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

Christoffer BLEGVAD^{1,5}, Alexander EGEBERG¹, Tilde E. TIND NIELSEN^{1,5}, Gunnar H. GISLASON²⁻⁴, Claus ZACHARIAE¹, Anne-Marie NYBO ANDERSEN⁵ and Lone SKOV¹

¹Department of Dermatology and Allergy, ²Department of Cardiology, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, ³The Danish Heart Foundation, ⁴The National Institute of Public Health, University of Southern Denmark, and ⁵Section of Social Medicine, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

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 1,194,712 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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Corr: Christoffer Blegvad, Department of Dermatology and Allergy, Herlev and Gentofte Hospital, Kildegårdsvej 28, DK-2900 Hellerup, Denmark. E-mail: christoffer.blegvad.01@regionh.dk

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 disfigurement 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 concomitant 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 (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

Autoimmune disease	ICD-10 code
Psoriatic arthritis ^a	M07.0-3, M08, M09.0
Rheumatoid arthritis	M05, M06
Unspecified IBD	Patients with both K50 and K51
Crohn's disease	K50
Ulcerative colitis	K51
Coeliac disease	K90.0
Type 1 diabetes	E10
Autoimmune thyroiditis	E06.3
Vitiligo	L80

^aIncludes psoriatic arthritis, juvenile idiopathic arthritis, and juvenile psoriatic arthritis.
IBD: inflammatory bowel disease; ICD-10: International Classification of Diseases, 10th Revision.

in accordance with the Anatomical Therapeutic Chemical (ATC) classification system (34).

Lifetime psoriasis was defined as having either an ICD code of psoriasis (ICD-10 L40, not including L40.5 arthropathic psoriasis) or by the second claimed prescription of topical vitamin D analogues (ATC code D05AX). Topical vitamin D analogues are the favoured first-line psoriasis treatment in Denmark and are registered exclusively for psoriasis. The use of prescription claims allowed us to also identify milder psoriasis cases not treated in a hospital setting. The second claimed prescription was used to ensure persistent medical therapy. Children with life-time psoriasis were compared, with respect to life-time diagnosis of 9 selected autoimmune diseases, with children without psoriasis.

Information on the life-experience of the 9 autoimmune diseases in the Danish National Patient Register was traced. The 9 diseases of interest were *a priori* selected based on paediatric relevance (Table I). We decided to group together psoriatic arthritis, juvenile psoriatic arthritis, and juvenile idiopathic arthritis (JIA) since their clinical signs and symptoms may be difficult to distinguish in young patients (35).

Statistical analysis

For baseline characteristics means and standard deviations (SDs) were used to describe continuous variables, and frequencies and percentages for categorical variables. Logistic regression was used to estimate crude and adjusted odds ratios (ORs) (in which age, sex, and healthcare consumption were considered) for the correlation between a psoriasis diagnosis and other autoimmune diseases. Healthcare consumption was defined as the number of dermatology visits. A significance level of 0.05 was used and results were reported with 95% confidence intervals (95% CIs)

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

	General population (n = 1,194,712)	Psoriasis (n = 1,925)
Age, years, mean (SD)	9.2 (5.2)	13.8 (3.4)
Sex, n (%)		
Girls	582,382 (48.8)	1,053 (54.7)
Boys	612,330 (51.2)	872 (45.3)
Region of origin, n (%)		
Scandinavian	1,070,853 (89.6)	1,696 (88.1)
Western/Southern Europe	34,410 (2.9)	67 (3.5)
Africa	18,500 (1.6)	26 (1.4)
America	2,147 (0.2)	0 (0.0)
Asia	54,374 (4.6)	116 (6.0)
Oceania	211 (0.0)	0 (0.0)
Eastern Europe	13,825 (1.2)	20 (1.0)
Other/unknown	392 (0.03)	0 (0.0)
Native, n (%)	1,066,942 (89.3)	1,692 (87.9)
Migrant, n (%)	29,469 (2.5)	43 (2.2)
≥ 1 parent were migrants	98,246 (8.2)	190 (9.9)

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).

This cross-sectional study of childhood co-existence of psoriasis and autoimmune diseases was undertaken in accordance with the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" statement (36). Approval was obtained from the Danish Data Protection Agency (ref. 2007-58-0015, int. ref. GEH-2014-018, I-Suite 02736), while approval by The National Committee on Health Research Ethics is not required for register studies in Denmark.

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-

Table III. Results showing crude and adjusted associations between psoriasis and included autoimmune diseases

	General population n (%)	Psoriasis n (%)	Crude OR	95% CI	p-value	Adjusted OR ^b	95% CI	p-value	Adjusted OR ^c	95% CI	p-value
Psoriatic arthritis ^a	2,668 (0.2)	81 (4.2)	19.63	15.66–24.60	<0.0001	12.33	9.82–15.48	<0.0001	10.08	7.97–12.74	<0.0001
Rheumatoid arthritis	251 (0.02)	6 (0.31)	14.88	6.61–33.48	<0.0001	8.12	3.60–18.33	<0.0001	6.61	2.75–15.87	<0.0001
Unspecified IBD	182 (0.02)	3 (0.16)	10.24	3.27–32.09	0.0001	5.04	1.60–15.81	0.0056	3.67	1.01–13.35	0.0488
Crohn's disease	534 (0.04)	4 (0.21)	4.66	1.74–12.47	0.0022	2.64	0.98–7.07	0.0539	1.51	0.47–4.88	0.4868
Ulcerative colitis	501 (0.04)	3 (0.16)	3.72	1.19–11.58	0.0234	2.11	0.68–6.57	0.1989	1.83	0.56–6.00	0.3205
Celiac disease	1,723 (0.14)	7 (0.36)	2.53	1.20–5.32	0.0146	1.77	0.84–3.72	0.1336	1.15	0.50–2.63	0.7439
Type 1 diabetes	2,529 (0.21)	10 (0.52)	2.46	1.32–4.59	0.0046	1.47	0.79–2.74	0.2280	1.08	0.56–2.12	0.8111
Autoimmune thyroiditis	263 (0.02)	4 (0.21)	9.46	3.52–25.41	<0.0001	4.38	1.63–11.78	0.0035	3.12	1.01–9.63	0.0481
Vitiligo	199 (0.02)	6 (0.31)	18.77	8.32–42.33	<0.0001	11.74	5.18–26.60	<0.0001	4.76	1.71–13.20	0.0027
One of the above autoimmune diseases	8,046 (0.7)	102 (5.3)	8.30	6.79–10.14	<0.0001	5.35	4.34–6.49	<0.0001	4.40	3.56–5.43	<0.0001
Two or more of the above autoimmune diseases	408 (0.0)	11 (0.6)	17.65	9.68–32.18	<0.0001	9.83	5.38–17.97	<0.0001	7.27	3.91–13.50	<0.0001

^aIncludes psoriatic arthritis, juvenile idiopathic arthritis, and juvenile psoriatic arthritis; ^badjusted for age and sex; ^cadjusted for age, sex, and number of dermatology visits.
OR: odds ratio; IBD: inflammatory bowel disease.

mate. All results are shown in **Table III**. In general, both rheumatoid arthritis and the combined psoriatic arthritis group showed strong associations with psoriasis. As expected, psoriatic arthritis had the most evident association (adjusted OR 10.08; 7.97–12.74), while the association was less pronounced for rheumatoid arthritis (adjusted OR 6.61; 2.75–15.87). Vitiligo (adjusted OR 4.76; 1.71–13.20) and autoimmune thyroiditis (adjusted OR 3.12; 1.01–9.63) were also more prevalent among children with psoriasis. Among the remaining diseases; IBDs, coeliac disease, and type 1 diabetes, only the category of “unspecified IBD” remained significantly associated with psoriasis after adjustment for confounding factors (adjusted OR 3.67; 1.01–13.35). Overall, psoriasis was significantly associated with having at least one autoimmune disease (adjusted OR 4.40; 3.56–5.43). Furthermore, having more than one autoimmune disease showed an even stronger association with psoriasis (adjusted OR 7.27; 3.91–13.50) (Table III).

DISCUSSION

In our study, psoriatic arthritis, rheumatoid arthritis, vitiligo, autoimmune thyroiditis, and unspecified IBD were significantly associated with psoriasis in children. Furthermore, children with psoriasis had a significantly higher risk of having multiple concurring autoimmune diseases compared with children without psoriasis. Our results suggest that psoriasis in children is associated with some, but not all, of the autoimmune diseases previously shown in adults (10, 37). Only 2 previous studies in children have included narrow ungrouped selections of autoimmune diseases, but both studies lacked adjustments for confounding factors including age, sex, and healthcare consumption (3, 28).

Adjustment for respectively age and sex, and age, sex, and healthcare consumption yielded similar results with the latter being the more conservative. As expected, psoriatic arthritis was strongly associated with psoriasis, but also rheumatoid arthritis was significantly associated with psoriasis, which confirms previous findings in children and adults (3, 10). Children with psoriasis had an increased risk of vitiligo, which is in agreement with observations in adults (10, 37). However, a study in children could not show this (28). One reason for the observed association between psoriasis and vitiligo could be due to misclassification of healed depigmented psoriasis lesions, but this explanation seems less likely, since the diagnosis of vitiligo in our study is based on a hospital diagnosis and is therefore probably given by a trained dermatologist. Conversely, vitiligo may be identified more often, since the children with psoriasis are seen by dermatologists. We did not find the individual IBDs (Crohn’s disease and ulcerative colitis) associated with psoriasis, even though previous studies in adults have shown this (10, 38). Previous studies in children

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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