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CLINICAL REPORT

Throat Infections are Associated with Exacerbation in a Substantial Proportion of Patients with Chronic Plaque Psoriasis

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Streptococcal throat infections are known to trigger or exacerbate psoriasis, and several studies support the benefit of tonsillectomy. To evaluate the potential of tonsillectomy as a treatment, we used a retrospective study-specific questionnaire to assess the proportion of psoriasis patients with sore throat-associated psoriasis exacerbations. Our survey sampled 275 psoriasis patients. Of patients with plaque psoriasis, 42% reported sore throat-associated psoriasis exacerbations, and of patients with confirmed streptococcal infections, 72% reported aggravation. Notably, women and patients with early onset psoriasis were more likely to report psoriasis exacerbation after a sore throat ($p<0.001$, $p=0.046$, respectively). Other psoriasis aggravation factors were more common in patients with sore throat-associated exacerbations ($p<0.01$). Of tonsillectomized patients, 49% reported subsequent improvement and had more frequent sore throat-associated aggravation of psoriasis than patients who did not improve after tonsillectomy ($p=0.015$). These findings suggest a closer association between sore throats, streptococcal throat infections and plaque psoriasis than reported previously. ***Key words: chronic plaque psoriasis; sore throat; streptococcal throat infections; tonsillectomy.***

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Psoriasis is a multifactorial disease caused by a combination of genetic and environmental factors. The disease has a strong genetic basis; more than 60 susceptibility loci have been identified (1, 2), including HLA-Cw6, carriage of which is associated with an approximate 10-fold increased risk of developing psoriasis (3). Numerous environmental agents have been reported to trigger and/or exacerbate psoriasis, including psychological stressors, physical trauma, cold climate, cigarette smoking, alcohol intake, and certain drugs (4–7). Similarly, various microorganisms have been implicated, including fungi (*Malassezia, Candida albicans*) and viruses (papillomaviruses, retroviruses) (7). However, throat infections with β-haemolytic streptococci have most convincingly been linked with the initiation and exacerbation of psoriasis.

The association between guttate psoriasis and streptococcal infections has been recognized for 100 years (6, 8–10). However, only a few retrospective (11, 12) and one prospective study (13) have linked exacerbation of plaque psoriasis with streptococcal throat infections. Moreover, such infections are approximately 10 times more frequent in patients with plaque psoriasis compared with age- and sex-matched household controls (13). It has been reported that tonsils from patie nts with psoriasis are more frequently infected with β-haemolytic streptococci, especially group C streptococci, than are recurrently infected tonsils from patients without psoriasis (14). Nevertheless, the immunological basis for the association of psoriasis and streptococcal throat infections is still under investigation.

Palmoplantar pustulosis (PPP) is a painful chronic inflammatory condition, restricted to the palms and/or soles, which was previously regarded as a variant of pustular psoriasis, but is now categorized with acropustular diseases (15). Up to 20% of patients with PPP have concomitant plaque psoriasis (16), and although PPP and plaque psoriasis have different sites of predilection and pathomechanisms (16), they may share common triggering mechanisms. Streptococcal throat infections have been linked to PPP and studies have indicated that PPP may improve after tonsillectomy (17–19).

We have recently reported that patients with plaque psoriasis and a history of sore throat-associated psoriasis exacerbation improve after tonsillectomy (20). The main aim of the current study was to estimate the proportion of patients with plaque psoriasis who experienced disease aggravation after sore throats or streptococcal throat infections, and therefore might be more likely to benefit from tonsillectomy.

METHODS

Study design and cohort

This study is a retrospective large case series that took place from January 2011 to April 2011 at the following dermatology

outpatient units in Iceland: the dermatology outpatient centre at Landspitali – The National University Hospital of Iceland, Reykjavik; Hudlaeknastodin dermatology clinic, Kopavogur; and the Blue Lagoon geothermal clinic, Grindavik (21). A total of 374 patients with psoriasis visiting these clinics were invited to participate; 275 (127 men and 148 women) agreed (73.5% response rate). All participants were over 18 years of age and had been diagnosed with psoriasis by a dermatologist. The study was approved by the National Bioethics Committee of Iceland, the Data Protection Authority of Iceland and performed in compliance with the 1964 Declaration of Helsinki and its later amendments.

A self-report anonymous questionnaire, composed of 15 multiple-choice and short-answer questions (Appendix S1[1]), was designed. Participants were asked to answer as accurately as possible. The questionnaire addressed 5 main topics: (*i*) general demographics; (*ii*) psoriasis subtype, age at onset and whether psoriasis onset had been associated with a sore throat or streptococcal throat infection; (*iii*) frequency of sore throats, defined by a painful inflammation/infection of the mucus membranes in the pharynx, and the frequency of streptococcal throat infections diagnosed by a throat culture, rapid antigen detection test (strep test) or by a physician. Further questions covered: exacerbation of psoriasis during or within 3 weeks of a sore throat or streptococcal throat infection; (*iv*) psoriasis aggravating factors other than sore throat, including general malaise, cold climate, stressful life events, alcohol intake, diet and drugs; (*v*) whether the participant had been subjected to tonsillectomy after the onset of psoriasis; age at time of surgery; and whether the tonsillectomy was associated with changes in the activity of their skin disease.

Statistical analysis

Patient demographics were summarized descriptively. Categorical variables were compared with χ^2 and Fisher's exact test. Level of statistical significance was set at $p \leq 0.05$. A logistic regression model of sore throat aggravation was pursued. All variables with a $p < 0.1$ were entered into the logistic regression model. Odds ratio and 95% confidence intervals were then estimated. All statistics were performed in R, version 2.10 (The R Foundation, Austria).

RESULTS

All 275 recruited participants, 127 men and 148 women, completed the study questionnaire. See Table I for demographic information. The majority of responders (75%) had been diagnosed with plaque psoriasis, 14% with both guttate and plaque psoriasis and 8% with guttate psoriasis. Four patients reported PPP, but 5 of the 275 study participants did not belong to any of the above categories. Early-onset psoriasis, defined as age at onset of 40 years or less (22), was reported by the majority of study participants (87%).

Psoriasis exacerbation associated with a sore throat was reported by 42% of patients with plaque psoriasis, 67% of patients with guttate psoriasis, and 70% of patients with a history of both guttate and plaque psoriasis. This was also the case for 2 out of 4 patients with PPP. Moreover, of the 140 participants with a history of confirmed streptococcal throat infections (Table II), 75% reported streptococcal-associated psoriasis exacerbation. This applied to 72% of patients with plaque psoriasis, 94% of patients with guttate psoriasis, and 79% of patients with both guttate and plaque psoriasis. Furthermore, patients who reported sore throat-associated aggravation were more likely to report streptococcal-associated psoriasis exacerbation (93% vs. 7%, $p < 0.001$). This also applied to subgroups of psoriasis patients: plaque psoriasis (92% vs. 8%, $p < 0.001$), guttate psoriasis (94% vs. 6%, $p = 0.01$) and patients with both guttate and chronic plaque psoriasis (100% vs. 0%, $p = 0.005$). A significantly higher ratio of patients with early-onset psoriasis reported psoriasis exacerbation associated with a sore throat, compared with patients with late-onset psoriasis (51% vs. 30%, $p = 0.046$).

Sore throat-associated aggravation was notably more common among women than men (61% vs. 32%, $p < 0.001$). Even after adjustment for the influence of age, psoriasis subtypes (see Table I), and other psoriasis exacerbation factors, females still had a significantly higher risk of sore throat-associated psoriasis aggravation (odds ratio (OR) = 2.5, 95% confidence interval (CI) 1.37–4.58, $p = 0.003$). Psoriasis exacerbation associated with general malaise, cold climate, stress, consumption of alcohol or various diets were reported significantly more often by patients who also reported sore throat-associated psoriasis aggravation (Table III), and this difference was still significant for cold climate and general malaise, after adjustment for age, gender and psoriasis subtypes (OR = 9.2 and 3.0, 95% CI 3.83–22.3 and 1.58–5.74, $p < 0.001$, respectively). There were no differences between men and women in this respect.

Table I. *Baseline characteristics of the 275 participating patients with psoriasis*

Characteristics	
Men, % (*n*)	47 (127)
Age, years, mean ± SD	42.3 ± 14.2
Age at psoriasis onset, years, mean ± SD	22.3 ± 13.4
Early onset psoriasis (onset before or at 40 years), % (*n*)	87 (240)
Late onset psoriasis (onset after the age of 40 years), % (*n*)	10 (27)
Psoriasis subtype, % (*n*)	
Plaque psoriasis	75 (207)
Guttate psoriasis	8 (21)
Guttate and plaque psoriasis	14 (38)
Psoriasis nail changes	42 (116)
Psoriatic arthritis	20 (56)
Palmoplantar pustulosis, % (*n*)	1 (4)

SD: standard deviation.

Table II. *Streptococcal-associated psoriasis exacerbations among participants with confirmed[a] streptococcal infections*

	% (*n*)
Participants with confirmed streptococcal throat infections[a]	51 (140)
Streptococcal-associated psoriasis exacerbation	75 (105)
Plaque psoriasis	72 (69/96)
Guttate psoriasis	94 (15/16)
Guttate and plaque psoriasis	79 (19/24)
Palmoplantar pustulosis	50 (1/2)

[a]Confirmed by throat culture, rapid antigen detection test or a physician.

[1]http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2408

Table III. *Associations between sore throat-associated exacerbations and other factors reported to aggravate psoriasis*

Psoriasis exacerbating factors	*n*	Patients with sore throat-induced exacerbation % (*n*)	Patients without sore throat-induced exacerbation % (*n*)	*p*-value
General malaise	65	88 (57)	12 (8)	<0.001
Cold climate	162	64 (103)	36 (59)	<0.001
Stress	173	64 (110)	36 (63)	<0.001
Alcohol	68	71 (48)	29 (20)	0.005
Diet[a]	36	75 (27)	25 (9)	0.01
Drugs[b]	9	78 (7)	22 (1)	n.s.

[a]Not specified. [b]Including lithium, beta-blockers, penicillin and methotrexate.

Of the 275 participants, 56 (20%) had been tonsillectomized after the onset of psoriasis (Table IV), and 48% of these reported that tonsillectomy was associated with improvement in their psoriasis. Interestingly, 18/37 (49%) of patients with plaque psoriasis and 3/4 (75%) of guttate patients noted an improvement in psoriasis after tonsillectomy. This also applied to 6/11 (55%) of patients with both guttate and plaque psoriasis (Table IV). Patients who noted improvement after tonsillectomy more frequently reported sore throat-associated aggravation ($p = 0.015$). All patients who reported improvement after tonsillectomy also reported early onset of psoriasis.

DISCUSSION

Psoriasis is a heterogeneous disease with respect to both genetic (1, 2) and pathological components (23, 24) and several external factors have been reported to contribute to the onset and exacerbation of psoriasis (4–6). However, streptococcal throat infection is the only environmental factor that has convincingly been connected to the immunological mechanisms thought to operate in psoriasis (25, 26), especially in patients carrying the HLA-Cw6 allele. With the HLA-Cw6 as the major psoriasis susceptibility allele, the $CD8^+$ T cells are thought to be the major effector cells in psoriasis, as they may respond to peptide antigens presented in the context of HLA-Cw6. Furthermore, chronic stimulation by streptococci in the tonsils gives rise to a set of pathogenic skin-homing (CLA^+) T cells (27). The link between streptococcal throat infections and psoriasis is supported by several lines of research, including increased T-cell responses to streptococcal-derived peptides (28–30), shared T cell receptor rearrangements in psoriasis tonsil and skin-homing and skin-resident T cells (31), increased streptococcal-reactive immunoglobulin G (IgG) titres in the blood of patients with plaque psoriasis (32) and increased throat carriage rate of streptococci among patients with psoriasis (13, 14). Once generated in the tonsils, skin-homing T cells can migrate to the dermis and epidermis, where they are thought to cross-react with skin-derived epitopes, such as keratins (28, 29, 33, 34), maspin, ezrin, PRDX2, hsp27 (30) or melanocyte-derived peptides (35), driving the cutaneous inflammation characteristic of psoriasis. Several studies have indicated that psoriasis can improve after tonsillectomy (26, 36), but indications for such treatment remain to be established. However, most of the patients who have been treated in this way had a history of psoriasis exacerbation in association with sore throats and/or streptococcal throat infections.

Table IV. *Effects of tonsillectomy reported by 56 patients with psoriasis who were tonsillectomized after onset of their psoriasis*

Improvement after tonsillectomy, % (*n*)	48 (27/56)
Plaque psoriasis	49 (18/37)
Guttate psoriasis	75 (3/4)
Guttate and plaque psoriasis	55 (6/11)
Not sure or no improvement, % (*n*)	52 (29/56)

We report here that 42% of patients with plaque psoriasis experienced worsening of their disease in association with sore throat. Furthermore, 72% of the participants with plaque psoriasis and confirmed streptococcal throat infections reported exacerbation of their skin lesions. This is a higher frequency than previously reported by Wardrop et al. (11), where 33% of patients with plaque psoriasis associated worsening of psoriasis with sore throat compared with 3% of matched eczema controls. Note, our study was designed as a retrospective questionnaire and could therefore be limited by recall bias. Sore throat-associated psoriasis aggravation was more common among women ($p = 0.001$). It is not clear why this gender difference exists, but it has been observed that women are more frequently affected with recurrent tonsillitis than men (37). Female sex hormones or altered skin corticosteroid levels might be involved, but we are not aware of any reports on this issue. To that end, it might be interesting to assess prospectively whether postmenopausal women are less sensitive to psoriasis exacerbation after a sore throat and/or a streptococcal throat infection. Patients reporting sore throat-associated aggravation of psoriasis also noted worsening in relation to various other aggravation factors, such as general malaise, stress, alcohol or cold weather. Notably, such associations were not reported by those participants who did not associate sore throat with psoriasis exacerbation. Chronic plaque psoriasis has previously been subdivided into stable and dynamic types (38). Patients with the dynamic type have a more fluctuating course, appear to be more influenced by the various exacerbating factors listed above, and are more often carriers of HLA-Cw6 than patients with a relatively stable disease. This form of plaque psoriasis has even been considered somewhat similar to guttate psoriasis (39). Beside the association between sore throat-associated psoriasis aggravation and other psoriasis exacerbating factors, our data also show that patients with early-onset psoriasis are more prone to sore throat-induced psoriasis aggravation. This suggests that these patients have the dynamic phenotype of plaque

psoriasis, and thus might be appropriate candidates for tonsillectomy. However, our study cohort was limited to Icelandic patients with psoriasis, and Iceland's geographical isolation might have influenced the development of patients more affected by environmental trigger factors, such as streptococcal throat infections.

The tonsils are a major target for streptococcal infections in humans, which are the most common cause of bacterial pharyngitis (40). The high level of streptococcal throat carriage and infections in patients with plaque psoriasis is noteworthy, with the carrier rate for groups A, C and G streptococci as high as 44% (14). Long-term treatment with antibiotics has not been effective for psoriasis (41). Streptococci can exist in both the extracellular and intracellular spaces, forming intracellular reservoirs inside endothelial cells and macrophages within the tonsils (42). At best, antibiotic therapy only manages to reduce the bacterial load in the tonsils, leaving quiescent intracellular streptococci in the tonsillar epithelia and macrophages (42). These streptococci can reactivate, re-colonize and cause symptoms again, whereas tonsillectomy might remove this pool of streptococci.

This, and a number of other studies, support the association between psoriasis and streptococci (11–13, 20). Despite the lack of large controlled clinical trials, tonsillectomy is commonly advocated for patients with recurrent guttate psoriasis. Furthermore, according to a European expert group consensus, tonsillectomy may now be indicated for juvenile psoriasis patients with a positive streptococcal culture and more than 3 recurrent infections (43). Our findings might help to identify patients with plaque psoriasis who could benefit from tonsillectomy, but they need to be confirmed in prospective and more structured studies.

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The authors declare no conflicts of interest.

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