3)	0.0% (n=0)
Azathioprine	1.2 % (n=2)	0.0 % (n=0)
Azulfidine	7.6 % (n=13)	1.2 % (n=2)
Cyclosporine	17.4 % (n=30)	2.9 % (n=5)
Corticosteroids	40.1 % (n=69)	10.5 % (n=18)
Efalizumab	0.6 % (n=1)	0.0% (n=0)
Etanercept	7.6 % (n=13)	1.7 % (n=3)
Fumaric acid esters	18.6 % (n=32)	3.5 % (n=6)
Golimumab	0.6 % (n=1)	0.6 % (n=1)
Infliximab	4.1 % (n=7)	1.2 % (n=2)
Leflunomide	8.7 % (n=15)	1.2 % (n=2)
Methotrexate	27.9 % (n=48)	6.4 % (n=11)
Ustekinumab	3.5 % (n=6)	0.6 % (n=1)
UV-Therapy	72.1 % (n=124)	21.5 % (n=37)

manifestation had received on average 2.0 ± 1.5 different systemic drugs or UV-therapies. Those with additional PV had undergone 2.4 ± 2.0 therapies; those with additional PsA without PV had received 3.6 ± 2.6 treatments; and those with both PsA and PV had been given 4.9 ± 2.5 different therapies (**Figure 7**). The PPPASI was available for 52 patients with PPP who were not currently receiving systemic therapy and was found to be 13.4 ± 8.9. In 25 systemically-treated PPP patients the respective value was 10.4 ± 7.9. When comparing the DLQI of patients with and without current systemic therapy, the mean DLQI in 27 patients with current systemic therapy was 10.7 ± 5.3 and the mean DLQI in 50 patients without current systemic therapy was 12.9 ± 7.7. However, this difference in DLQI was not statistically significant.

Discussion

Palmoplantar pustulosis is a rare chronic inflammatory disease of the skin. Thus, detailed analyses of clinical parameters in large cohorts of PPP are rare. There is an ongoing controversy whether PPP is a subtype of psoriasis or if it constitutes a separate condition [1]. However, on a genetic level, PPP, in contrast to PV, is not associated with psoriasis risk alleles within the psoriasis susceptibility region 1 (PSORS1, [2]).

Concomitant PV in PPP patients has consistently been reported in previous studies, with a frequency of between 8% and 61.6% (overview in [3]). In two larger population studies, the rates of concomitant PV were 18% [2] and 24% [4]. These values are in agreement with the PV rate of 25% that we observed in the present study. Interestingly, more than half of our PPP patients who also suffered from PV reported that both diseases manifested at the same time (defined as manifestation within the same year of life), suggesting that there are shared features in their pathogenesis or triggering factors in PPP and PV.

In our study, 28.5% of PPP-patients concomittantly suffered from PsA. A previous study performed in 1971 reported a frequency of PsA in PPP patients of 13% [4]. In other studies rates of between 8% [5] and 25.6% have been reported [3]. Interestingly, more than half of the PPP patients with a concomitant diagnosis of PsA in our study do not suffer from additional PV. Despite the ongoing discussion as to whether PPP

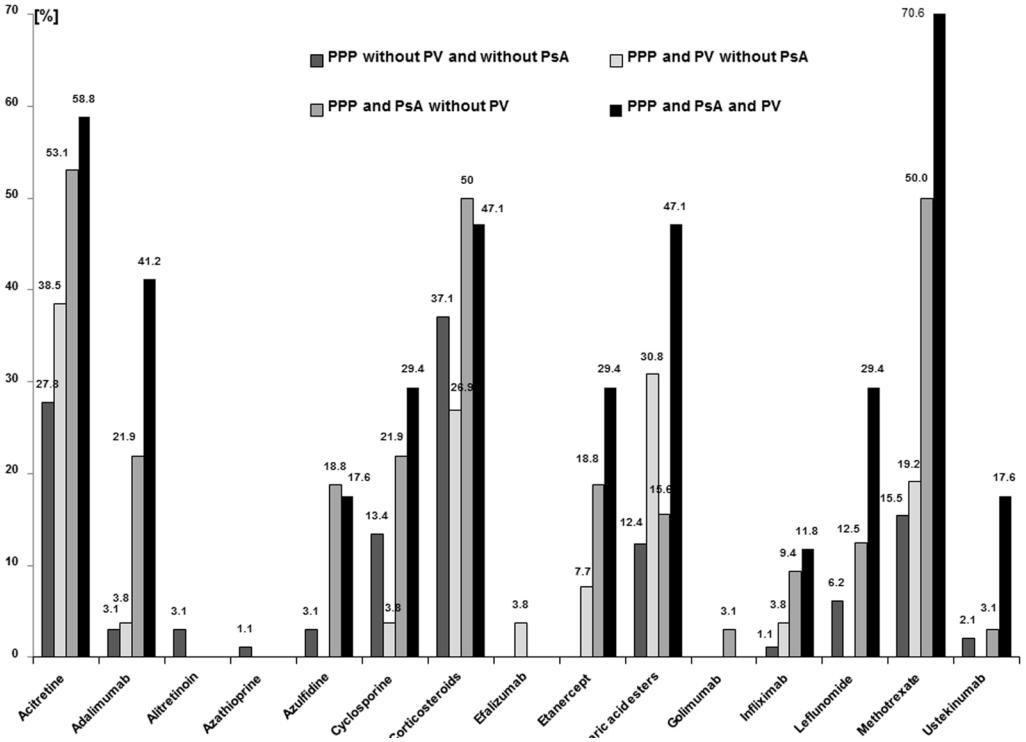

Figure 6. *Frequency of different systemic therapies ever used in patients with PPP with or without PV and/or PsA.*

is a subtype of PV or a separate disease, in clinical practice PPP is likely considered a psoriatic skin disease in some cases, in particular when using the CASPAR criteria for diagnosing PsA [6]. Alternatively, arthritis in PPP patients could be classified as SAPHO-syndrome, with PPP being the most common skin manifestation in this syndrome [7]. Using the inclusion and exclusion criteria formulated by Benhamou et al. the presence of osteoarticular manifestations in PPP patients is a sufficient diagnostic criterion for SAPHO-syndrome, unless no exclusion features are met [8]. Thus, if PPP is a separate entity and not a subtype of PV, the diagnosis of PsA has to be critically balanced against the diagnosis of SAPHO-syndrome in patients presenting with osteoarticular manifestations.

A family history of psoriasis was present in 30.2% of our patients and was highest in PPP patients concomittantly suffering from both PV and PsA. In previous large studies, family history of psoriasis was reported to be present in 10-11% [4, 9] to 22% of patients [10].

In our study, the average DLQI was 12.2, with 53.2% of patients possessing a DLQI > 10 indicating a severe impairment of life quality attributable to the skin disease. The percentage of patients with a DLQI > 10 was higher in PPP patients from our study compared to the 21.3% of patients who had PV only from the PsoHealth3 study performed in 2013/2014 [11]. The high DLQI is consistent with results from a previous study, which demonstrated that psoriasis patients with palmoplantar involvement had significantly higher impairment of mobility and usual activities compared to psoriasis patients without palmoplantar involvement [12].

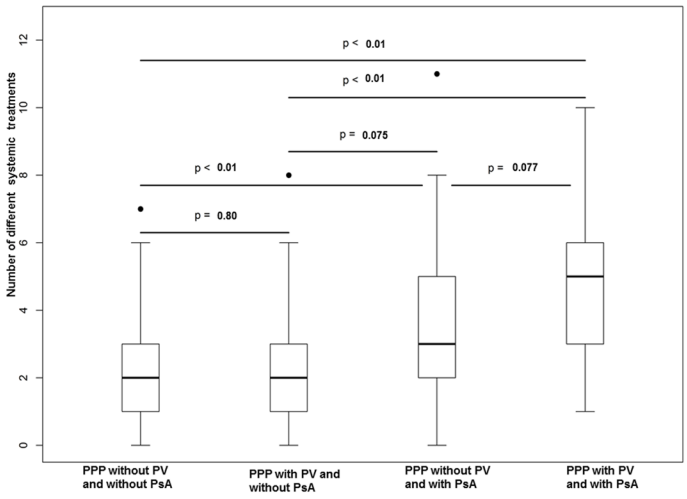

Figure 7. *Number of different systemic therapies (including UV-therapy) in patients with PPP with or without PV and/or PsA.*

In our patient population almost all PPP sufferers were smokers or ex-smokers, confirming the results of previous studies, in which the proportion of never-smokers was also below 10% [5, 10, 13, 14]. For PV, an association with smoking is also well documented by meta-analyses. However, the prevalence of PV smokers is lower than in the PPP population [15, 16].

As a further exacerbating factor of PPP, stress was reported by 56.4% of our PPP patients. In two other studies of PPP patients, stress was mentioned as an exacerbating factor by 45.7% of 57 patients and by 90% of 21 patients [10, 17]. Similarly in PV, data suggest that stressful life events and psychosocial stress may constitute exacerbating factors [18].

Almost one third (31.4%) of PPP patients reported mechanical stress at work as an exacerbating factor of disease. It will be interesting to investigate to what extent PPP can be triggered or worsened by mechanical stress at work.

In 17% of patients a tonsillectomy had been performed in the past. In this retrospective analysis only three patients were able to answer any question relating the effect of tonsillectomy to their PPP. Thus, no statement of the value of tonsillectomy in the care of PPP patients can be extracted from this study. Tonsillectomy has been shown to be beneficial for the management of PPP in a study in Japan. Therefore, additional prospective studies should be performed to investigate its effect in other races [19]. Furthermore, data regarding a possible protective effect of tonsillectomy on the risk of developing PPP are lacking. Thus, future case-control studies may provide further insight.

Palmoplantar pustulosis and BMI

Overweight state was noted in 62.2% of PPP patients (defined by a BMI ≥ 25), and 22.1% of PPP patients suffered from obesity (BMI ≥ 30). In a study published in 2007 that had only included female PPP patients, the BMI was reported to be 26.5 ± 4.3 [5]. This is in close alignment with the mean BMI of 27.1 ± 5.5 that we observed in our study.

In PV, an association with obesity has been convincingly demonstrated [20]. Furthermore, a cohort study has suggested that obesity is also a risk factor for the development of PV [21]. In the PPP patients from our study, the BMI value was higher than the value of the general population of Germany and somewhat lower than the BMI of PV patients from the German PsoHealth3 study [22]. However, the BMI differences in these three study populations can be linked to the different age ranges within each group. In the general population BMI increases with age, whereas in our PPP group the BMI was highest in patients below 40 years of age. In this younger age group the BMI was even higher than in the PV patients from the PsoHealth3 study. For the PPP patients in this study the BMI was lowest in the age group of 65 years or above. Within this group the BMI was even lower than in the general population. An explanation for this low BMI could be that obesity is more important as a triggering factor for PPP in younger patients, whereas in older patients, smoking might be the most prominent risk factor. However, a selection bias cannot be excluded, as obese patients have a higher mortality and could therefore be underrepresented in the group of older PPP patients.

Therapy

Thus far, no treatment guidelines for PPP exist. UV-therapies [including psoralen-UVA (PUVA) therapy] and acitretin as a systemic agent have been licensed for the treatment of PPP. This is reflected by the usage of therapies in the PPP patients of our study. Thus, 72.1% had received UV-therapy and 37.8% systemic acitretin therapy. Other conventional systemic drugs have been used less frequently. Furthermore, biologic agents, mainly TNF antagonists, have been used in some patients.

Most drugs, including the biologics, had already been discontinued by PPP patients before study entry. The reasons for discontinuation of previous medications was not collected. However, poor efficacy in management of PPP or another psoriatic manifestations such as PsA may have played a major role in patients ceasing treatment and is compatible with the known recalcitrance of PPP to systemic therapy [23]. The high frequency of prior or current systemic corticosteroid therapy in 40.1% of PPP patients is notable. Systemic treatments were used least frequently by patients with PPP only, despite the presence of a severe impairment of life quality. This possibly reflects the lower number

of licensed drugs for PPP as compared to the approval of multiple systemic agents for PV and PsA.

Overall, our data underline the urgent need for more approved, as well as new drugs to increase the therapeutic armamentarium available for the treatment of PPP.

Conclusion

To our knowledge this is the largest study to investigate the disease burden, clinical characteristics, and comorbidity of PPP in Caucasian patients. Almost half of the 172 PPP patients included in this study had a concomitant diagnosis of PV and/or PsA. As in other studies, most patients were female and smokers. BMI was high with an average of 27.1, particularly in young patients (< 40 years of age). Although quality of life was severely impaired in PPP patients, less than half of patients were on systemic treatment or UV-therapy at the time of inclusion in this study. However, even patients who were receiving systemic therapies displayed high disease activity. Thus, our study documents the acute need for new effective therapies to support the care of patients with PPP.

Conflicts of Interest

Y*vonne Frambach* has been an advisor and/or received speakers' honoraria and/or received grants and/or participated in clinical trials of the following compa*nies: Abbott /AbbVie, Almirall Hermal, Basilea Pharmaceutica, Biogen Idec, Bioskin, Cepha*lon, Essex Pharma, Eli Lilly, Forward Pharma, Galderma, Intendis GmbH, Hexal, Isotechnika, Janssen-Cilag, Leo Pharma, Merck Serono, Novartis Pharma, Pfizer, Photocure ASA, Photonamic, Schering-Plough, Wyeth Pharma.

Arnd Jacobi has been an advisor and/or received speakers' honoraria and/or received grants and/or participated in clinical trials of the following companies Abbvie, Pfizer, Biogen, Janssen, MSD, Celgene, Novartis, UCB, Leo-Pharma, Medac, Lilly.

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