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A cross-sectional study in Denmark

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Autoimmune Disease in Children and Adolescents with Psoriasis: A Cross-sectional Study in Denmark

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Psoriasis is an immune-mediated inflammatory disease, which, in studies among adults, have been shown to cluster with autoimmune disease. The aim of this cross-sectional register study was to examine possible associations between 9 pre-selected autoimmune diseases and psoriasis in children and adolescents. The study population consisted of all individuals living in Denmark, age under 18 years on 31 December 2012. A total of 1,925 children and adolescents with psoriasis and 1,94,712 without psoriasis were identified. Psoriatic arthritis (adjusted odds ratio (OR) 10.08; 7.97–12.74), rheumatoid arthritis (adjusted OR 6.61; 2.75–15.87) and vitiligo (adjusted OR 4.76; 1.71–13.20) showed strong associations with psoriasis. In addition to increased risk of selected autoimmune diseases, the presence of psoriasis was associated with increased risk of multiple concurrent autoimmune diseases compared with children and adolescents without psoriasis. Clinicians should be aware of extracutaneous symptoms when treating children and adolescents with psoriasis.

Key words: psoriasis; autoimmune disease; children; adolescents; comorbidity.

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Psoriasis is chronic inflammatory skin condition with an autoimmune pathogenetic component and a strong, but complex, genetic inheritance (1, 2). The estimated prevalence of psoriasis in the western world is 3–4% in adults and 0.4–1.37% in children and adolescents (henceforth “children”) (3–7). The prevalence rate increases approximately linearly, from 0.12% at an age of 1 year to 1.24% at 18 years of age (3). Incidence of psoriasis is bimodal, with a large peak at 16–22 years and a smaller peak at 57–60 years, probably reflecting different disease entities (8). The disease can be debilitating for patients due to pruritus and visible disfiguration resulting from presence of red plaques with silvery scales, in turn leading to decreased quality of life (9). In addition, patients with psoriasis have an increased risk of several comorbidities, such as cardiovascular disease, metabolic syndrome, and psoriatic arthritis (10–18).

Studies suggest that some of the comorbidities and associated risk factors that are seen in adults with psoriasis may also be present in children with psoriasis. Indeed, studies have suggested increased presence of arterial hypertension, metabolic syndrome, and autoimmune diseases, including rheumatoid arthritis and Crohn’s disease, in paediatric psoriasis (3, 19–28).

Autoimmune diseases, such as rheumatoid arthritis and inflammatory bowel disease (IBD), have a profound negative effect on quality of life (29, 30). They are therefore a potential additional disease burden to keep in mind when treating patients with psoriasis. Autoimmune diseases display a heightened immune response against the person’s own tissue, cells, and cellular components, such as DNA, keratin, or, for psoriasis, a melanocytic autoantigen. A recent study confirmed that psoriasis shares genetic susceptibility loci with a range of autoimmune diseases including IBD (2, 31). In order to further examine the risk of comorbid autoimmune disease and clustering of autoimmune diseases in children with psoriasis compared with healthy controls, we conducted a cross-sectional study using the total paediatric population in Denmark.

METHODS

Population

All inhabitants under the age of 18 years who were alive and resident in Denmark on 31 December 2012 were identified. All residents in Denmark are assigned a unique personal 10-digit identification number at birth or immigration, which enables linkage on the individual level between different Danish administrative registers. This study used data from the Danish Civil Registration System, the Danish National Patient Register, and the Danish National Prescription Registry. Data on age, sex, vital- and migration status were available from the Danish Civil Registration System, the Danish National Patient Register, and the Danish National Prescription Registry. Data on age, sex, vital- and migration status were available from the Danish Civil Registration System (32). Established in 1978, the Danish National Patient Register contains information on all hospital-based inpatient and, since 1994, outpatient consultations. Diagnosis are recorded according to the International Classification of Diseases, 8th Revision (ICD-8) until 1994, and the 10th Revision (ICD-10) thereafter (33). Information on psoriasis and a number of autoimmune diseases was obtained from here. The Danish National Prescription Registry contains detailed information on the individual level on every Danish pharmacy-dispensed medication since 1994, coded...
Table I. Included autoimmune diseases

<table>
<thead>
<tr>
<th>Autoimmune disease</th>
<th>ICD-10 code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriatic arthritis</td>
<td>M07.0-3, M06, M09.0</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>M05, M06</td>
</tr>
<tr>
<td>Unspecified IBD</td>
<td>Patients with both K50 and K51</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>K50</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>K51</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>K90.0</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>E10</td>
</tr>
<tr>
<td>Autoimmune thyroiditis</td>
<td>E06.3</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>L80</td>
</tr>
</tbody>
</table>

*aIncludes psoriatic arthritis, juvenile idiopathic arthritis, and juvenile psoriatic arthritis.

IBD: inflammatory bowel disease; ICD-10: International Classification of Diseases, 10th Revision.

Table II. Demographics of the children with psoriasis in the general population

<table>
<thead>
<tr>
<th></th>
<th>General population (n = 1,194,712)</th>
<th>Psoriasis (n = 1,925)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>9.2 (5.2)</td>
<td>13.8 (3.4)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>582,382 (48.6)</td>
<td>1,053 (54.7)</td>
</tr>
<tr>
<td>Boys</td>
<td>612,330 (51.2)</td>
<td>872 (45.3)</td>
</tr>
<tr>
<td>Scandanavian</td>
<td>1,070,853 (89.6)</td>
<td>1,696 (88.1)</td>
</tr>
<tr>
<td>Western/Southern Europe</td>
<td>34,410 (2.9)</td>
<td>67 (3.5)</td>
</tr>
<tr>
<td>Africa</td>
<td>18,500 (1.6)</td>
<td>26 (1.4)</td>
</tr>
<tr>
<td>America</td>
<td>2,147 (0.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Asia</td>
<td>54,374 (4.6)</td>
<td>116 (6.0)</td>
</tr>
<tr>
<td>Oceania</td>
<td>211 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>13,825 (1.2)</td>
<td>20 (1.0)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>392 (0.03)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Native, n (%)</td>
<td>1,066,942 (89.3)</td>
<td>1,092 (87.9)</td>
</tr>
<tr>
<td>Migrant, n (%)</td>
<td>29,469 (2.5)</td>
<td>43 (2.2)</td>
</tr>
<tr>
<td>≥ 1 parent were migrants</td>
<td>98,246 (8.2)</td>
<td>190 (9.9)</td>
</tr>
</tbody>
</table>

*p-value: 0.0001

SD: standard deviation.

where applicable. All analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA) and STATA software version 13.0 (StataCorp, College Station, TX, USA).

RESULTS

A total of 1,925 children with a diagnosis of psoriasis and 1,194,712 children without such a diagnosis (Table II) were identified. The majority of the study population was of Danish descent. Children with psoriasis were more likely to be female (54.7% vs. 48.8%). Adjusting for age, sex, and healthcare consumption showed similar results as when adjusting for age and sex only. The presented results below are adjusted for age, sex and healthcare consumption, which give the most conservative esti-
have shown conflicting results. In one study Crohn’s disease was found to be more prevalent in children with psoriasis, while another paediatric study failed to show a significant association between the respective IBDs and psoriasis (3, 28). In contrast to previous studies, we did not find a significant association between coeliac disease and psoriasis (39, 40). One possible explanation for the above-mentioned discrepancies could be that our study population is inherently young. The children have therefore not reached an age where the prevalence of the studied autoimmune diseases has reached a level where a possible association can be shown. This could either be because the diseases have not yet developed or due to a delayed hospital diagnosis based on still unspecific symptoms. For example, in the case of IBD the incidence rate does not peak until 15–29 years of age, with the gradient of the curve increasing sharply to this point (41). The study by Augustin et al. (3), showing a significant association between Crohn’s disease and psoriasis in children, did not control for any potential confounding factors; consequently, their results were similar to our unadjusted results. A modest, but significant, association was found between psoriasis and autoimmune thyroiditis in children, even though such an association has not been found in adults with psoriasis (42, 43). In our study, we did not find any association between psoriasis and type 1 diabetes; an observation in accordance with previous findings from adults with psoriasis (10). The previous studies on the association between psoriasis and diabetes in children have focused either on type 2 diabetes or diabetes in general with no discrimination between type 1 and type 2 diabetes (3, 28, 44). Interestingly, the results of the current study suggest that children with psoriasis in general have a higher risk of having autoimmune diseases. This clustering of autoimmune disease has also been shown in adults with psoriasis and is supported by the fact that many of these autoimmune diseases share genetic loci (10, 31, 45). The results of the current study also suggest that psoriasis is associated with an even higher risk of having multiple autoimmune diseases, and this has not been proven in adults (10).

The current study has several strengths; it was based on a large nationwide register; we were able to include also milder psoriasis cases via vitamin D analogue usage; and it was possible to adjust for important confounders. All inhabitants in Denmark have equal access to tax-supported healthcare without charge, including treatment in hospital-based settings and by general practitioners. Selection bias was thus minimized. Although vitamin D analogues are not officially recommended for use in children, a recent consensus paper confirmed that practicing dermatologists agree on and recommend the use of topical vitamin D analogues as a first-choice in paediatric psoriasis (34). A recent review also demonstrated that topical vitamin D analogues are efficacious and generally safe for paediatric use (35). Due to the
natural history of many autoimmune diseases, it may be difficult to determine the exact time of disease onset, e.g. patients may have had symptoms for years before seeking medical attention or before a correct diagnosis is assigned. Thus, we opted for a cross-sectional study design as this does not include temporal assessment. All the investigated associations were found to be significant in the unadjusted form, which emphasizes the importance of considering confounding factors. In particular, healthcare consumption among patients with psoriasis could bias the observed comorbidity, due to an increased number of doctor’s visits compared with the general population. This is supported by the fact that all results are more conservative when healthcare consumption is included in the model (Table III). The current study is limited by its descriptive nature and offers no causal explanations. The provided data are very much dependent on correct clinical diagnosis, but the included autoimmune diseases are most likely diagnosed by hospital specialists in relevant fields, e.g. arthritis by rheumatologists, IBD by gastroenterologists, etc. The decision to group together psoriatic arthritis, juvenile psoriatic arthritis, and JIA on the basis of diagnostic difficulties is supported by the fact that a sub-analysis showed that some children with psoriasis had a diagnosis of JIA, while some children without psoriasis had a diagnosis of psoriatic arthritis (data not shown). Furthermore, clinical presentation of the aforementioned paediatric diseases can be very similar and thus difficult to distinguish (35). Since Crohn’s disease and ulcerative colitis are more easily distinguished through different diagnostic methods (e.g. endoscopy and histology) we decided not to group them together in a single IBD entity. Furthermore, the respective diseases have different genetic and environmental risk factors (46). The prevalence of psoriasis in children is relatively low, and most of the autoimmune diseases studied are themselves rare. Consequently, the absolute number of observed children with concomitant autoimmune diseases is small. This yields broad confidence intervals, and the results should be interpreted accordingly. The absolute numbers of cases in the psoriasis group for both autoimmune thyroiditis and the categories of IBD are between 3 and 4. Therefore, just one case could be decisive. With regards to generalizability, our study is predominantly in children of Danish descent, and the results on clustering of autoimmune disease are in agreement with previous findings in adults (10).

Conclusion

Autoimmune diseases are known to cluster and can have a severe effect on quality of life. This study shows that children and adolescents with psoriasis are at increased risk of having one or more selected autoimmune diseases compared with the general population. Although many of these conditions remain rare, clinicians should keep these associations in mind when treating psoriasis in children, as they may add to the total disease burden. In particular, focus on extra-cutaneous symptoms is advised.

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Conflicts of interest: AE has received research funding from Pfizer and Eli Lilly, and honoraria as a consultant and/or speaker from Pfizer, Eli Lilly, Novartis, Galderma, and Janssen Pharmaceuticals. CZ has served as a scientific consultant for Abbvie, Pfizer, Janssen-Cilag, Merck & Co., Inc., Eli Lilly, Takeda and Novartis and clinical study investigator for AbbVie, Amgen, Eli Lilly, Merck & Co., Inc., Takeda and Novartis. LS has been a paid speaker for Pfizer, AbbVie, Eli Lilly, Novartis and LEO Pharma, and has been a consultant or served on Advisory Boards with Pfizer, AbbVie, Janssen Cilag, Novartis, Eli Lilly, LEO Pharma and Sanofi. She has served as an investigator for Pfizer, AbbVie, Eli Lilly, Novartis, Amgen, Regeneron and LEO Pharma and received research and educational grants from Pfizer, AbbVie, Novartis, Sanofi, Janssen Cilag and Leo Pharma.

REFERENCES

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