Association of Psoriatic Disease With Uveitis
A Danish Nationwide Cohort Study

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IMPORTANCE Psoriasis, psoriatic arthritis, and uveitis are inflammatory disorders with significant overlap in their inflammatory pathways. Limited evidence is available about the relationship between psoriatic disease and uveitis.

OBJECTIVE To investigate the potential bidirectional relationship between psoriatic disease, including psoriasis and psoriatic arthritis, and uveitis.

DESIGN, SETTING, AND PARTICIPANTS We performed a nationwide cohort study of the Danish population from January 1, 1997, through December 31, 2011. We included 74 129 Danish patients with psoriasis who were 18 years or older during the study period. Patients were identified through administrative registries, and information on age, sex, socioeconomic status, medication, and comorbidity was obtained using individual-level linkage of administrative registers. We performed data analysis from January 27 through March 4, 2015.

EXPOSURES Diagnosis of mild or severe psoriasis or psoriatic arthritis for uveitis risk and diagnosis of uveitis for the risk for psoriasis or psoriatic arthritis.

MAIN OUTCOMES AND MEASURES Diagnosis of uveitis, mild psoriasis, severe psoriasis, or psoriatic arthritis. We calculated incidence rates (IRs) and estimated IR ratios adjusted for potential confounders using Poisson regression.

RESULTS We identified 74 129 cases of psoriasis and psoriatic arthritis and 13 114 cases of uveitis. The IRs (95% CIs) for uveitis were 2.02 (1.99-2.06), 2.88 (2.33-3.56), 4.23 (2.40-7.45), and 5.49 (3.36-8.96) for the reference population and those with mild psoriasis, severe psoriasis, and psoriatic arthritis, respectively. In the reference population, these IRs (95% CIs) were 9.37 (9.30-9.45), 1.12 (1.10-1.15), and 1.04 (1.01-1.06), and in patients with uveitis, these statistics were 15.51 (12.92-18.62), 2.66 (1.72-4.13), and 4.25 (3.00-6.01) for mild psoriasis, severe psoriasis, and psoriatic arthritis, respectively. Adjusted IR ratios (95% CIs) for uveitis were 1.38 (1.11-1.70 [P = .02]), 1.40 (1.07-2.81 [P = .34]), and 2.50 (1.53-4.08 [P < .001]) for patients with mild psoriasis, severe psoriasis, and psoriatic arthritis, respectively. For patients with uveitis, IR ratios (95% CIs) were 1.59 (1.32-1.91 [P < .001]) for mild psoriasis, 2.17 (1.40-3.38 [P < .001]) for severe psoriasis, and 3.77 (2.66-5.34 [P < .001]) for psoriatic arthritis, respectively.

CONCLUSIONS AND RELEVANCE We found a bidirectional association between psoriatic disease and uveitis. Increased focus on eye symptoms in patients with psoriasis and psoriatic arthritis and on skin and joint symptoms in patients with prior or current uveitis may be appropriate.

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Psoriatic arthritis is a common systemic inflammatory disease that is associated with significant morbidity and mortality, particularly in individuals with moderate to severe disease. The inflammatory response in psoriasis is promoted by helper T cells Th1 and Th17, and Tfh1 cell activity and production of interleukin-17 (IL-17) by Th17 cells is associated with active ocular inflammation in patients with uveitis. The occurrence of uveitis in spondyloarthropathies has been well described, but the data on the risk for uveitis in patients with psoriatic arthritis are inconsistent, and even less evidence is available on the risk for uveitis in patients with psoriasis with or without arthritis. Furthermore, no data exist on the risks for psoriatic arthritis in patients with uveitis.

Methods

Data Sources and Study Population

The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations. Study approval was obtained from the Danish Data Protection Agency, and approval from an ethics committee is not required for register studies in Denmark. All data were encrypted and rendered anonymous when used for research purposes. The unique personal identification number, which is assigned to each citizen at birth or immigration, allows linkage across national registries, and all citizens have free, equal, and universal access to health care in Denmark. Data on morbidity were retrieved from the Danish National Patient Register, in which hospital admissions, procedures, and diagnoses have been recorded since 1978 using codes from the International Classification of Diseases, Eighth Revision (ICD-8), until 1994 and the International Statistical Classification of Diseases, Tenth Revision (ICD-10), thereafter. Hospital procedures (including hospital-based pharmacologic treatment, eg, therapy with a biological agent) are coded in the Danish National Patient Register as treatment procedures (SKS) codes (http://www.ssi.dk/sks). Data (eg, date of dispensing, dosage, formulation, quantity) on all pharmacy-dispensed medications are accurately registered according to the international Anatomical Therapeutical Chemical (ATC) classification in the Danish Registry of Medicinal Products Statistics since 1994. Information on tax-reported household income is registered by Statistics Denmark.

The study cohort consisted of the entire Danish population 18 years or older starting January 1, 1997, and followed up until December 31, 2011, or until a diagnosis of an end point, migration, or death from any cause. Patients with prevalent psoriasis or uveitis at baseline were excluded to enable evaluation of the temporal relationship between exposure and outcome and to ensure accurate risk-time allocation. Patients with psoriasis were identified when they dispensed their second prescription of topical vitamin D derivatives (ATC D05AX), which is the favored first-line treatment for psoriasis in Denmark, or by their first inpatient or outpatient consultation for psoriasis (ICD-8 codes M07.0 and M07.19 and ICD-10 code L40) or psoriatic arthritis (ICD-8 code M07.09 and ICD-10 codes M07.0-M07.3). Patients were defined as having severe psoriasis if they received treatment consistent with severe disease, that is, treatment with biological agents (ATC L04AB01, L04AB02, L04AB04, L04AC05, L04AA21; SKS BOHJ18A1-BOHJ8B3, BOHJ18B3), cyclosporine (ATC L04AD01, SKS BOHJ20), hydroxyurea (ATC L01AA05, SKS BWHA18I), psoralens (ATC D05BA, SKS BNGA1), retinoids (ATC D05BB, SKS BQHB30), or methotrexate sodium (ATC L03BA01, L04AX03, SKS BWHA115). Patients with uveitis were identified by their first inpatient or outpatient hospital diagnosis of uveitis (ICD-8 code 364, ICD-10 codes H20.0-H20.9) recorded in the National Patient Registry. Based on the ICD codes, comorbidities (Table 1) were described at study entry and up to 5 years prior to study entry, and the information was updated continuously throughout the study period. Inflammatory bowel disease, herpes zoster, and sarcoidosis were included as potential confounding comorbidities because they have been associated with uveitis and psoriasis.
psoriasis.\textsuperscript{15-17} We calculated an index of socioeconomic status based on the mean gross annual income (standardized by age) ranging from 0 (lowest income group) to 4 (highest income group) during a 5-year period before study inclusion. The outcome of this study was the first occurrence of mild psoriasis, severe psoriasis, or psoriatic arthritis in patients with uveitis and the first occurrence of uveitis in patients with mild psoriasis, severe psoriasis, or psoriatic arthritis.

**Statistical Analysis**

We performed data analysis from January 27 through March 4, 2015. Baseline characteristics were presented as frequencies with percentages for categorical variables and means (SDs) for continuous variables. We summarized incidence rates (IRs) per 10 000 person-years at risk. Outcomes before an index date in the psoriasis groups were allocated in the reference group to obtain a more accurate exposure time allocation. Likewise, patients contributed risk time in the mild psoriasis group until they fulfilled the criteria for severe psoriasis, if appropriate. For psoriatic arthritis, we performed subanalyses with the ICD-10 code M072, which is specific for psoriatic spondylitis. Poisson regression models were used to calculate crude and age- and sex-adjusted IR ratios (IRRs) and IRRs adjusted for age, sex, socioeconomic status, and comorbidities (Table 1). Two-tailed $P < .05$ was considered statistically significant, and results were reported with 95% CIs where applicable. All statistical analyses were performed with STATA software (version 11.0; StataCorp) and SAS software (version 9.2; SAS Institute Inc).

**Results**

From January 1, 1997, through December 31, 2011, 5 536 422 Danish citizens were 18 years or older. The study flowchart is shown in the Figure, and a total of 27 544 individuals with a history of psoriasis or uveitis before the start of the study were excluded. The final study cohort consisted of 5 508 878 Danish citizens with a maximum follow-up of 15 years. During the study, we identified 74 129 patients with incident psoriasis and 13 114 patients with incident uveitis. Of patients with psoriasis, 60 145 and 7249 were classified as having mild and severe psoriasis, respectively, and 6735 patients were classified as having psoriatic arthritis. Among the patients with psoriatic arthritis, we identified 294 with a specific diagnosis of psoriatic spondylitis. The baseline characteristics of the study population are shown in Table 1. Patients with mild psoriasis, severe psoriasis, and uveitis were slightly (approximately 2-3 years) older than their respective reference populations. Moreover, the mean socioeconomic status was marginally lower in the reference population, and slightly more women (56.3%) than men had psoriatic arthritis.

**Risk for Uveitis in Patients With Psoriasis or Psoriatic Arthritis**

The results showed an overall increased risk for uveitis in patients with psoriasis and psoriatic arthritis (Table 2 and Table 3). The IRs (95% CIs) of uveitis per 10 000 person-years were 2.02 (1.99-2.06), 2.88 (2.33-3.56), 4.23 (2.40-7.45), and 5.49 (3.68-8.96) for the reference population and those with mild psoriasis, severe psoriasis, and psoriatic arthritis, respectively. Compared with the reference population, the fully adjusted Poisson regression analyses models (adjusted for age, sex, socioeconomic status, and comorbidities) demonstrated an increased risk (reported as IRRs [95% CIs]) for uveitis in mild psoriasis (1.38 [1.11-1.70]) and psoriatic arthritis (2.50 [1.53-4.08]), but not for severe psoriasis (1.40 [0.70-2.81]) ($P = .34$) (Table 4 and eFigure in the Supplement). In subanalyses of patients with psoriatic spondylitis (n = 294), the IR was 22.55 (95% CI, 5.64-90.16), and patients with psoriatic spondylitis had a more than 8-fold increased risk (reported as IRRs [95% CIs]) for uveitis in crude (9.09 [2.27-36.34], age- and sex-adjusted (9.11 [2.28-36.44]), and fully adjusted (8.35 [2.09-33.38]) models.
Table 2. Incidence Rates of Uveitis in the Reference Population and Patients With Psoriatic Disease

<table>
<thead>
<tr>
<th>Exposure Risk for Uveitis</th>
<th>Reference Population (n = 60 434 749)</th>
<th>Incident Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean grade of inflammation (n = 60 434 749)</td>
<td>Mild Psoriasis (n = 60 145)</td>
</tr>
<tr>
<td>No. of events</td>
<td>13 000</td>
<td>86</td>
</tr>
<tr>
<td>Person-years of exposure</td>
<td>64 224 089</td>
<td>198 483.1</td>
</tr>
<tr>
<td>IR (95% CI)</td>
<td>2.02 (1.99-2.06)</td>
<td>2.88 (2.33-3.56)</td>
</tr>
</tbody>
</table>

Abbreviation: IR, incidence rate.

Table 3. Incidence Rates of Mild Psoriasis, Severe Psoriasis, and Psoriatic Arthritis in the Reference Population and Patients With Uveitis

<table>
<thead>
<tr>
<th>Exposure Risk</th>
<th>Reference Population (n = 5 495 764)</th>
<th>Incident Diagnosis (n = 13 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild psoriasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>60 030</td>
<td>115</td>
</tr>
<tr>
<td>Person-years of exposure</td>
<td>64 049 148</td>
<td>74 143.1</td>
</tr>
<tr>
<td>IR (95% CI)</td>
<td>9.37 (9.30-9.45)</td>
<td>15.51 (12.92-18.62)</td>
</tr>
<tr>
<td>Severe psoriasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>7229</td>
<td>20</td>
</tr>
<tr>
<td>Person-years of exposure</td>
<td>64 464 955</td>
<td>75 079.3</td>
</tr>
<tr>
<td>IR (95% CI)</td>
<td>1.12 (1.10-1.15)</td>
<td>2.66 (1.72-4.13)</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>6703</td>
<td>32</td>
</tr>
<tr>
<td>Person-years of exposure</td>
<td>64 557 729</td>
<td>75 344.6</td>
</tr>
<tr>
<td>IR (95% CI)</td>
<td>1.04 (1.01-1.06)</td>
<td>4.25 (3.00-6.01)</td>
</tr>
</tbody>
</table>

Abbreviation: IR, incidence rate.

* Calculated per 10 000 person-years.

Risk for Psoriasis or Psoriatic Arthritis in Patients With Uveitis

The IRs (95% CIs) per 10 000 person-years for mild psoriasis, severe psoriasis, and psoriatic arthritis were 9.37 (9.30-9.45), 1.12 (1.10-1.15), and 1.04 (1.01-1.06), respectively, in the reference population, which included participants without uveitis. The corresponding IRs (95% CIs) for mild psoriasis, severe psoriasis, and psoriatic arthritis in patients with uveitis were 15.51 (12.92-18.62), 2.66 (1.72-4.13), and 4.25 (3.00-6.01), respectively (Tables 2 and 3). Fully adjusted analyses revealed an increased risk (reported as IRRs [95% CIs]) for mild psoriasis (1.59 [1.32-1.91]), severe psoriasis (2.17 [1.40-3.38]), and psoriatic arthritis (3.77 [2.66-5.34]) in patients with uveitis (Table 4 and eFigure in the Supplement). In subanalyses, the IR (95% CI) for psoriatic spondylitis was 0.05 (0.04-0.05) and 0.40 (0.13-1.23) for the reference and uveitis groups, respectively, and patients with uveitis had a significantly increased risk (reported as IRRs [95% CIs]) for psoriatic spondylitis in crude (8.81 [2.83-27.48]), age- and sex-adjusted (9.21 [2.95-28.74]), and fully adjusted (8.03 [2.56-25.22]) models.

Discussion

In this nationwide study of the Danish population, we demonstrated an increased risk for uveitis in patients with psoriasis and an even higher risk for uveitis in patients with psoriatic arthropathy. We also found an increased risk for mild psoriasis, severe psoriasis, and psoriatic arthritis in patients with uveitis. To the best of our knowledge, this study is the first to examine the bidirectional relationship between psoriatic disease, including psoriasis and psoriatic arthritis, and uveitis. The overall incidence of psoriasis and psoriatic arthritis in patients with uveitis was low (n = 167), as was the incidence of uveitis in patients with psoriasis and psoriatic arthritis (n = 114). However, our results remained consistent even after adjustment for potential confounding factors, and they clearly indicate that patients with psoriatic skin disease, even in the absence of psoriatic arthritis, are at increased risk for uveitis and that the reverse relationship may also be of clinical importance.

Only a few studies have previously investigated the association between psoriasis and uveitis.18 One study19 reported that 9 patients with psoriasis without joint involvement developed uveitis, of whom 7 individuals had psoriasis before the uveitis diagnosis. A cross-sectional study from Singapore also demonstrated a nonsignificant association between the severity of psoriasis and the risk for uveitis in a cohort of 100 Asian patients. In another study, 36 patients with uveitis and psoriasis without psoriatic arthritis were compared with 30 patients with HLA-B27-associated uveitis and 30 patients with idiopathic anterior uveitis. Among the patients with psoriasis and uveitis, 21 (58%) were seronegative for HLA-B27, whereas the mean grade of inflammation was significantly higher in patients who were seropositive for HLA-B27, whereas the mean grade of inflammation was significantly higher in patients who were seronegative for HLA-B27, whereas the mean grade of inflammation was significantly higher in patients who were seropositive for HLA-B27.20 Also, in a case-control study21 of 100 consecutive patients with psoriasis or psoriatic arthritis (mean Psoriasis Area and Severity Index score, 8.59) undergoing detailed ophthalmological examinations on referral to a dermatological clinic and 100 control individuals without ocular complaints, 58 patients with psoriasis and 25 controls displayed ocular abnormalities (predominantly blepharitis and conjunctivitis), and 2 cases of uveitis were identified in the psoriasis group vs none in the control group. However, a fundamental limitation in the aforementioned studies is their small sample size of selected patients. By the use of nationwide data from the entire Danish population, our study therefore expands the existing evidence considerably.

Although the fully adjusted models showed a 40% increased risk for uveitis in patients with severe psoriasis (IRR, 1.40), the result in this group was not statistically significant, arguably owing to the relatively low number of events (n = 12) in this specific patient group. The bidirectional relationship between psoriasis and psoriatic arthritis and uveitis suggests a shared pathogenic pathway, and increased systemic inflammation may contribute to the observed relationship. In potential support of such a hypothesis, several studies have reported a beneficial effect of anti-tumor necrosis factor therapy on the
frequency and severity of ocular attacks in patients with uveitis.22-24 Psoriasis is believed to be driven by TH1 and TH17 cells, and research also suggests that the immunopathogenesis of uveitis includes TH17- and TH1-dependent immune responses, such as with disease activity–correlated increases of IL-17 levels in the aqueous humor of patients with uveitis compared with healthy controls.7 Moreover, many other proinflammatory mediators that probably contribute to the pathogenesis of psoriasis, such as IL-2, IL-6, and tumor necrosis factor, have been found in increased concentrations in the aqueous humor of patients with uveitis.7,25 In addition, involvement of the IL-23 receptor in the pathogenesis of psoriasis is well established (eg, by promoting TH17-cell differentiation), and similar mechanisms have been suggested in experimental autoimmune uveitis.26-28 Along this line, increased susceptibility to psoriasis or ankyllosing spondylitis with uveitis has been reported in individuals with selected IL-23 receptor gene variants.27-29 As a major histocompatibility complex I gene thought to be responsible for antigen presentation to autoreactive cytotoxic T cells, HLA-B27 has been closely associated with the development of spondyloarthropathies, such as psoriatic arthritis.30 Similarly, several studies have demonstrated an association between HLA-B27 and uveitis, although the relationship among psoriasis, uveitis, and HLA-B27 is not fully understood.31-33 Several strengths and limitations apply to the interpretation of the present results. The nationwide databases in Denmark allow for analysis of a large number of patients while reducing selection bias. Complete registration and the prospective nature of ICD diagnostic codes in the Danish National Patient Register ensured that nonresponse and recall bias were minimal. Continuous update of comorbidities during the study period ensured accurate registration of potential confounding factors that could change over time. Although we demonstrated an increased risk for uveitis in patients with psoriasis, the observational design of our study does not allow us to establish any causal link. Although the occurrence of psoriasis in our study was similar to that of previous reports from Scandinavian countries, the incidence of uveitis in our cohort was somewhat lower than what was reported for a cohort from northern California.34,35 However, although uveitis is strongly associated with seropositivity for the major histocompatibility complex HLA-B27, the prevalence of HLA-B27 is much higher in North America compared with Denmark.36 Moreover, some patients in our study likely were treated for uveitis by ophthalmologists in private clinics, whereby they would not have received a hospital diagnosis. However, this occurrence would have led to underestimation of uveitis diagnoses and uveitis events in the registries and thereby have attenuated the true uveitis-related risks for psoriasis and psoriatic arthritis and the true psoriasis-related risk for uveitis. Furthermore, in subanalyses, the IRRs for uveitis in patients with psoriatic spondylitis and vice versa were based on a very limited number of events (<5). Finally, the Danish population is predominantly white, and a strong burden of uveitis and HLA-B27 has been attributed to geographic origin, with a prevalence of HLA-B27 in Denmark of approximately 8% (range, 6%-9%).33,36 Therefore, extrapolation of our results to patients of other ethnicities should be performed with caution.

Conclusions

We found an increased risk for mild psoriasis, severe psoriasis, and psoriatic arthritis in patients with uveitis and an in-
increased risk for uveitis in patients with psoriasis and psoriatic arthritis. Increased focus on eye symptoms in patients with psoriasis and psoriatic arthritis and on skin and joint symptoms in patients with uveitis may be appropriate.

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Study concept and design: Egeberg, Mallbris, Skov, Hansen.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Egeberg, Khalid, Hansen.
Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Egeberg, Khalid.

Obtained funding: Egeberg.

Administrative, technical, or material support: Egeberg, Gislason.

Study supervision: Gislason, Mallbris, Skov, Hansen.

Conflict of Interest Disclosures: Dr Egeberg is employed by Pfizer. Dr Mallbris is employed by Eli Lilly and Company. No other disclosures were reported.

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REFERENCES