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PRURITUS CHARACTERISTICS IN A LARGE ITALIAN COHORT OF PSORIATIC PATIENTS.

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Abstract

Background: Psoriasis (Ps) is a chronic systemic autoimmune disease associated with pruritus in 64–98% of patients. However, few modestly sized studies assess factors associated with psoriatic pruritus.

Objective: To investigate factors associated with Ps pruritus intensity.

Methods: Psoriasis patients 18 years or older seen in one of 155 centers in Italy between September 2005 and 2009 were identified from the Italian PsoCare registry. Patients without cutaneous psoriasis and those with missed information on pruritus were excluded.

Results: We identified 10,802 patients, with a mean age 48.8±14.3 years. Mild itch was present in 33.2% of patients, moderate in 34.4%, severe in 18.7% and very severe in 13.7%. Higher itch intensity was associated with female gender, lower educational attainment compared to university degree, pustular psoriasis, psoriasis on the head, face, palmoplantar areas, folds and genitalia, more severe disease, disease duration <15 years, and no or few prior systemic treatments.

Limitations: Effects of specific medication on itch were not assessed.

Conclusions: Pruritus should be evaluated during psoriasis visits, and physicians should be aware of patients at higher risk for itch. Further studies are needed to assess the effects of medications on itch, and establish therapy for psoriasis patients with persistent itch.

Keywords

pruritus; itch; psoriasis; pustular psoriasis; education; treatment

[*]A list of participating centres is provided in the Appendix 1

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Introduction

Psoriasis (Ps) is a chronic systemic inflammatory disease characterized by erythematous patches with a silvery white scale.[1] Associated symptoms include itch, burning and soreness.[2] Of these, cutaneous itch occurs in 64–98% of patients and has been described as the most problematic symptom.[2–15] Furthermore, it has been reported that up to 45% of patients do not experience itch relief with any therapy.[9,16] The itch is generally limited to lesional skin, however 20–30% experience itch on uninvolved skin and some suffer from generalized pruritus.[3,4,8,9] Worsening of psoriasis can occur due to increased scratching and subsequent koebnerization.[17]

Psoriasis associated itch has been shown to negatively impact health related quality of life (HRQOL) measurements, mood, sleep, appetite and libido. In addition, the presence of itch can mitigate the perceived effects of improved disease severity on HRQOL.[18–20] Evaluation of itch using the psoriasis itch VAS has been shown to be effective in accurately capturing patient perception of itch.[21–24]

However, data regarding factors which influence the severity of psoriatic itch are limited and conflicting. The aim of this study was to investigate factors associated to pruritus intensity in a large group of Italian patients with Ps.

Methods

This was a cross-sectional analysis of a group of patients included in the Italian PsoCare registry, involving 155 referral centers for the treatment of chronic plaque Ps in Italy.[25] The study was approved by the ethics committees of each participating center.

Entry criteria

All adult patients (18 years or older) observed in the clinics of participating centers between September 2005 and September 2009, with a confirmed diagnosis of chronic plaque Ps and with a first prescription of conventional or biological therapy for Ps (namely acitretin, cyclosporine, methotrexate, PUVA, etanercept, infliximab and adalimumab), were considered in the analysis.

Patients with a specific diagnosis of psoriasis arthritis (PsA) and without signs of Ps as well as patients without any assessment of pruritus intensity were excluded from the study.

Collected data

Data were collected by the treating physicians with the aid of a web based data collection form build with several internal quality controls and security systems, including patients anonymisation, regular backups and confidentiality checks.

For the purpose of this analysis, a selection of baseline variables was considered, including: demographics (age at entry, gender, marital status, highest educational attainment), personal habits (smoking, alcohol consumption), anthropometric measures (body mass index - BMI), history of comorbidities including PsA, presence of pustular Ps, duration of Ps since first

diagnosis, severity of Ps, pruritus intensity associated with Ps, body areas affected by Ps, previous and current systemic treatments for Ps, hospital admissions for Ps in the last 5 years and number of previous complete clinical remission associated with Ps.

Severity of Ps was assessed by means of psoriasis area severity index (PASI),[1] while the intensity of pruritus associated with Ps was self-assessed by the patient through an anchored visual scale (VAS) ranging from 0 (no pruritus) to 10 (the worst imaginable pruritus).[21]

Patients' main comorbidities, including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, diabetes mellitus, chronic kidney disease, hemiplegia, leukemia, malignant lymphoma, solid tumor, liver disease and acquired immune deficiency syndrome (AIDS), were synthesized by using Charlson comorbidity index (CCI).[26]

Statistical analysis

For descriptive purposes continuous data were presented as means with standard deviations (SD), while categorical data as numbers with percentages. For analysis purposes, continuous data were also categorized by using clinical relevant thresholds as cutoff points. The Mann-Whitney U test and the Kruskal-Wallis test were used to assess differences in the distribution of pruritus intensity across dichotomous variables or categorical variables with three or more categories respectively. In case of ordinal data, when the first test was significant, Cuzick's test for trend was also performed.

All factors with p-value<0.15 in the univariate analysis were evaluated for inclusion in multivariable linear regression analysis with forward stepwise selection algorithm. The effect of selected independent factors were expressed in terms of pruritus intensity absolute variations along with their 95% confidence intervals (CI) and p-values. All tests were considered statistically significant at p-value <0.05. Analyses were carried out by using SPSS software v.20.0 (IBM Corp., Armonk, NY, US).

Results

Overall 10,802 patients (mean age 48.8 ± 14.3 years, male:female ratio = 1.97) were included in the study (Table 1). Their average BMI was 27.1 ± 4.9 kg/m^2 and 41.0% were current smokers. Most subjects (69.8%) were married, with upper secondary (36.8%) or university (11.9%) degree. Regarding comorbidities, the average CCI was 0.31 ± 0.81 and only 16.9% of patients had an index of 1 or higher. Pustular Ps was present in 3.1% of subjects, while PsA in 27.7% of patients. Clinical characteristics of Ps in the study population are shown in Table 2. The mean PASI score among patients was 17.7 ± 11.0, with an average disease duration of 16.4 ± 12.7 years. The mean pruritus intensity was 4.6 ± 3.2 on a VAS scale, with 32.4% of patients reporting a score of 7 or higher. Ps was more frequently observed at limbs (90.7%), trunk (81.6%) and head (75.0%). 34.2% of patients had an hospital admission for Ps in the 5 years before entry in the study and 31.8% reported at least one previous complete clinical remission of Ps. Regarding treatments for Ps, most of subjects (62.7%) had performed at least one systemic therapies before entry in the study.

The most prescribed systemic treatments for Ps at entry were etanercept (30.0%), cyclosporine (24.8%), acitretin (15.6%) and methotrexate (11.9%).

Univariate and multivariable analysis

Univariate and multivariable analysis of factors associated with pruritus at entry in the study is presented in Table 3. Factors potentially associated with pruritus intensity at univariate level and considered for inclusion in the multivariable analysis were: gender, BMI, smoking habits, educational attainment, marital status, PASI score, disease duration, CCI, Pustular Ps, PsA, affected body areas including head, face, trunk, limbs, nails, palmoplantar region, folds and genitalia, number of previous systemic treatments for Ps and hospital admission for Ps in the last 5 years. In the multivariable analysis, independent factors associated with an increased intensity of pruritus are female gender, a primary or lower secondary education as compared to university degree, with a significant increasing trend towards lower educational attainment, a moderate or severe Ps condition, with an increasing trend towards higher PASI score (greater than 10), a disease duration less than 15 years, with an increasing trend towards lower duration, presence of pustular Ps, presence of Ps at the head, face, palmoplantar areas, folds and genitalia, no or few previous systemic treatments for Ps, with an increasing trend towards a lower numbers of treatments.

Discussion

In this cohort, 33.2% of patients experienced mild itch, 34.4% moderate itch, 18.7% severe itch and 13.7% experienced very severe itch. Demographic characteristics associated with higher itch intensity are female gender, lower secondary and primary educational attainment compared to university degree. Psoriatic disease characteristics associated with higher itch intensity are pustular psoriasis, psoriasis on the head, face, palmoplantar areas, folds and genitalia, more severe disease, disease duration <15 years, with greater itch among newly diagnosed patients, and no or few prior systemic treatments. Age, drinking and previous remission of psoriasis were not associated with itch severity.

Similarly to our cohort, the majority of studies did not describe a relationship between itch and age.[7] One of the first studies reported no differences in age between patients experiencing mild, moderate or severe pruritus in a cohort of 82 patients.[5] Later Yosipovitch et al examined 101 patients and found no differences in age between patients with itch and without itch.[3] In addition, Szepietowski et al and Stinco et al found no association between age and itch in 100 and 230 patients respectively.[4,10] In contrast, Janowski et al examined 174 patients and reported higher rates of itch among older patients.[15] Higher rates of itch among older patients were also reported by Sampogna et al in a cohort of 936 patients.[6]

Alcohol is postulated to increase itch severity based on a mouse study.[27] Zou et al found no correlation between alcohol use and itch severity.[28] Similarly in a study of 80 patients, there was no relationship between alcohol use and itch.[5,8] Stinco et al and Cheng et al also reported no differences in drinking habits between patients who itch and those who do not.[7,10] Finally, a prospective study found no correlation between severity of itch and self-reported drinking.[5] These findings are corroborated by our cohort. Smoking was rarely

assessed, and in contrast to our findings, Stinco et al and Cheng et al report no differences in itch occurrence, however this could be due to their smaller cohort size. [7,10]

Data regarding pruritus and education is conflicting. Among our cohort, patients with lower levels of education, particularly lower secondary level and primary educational level demonstrated higher incidence of itch. Similarly in Sampogna et al, lower educational level was associated with increased itch.[6] In contrast Reich et al found no relationship between itch and educational level, while Yosipovitch et al found no correlation between educational level and itch incidence.[3] These differences are potentially due to more modest cohort sizes or different categorizations of educational level.

In our cohort, itch intensity was higher among females. Similarly Amatya et al found a four fold higher rate of itch among female patients.[8] In addition, Sampogna et al demonstrated higher itch frequency among female psoriasis patients.[6] In contrast, a study of 230 plaque psoriasis patients did not demonstrate differences in itch occurrence between males and females.[10] Similarly Janowski et al noted no differences in itch frequency between males and females;[15] however the rates of itch in both groups were high. Other studies also found no difference in itch occurrence and/or frequency between males and females,[3–5, 7, 12] possibly due to an initial high rate of itch and smaller cohort size.

In our cohort, patients with pustular psoriasis experienced more itch compared to those without. In contrast, Sampogna et al demonstrated higher incidence of itch among arhtropathic and palmo-plantar psoriasis, but not pustular psoriasis.[6] Conversely Szepietowski et al found no differences in itch intensity between patients with psoriasis vulgaris and arhtropathic psoriasis.[4] Lastly, Yosipovitch et al found no differences in itch between plaque, guttate and erythrodermic psoriasis, however he did not evaluate pustular psoriasis.[3]

The body areas most affected by itch in our cohort were genitalia, folds, palms/soles, face and head. Genital itch is previously reported to not always occur in the presence of plaques.[29,30] Janowski et al reported that patients with lesions on visible areas were itchy more often than those which could be covered.[15] This is potentially attributed to psychosocial effects, however these claims require addditional investigation. Yosipovitch et al reported more itch on the legs, arms, buttocks and abdomen with rare involvement of the face and neck, potentially due to lower frequency of psoriatic plaques in those areas.[3] Stinco et al, Amatya et al and Szepietowski et al report that itch is most common on the lower extremities,[4,8,10] however we did not observe the same pattern on multivariate analysis after adjusting for other factors.

The interplay between psoriasis severity and itch has had conflicting reports. Among our patients, rates of itch were higher in patients with more severe disease as measured by PASI. Stinco et al and Janowski et al similarly assessed the relationship between PASI and disease severity and reported that itch frequency was higher among those with higher PASI.[15] Furthermore, itch severity and frequency were associated with degree of erythema, desquamation, perilesional irritation, plaque elevation and lesion severity.[5] Similar reports were made by Sampogna et al and Szepietowski et al.[4,6] In contrast, Reich et al

demonstrated no difference between psoriasis severity and presence/intensity of itch.[21] Similarly, Roblin et. al., reported no correlation between itch and psoriasis disease severity in 157 patients.[16] Yosipovitch et al, Czarenka et al and Nakamura et al did not report an impact of psoriasis severity on itch levels.[3,12,31] In our cohort shorter disease duration was associated with higher reported levels of itch. Previous studies have not described a difference in itch levels based on disease duration.[4,5,15] Specifically, Szepietowski et al did not find a correlation between disease duration and itch severity.[4] Furthermore, Gupta et al reported that duration of psoriasis did not differ between patients experiencing mild, moderate or severe pruritus.[5] Finally, Janowski et al reported no differences in disease duration in patients who experience itch all the time, often, sometimes or rarely/never.[15] The differences in these findings could be due to the study population, and due to the categorization of itch.

Evidence for antipruritic therapy is limited, and many patients do not receive specific treatments and are unsatisfied with the efficacy of therapeutic options.[8] The most common topical treatments used were emollients, and corticosteroids, however the majority of patients reported limited short term benefits, and no long term effects.[3,8,10] Antihistamines were used in 25%−50% of patients, and the majority reported short term, but not long term effects.[3,8] Similarly, phototherapy is antipruritic in 25–50% of patients. [3,8] Immunomodulatory therapy with methotrexate and acitretin similarly did not reduce itch. [3,8] Biologics however may have a role in reducing psoriatic itch. A study of 270 patients with moderate-to-severe psoriasis found that pruritus was improved after 12 weeks and lead to clinically meaningful improvements in QOL.[2] Results with ixekizumab were even more promising, with patients experiencing reductions in itch within 1 week of treatment, and significant improvement in itch compared to etanercept by week 12.[32] Finally, topical tropomyosin kinase A inhibitor CT327 is novel medication, which has no effect on psoriasis severity, however can be used for patients who suffer from pruritus.[16]

In conclusion, itch intensity was associated with female gender, lower secondary and primary educational attainment compared to university degree. It was also associated with psoriasis severity as assessed by PASI score, with pustular psoriasis, psoriasis on the head, face, palmoplantar areas, folds and genitalia, more advanced disease, and disease duration <15 years, with greater itch among newly diagnosed patients. Prior studies demonstrated that emollients, corticosteroids, antihistamines, methotrexate and acitretin have limited effect on itch. Biologics such as etanercept and ixekizumab are particularly helpful and in patients with mild disease the topical tropomyosin kinase A inhibitor CT327 may be efficacious. Further studies are needed to assess the effects of medications on itch, and establish therapy for psoriasis patients with persistent itch.

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APPENDIX 1

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Table 1-

General characteristics and history of comorbidities of patients included in the study

		N=10,802*	%
Age, yrs	*mean, SD*	*48.8*	*14.3*
	18–29	1028	9.5%
	30–44	3308	30.6%
	45–59	3851	35.7%
	60+	2615	24.2%
Gender	Male	7164	66.3%
	Female	3638	33.7%
BMI, kg/m^2	*mean, SD*	*27.1*	*4.9*
	<20.0	429	4.1%
	20.0–24.9	3364	32.3%
	25.0–29.9	4233	40.6%
	30.0+	2393	23.0%
Smoking habits	Never	4134	38.9%
	Current	4353	41.0%
	Ex-smoker	2141	20.1%
Drinker	No/occasionally	6210	59.9%
	Regular	3935	38.0%
	Ex-drinker	218	2.1%
Education, yrs	*mean, SD*	*10.2*	*4.0*
	0–5 (primary)	1807	17.0%
	6–8 (lower secondary)	3649	34.3%
	9–13 (upper secondary)	3920	36.8%
	≥14 (university or higher)	1265	11.9%
Marital status	Unmarried	2365	22.2%
	Married/ Common-law husband/wife	7426	69.8%
	Divorced	505	4.7%
	Widowed	345	3.2%
CCI	*mean, SD*	*0.31*	*0.81*
	0	8972	83.1%
	1–2	1226	11.3%
	>2	604	5.6%
Pustular Psoriasis	No	10463	96.9%
	Yes	339	3.1%
PsA	No	7811	72.3%

		N=10,802*	%
	Yes	2991	27.7%

BMI: body mass index, CCI: Charlson comorbidity index, PsA: psoriasis arthritis, SD: standard deviation

*Numbers may not add up to the total due to missing data

Table 2-

Clinical characteristics of psoriasis in the study population

		N*	%
PASI score	*mean, SD*	*17.7*	*11.0*
	<10	1554	19.9%
	10–20	3888	49.9%
	>20	2348	30.1%
Disease duration, yrs	*mean, SD*	*16.4*	*12.7*
	0–4	2091	19.7%
	5–14	3259	30.7%
	15–29	3559	33.6%
	≥30	1690	15.9%
Pruritus intensity, VAS	*mean, SD*	*4.6*	*3.2*
	0 – 2.9 (Mild)	3589	33.2%
	3.0 – 6.9 (moderate)	3712	34.4%
	7.0 – 8.9 (Severe)	2024	18.7%
	9.0 – 10.0 (Very severe)	1477	13.7%
Affected body areas**	Head	7956	75.0%
	Face	2764	26.0%
	Trunk	8659	81.6%
	Limbs	9623	90.7%
	Nails	4058	38.2%
	Palms/Feet	2657	25.0%
	Folds	2662	25.1%
	Genitalia	1977	18.6%
Previous systemic treatments for Ps	*mean, SD*	*1.2*	*1.2*
	0	4025	37.3%
	1	2892	26.8%
	2	2321	21.5%
	3+	1564	14.5%
Hospital admission for Ps in the last 5 yrs	No	7113	65.8%
	Yes	3689	34.2%
Previous clinical remission for Ps	No	7370	68.2%
	Yes	3432	31.8%

BMI: body mass index, PASI: psoriasis area severity index, SD: standard deviation, VAS: visual analogue scale

*Numbers may not add up to the total due to missing data

**Multiple areas are possible

Table 3-

Univariate and multivariable analysis of factors associated with pruritus at entry in the study

		Univariate analysis*		Multivariable analysis**	
		VAS Pruritus mean (SD)	P	VAS pruritus variation (95% CI)	P
Age, yrs	18–29	4.7 (3.1)	0.20	-	-
	30–44	4.6 (3.3)		-	-
	45–59	4.6 (3.2)		-	-
	60+	4.5 (3.2)		-	-
Gender	Male	4.4 (3.2)	<0.001	Ref	
	Female	5.0 (3.3)		0.74 (0.59, 0.89)	<0.001
BMI, kg/m^2	<20.0	4.9 (3.3)	0.03	-	-
	20.0 – 24.9	4.5 (3.2)	(0.21)	-	-
	25.0 – 29.9	4.6 (3.2)		-	-
	30.0+	4.7 (3.3)		-	-
Smoking habits	Never/Ex	4.5 (3.2)	<0.001	-	-
	Current	4.7 (3.3)		-	-
Drinker	No/Occasionally/Ex	4.6 (3.2)	0.96	-	-
	Regular	4.6 (3.2)		-	-
Education, yrs	0–5 (primary)	4.9 (3.3)	<0.001	0.40 (0.14, 0.67)	0.003
	6–8 (lower secondary)	4.7 (3.2)	(<0.001)	0.41 (0.18, 0.65)	0.001
	9–13 (upper secondary)	4.4 (3.2)		0.18 (−0.06, 0.41)	0.14
	≥14 (university or higher)	4.3 (3.2)		Ref	
Marital status	Unmarried	4.5 (3.2)	0.04	-	-
	Married / Common-law husband/wife	4.6 (3.2)		-	-
	Divorced	4.8 (3.4)		-	-
	Widowed	5.0 (3.4)		-	-
PASI score	<10	3.5 (3.2)	<0.001	Ref	
	10–20	4.6 (3.1)	(<0.001)	1.01 (0.83, 1.20)	<0.001
	>20	5.3 (3.1)		1.63 (1.42, 1.84)	<0.001
Disease duration, yrs	0–4	4.7 (3.3)	<0.001	0.42 (0.17, 0.66)	0.001
	5–14	4.7 (3.2)	(<0.001)	0.40 (0.18, 0.61)	<0.001
	15–29	4.5 (3.2)		0.09 (−0.12, 0.31)	0.39
	≥30	4.4 (3.2)		Ref	
CCI	0	4.5 (3.2)	0.001	-	-
	1–2	4.7 (3.3)	(<0.001)	-	-
	>2	5.0 (3.3)		-	-

		Univariate analysis*		Multivariable analysis**	
		VAS Pruritus mean (SD)	P	VAS pruritus variation (95% CI)	P
Pustular Ps	No	4.6 (3.2)	0.06	Ref	
	Yes	4.9 (3.3)		0.46 (0.0, 0.81)	0.049
PsA	No	4.7 (3.2)	<0.001	-	-
	Yes	4.3 (3.3)		-	-
Affected body areas					
Head	No	4.1 (3.3)	<0.001	Ref	
	Yes	4.8 (3.2)		0.48 (0.31, 0.65)	<0.001
Face	No	4.4 (3.2)	<0.001	Ref	
	Yes	5.0 (3.3)		0.27 (0.10, 0.44)	0.002
Trunk	No	4.1 (3.3)	<0.001	-	-
	Yes	4.7 (3.2)		-	-
Limbs	No	4.2 (3.3)	<0.001	-	-
	Yes	4.6 (3.2)		-	-
Nails	No	4.5 (3.2)	0.005	-	-
	Yes	4.7 (3.3)		-	-
Palms/Feet	No	4.5 (3.2)	<0.001	Ref	
	Yes	5.0 (3.3)		0.37 (0.20, 0.54)	<0.001
Folds	No	4.4 (3.2)	<0.001	Ref	
	Yes	5.3 (3.2)		0.34 (0.16, 0.52)	<0.001
Genitalia	No	4.4 (3.2)	<0.001	Ref	
	Yes	5.4 (3.3)		0.51 (0.31, 0.71)	<0.001
Previous systemic treatments for Ps	0	4.7 (3.2)	0.08	0.44 (0.21, 0.66)	<0.001
	1	4.6 (3.2)	(0.01)	0.27 (0.04, 0.51)	0.02
	2	4.5 (3.3)		0.13 (−0.11, 0.36)	0.29
	3+	4.5 (3.3)		Ref	
Hospital admission for Ps in the last 5 yrs	No	4.5 (3.2)	0.002	-	-
	Yes	4.7 (3.3)		-	-
Previous clinical remission for Ps	No	4.6 (3.2)	0.37	-	-
	Yes	4.5 (3.2)		-	-

BMI: body mass index, CCI: Charlson comorbidity index, CI: confidence interval, PASI: psoriasis area severity index, PsA: psoriasis arthritis, Ref: reference category, SD: standard deviation, VAS: visual analogue scale

*Mann-Whitney U test for dichotomous variables or Kruskal-Wallis test for variables with three or more categories. In case of ordinal data, when the first test was significant (P-value <0.05), Cuzick's test for trend was also performed

** Independent factors selected in multiple linear regression analysis with forward stepwise selection algorithm

Non significant after multivariable analysis.