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Title: The Epidemiology of Childhood Psoriasis: A Scoping Review

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What's already known about this topic?

- The prevalence of psoriasis in children is lower than adults
- A significant number of adults with psoriasis first developed skin disease in childhood
- Genetic and environmental factors both play an important role in the onset of psoriasis
- Disease associations, such as obesity, are an important area of current research activity

What does this study add?

- Mapping has shown a dramatic increase in the number of published studies over the past 25 years
- Studies have been concentrated in Europe, Asia and North America; these studies have largely been case series or cross-sectional studies
- Specific studies with standardised methodologies are needed to provide data on the frequency, clinical presentation, risk factors, associated diseases and long-term outcomes for child-onset psoriasis

The Epidemiology of Childhood Psoriasis: A Scoping Review

Abstract
Psoriasis is an inflammatory non-communicable skin disease which affects both adults and children. At present the epidemiology and natural history of psoriasis are not widely understood. This scoping review aimed to map the existing literature on the epidemiology of child-onset psoriasis, provide a comprehensive, clinically useful review and identify research gaps for future studies.

Search strategies were developed for OVID MEDLINE, OVID Embase, Google Scholar and hand-searching; 131 articles meeting the inclusion criteria and were mapped and 107 articles were included for data extraction.

Over 25 years there has been a dramatic increase in the volume of published observational epidemiological studies on child-onset psoriasis. The majority were case series or cross-sectional studies, concentrated in Europe, Asia and North America. The prevalence of childhood psoriasis was found to be higher in European countries, older children and females. Up to 48.8% of children had psoriasis in a first degree relative. The most frequent subtype was plaque psoriasis and initial site of presentation is most commonly scalp, limbs and trunk. Specific genetic differences have been found between the child-onset and adult-onset populations. Case-control studies and cohort studies investigating risk factors for psoriasis onset, comorbidities and long-term health outcomes were extremely limited.

The choice of study design and heterogeneity in methodology limit the validity and generalisability on the information, consistency of the results and comparability of the studies. Well-designed studies are needed to provide precise and consistent information about the frequency and clinical presentation, risk factors, associated diseases and long-term outcomes in child-onset psoriasis.

Introduction

Psoriasis is an inflammatory non-communicable skin disease which affects both adults and children [1]. Early onset disease may persist into adulthood. Lomholt examined a little over one-third of the population of the Faroe Islands and found that over 70% of those diagnosed with psoriasis had an age of onset before 20 years [2]. In Sweden 50% of the 5197 families surveyed by Swanbeck *et al* developed psoriasis before the age of 25 years [3]. In view of the likely common occurrence and chronic nature of child-onset psoriasis it is important that best practice management is initiated early and information is readily available for children and their families.

At present the epidemiology and natural history of psoriasis are not widely understood. Instead recent scientific activity on psoriasis has focused on disease pathophysiology [4,5], driven by the development of targeted biological therapies, and the role that systemic inflammation may play in psoriasis morbidity and mortality [6,7] . Epidemiological studies not only contribute to understanding distribution and determinants of disease, but also inform

primary and secondary prevention measures, including therapeutic interventions [8]. Additionally, they can help answer questions important to patients and health providers about how common, possible causes and long-term outcomes of the condition.

Scoping reviews aim to map the existing literature in a field of interest in terms of the volume, nature and characteristics of the primary research [9]. This scoping review also aimed to provide a comprehensive, clinically useful review of the epidemiology of child-onset psoriasis and identify research gaps for future studies. The four core questions addressed by this review were:

1. What are the prevalence, incidence and clinical presentation of childhood psoriasis?
2. What are the genetic and environmental factors associated with the onset of psoriasis in childhood?
3. What other conditions are associated with psoriasis in children?
4. What are the long-term outcomes for patients with child-onset psoriasis?

Method

The search strategy was designed with an information specialist (DG) (Appendix 1). OVID MEDLINE In-Process & Non-Indexed Citations and OVID MEDLINE 1948 to present, and OVID Embase were searched on 27th May 2015. The reference lists of 10% of studies included in the review and non-systematic review articles were hand searched to identify additional relevant studies. Google Scholar was searched using the terms 'epidemiology of psoriasis in children' and 'epidemiology of paediatric psoriasis' and the first 100 citations were reviewed on 15th September 2015.

Studies were included if they were observational studies of children with psoriasis, or studies with separated data for children, that provided primary epidemiological data on one of the four core questions. Children were defined as those with a disease onset under the age of 18 years; although flexibility was shown for studies with grouped data up to the age of 20 years. Systematic reviews of observational studies were included. Therapeutic intervention studies and single case reports were excluded. Non-English studies and conference abstracts were included as part of mapping the extent of the evidence, but results data were not extracted.

Titles, abstracts and full-text articles where available were screened by two authors (EBT and EA). The full-texts of studies which met the inclusion criteria were then independently assessed for eligibility by two authors (EBT and RM). Data extraction was undertaken by one author (EBT) using a structured form. The accuracy of the extracted data for 10% of included studies was checked by a second author (RM). Studies were categorised for mapping of the literature according to definitions provided in the publication and descriptions provided in the methods section.

The breadth of the review questions and the heterogeneity of the studies have necessitated narrative synthesis of the data. Critical appraisal of individual studies and meta-analysis was not performed within this scoping review.

Results

The search strategy yielded 2490 potential citations; after removal of duplicates, initial screening and review for eligibility 113 articles remained. A further 19 articles were identified through hand-searching and Google Scholar. In total 131 articles were mapped, after removal of non-English studies and conference abstracts, 107 articles were included in the results summary (Appendix 2).

Mapping of studies

The characteristics of included studies are presented in Table 1. There has been a linear increase in the number of observational studies on child-onset psoriasis over the past 20 years (1996-2000 n=8, 2011-2015 n=50). The majority of the study populations were based in Europe (65/131), in particular UK (10/131), Sweden (9/131), Germany (7/131) and Turkey (6/131).

Cross-sectional studies (75/131) and case series (30/131) were most common. Observational studies to date have concentrated on incidence or prevalence (47/131), age of onset, gender or family history (69/131) and clinical presentation of psoriasis (63/131)..

What are the prevalence, incidence and clinical presentation of childhood psoriasis?

Incidence and prevalence

Overall there were two incidence, 37 prevalence studies and one systematic review [10]. Seventeen prevalence studies were population- based [11-27]. Twenty studies were secondary/hospital care prevalence studies [28-47].

The prevalence of childhood psoriasis varied depending on the study population. Estimates reported from population-based studies range from 0% to 2.1%, the highest values were from European studies, Italy (2.1% [21]), Germany (1.3% [12]) and UK (1.3% for 10-19 year old [17]) compared to low prevalence in Taiwan (0% [15,27]) and Egypt (0.05% [26]). Studies which stratified prevalence according to age reported psoriasis to be more common after puberty, 0.6% to 1.3%, than before puberty, 0.1% to 0.5%. Psoriasis was a fairly common presentation in paediatric dermatology clinics with a reported prevalence of 0.7% to 6.2% of outpatient consultations

With regard to incidence studies, a health survey of Norwegian twins showed that incidence of psoriasis increased with age throughout childhood (0-3 years to 16-19 years) from 0.5 to 2.9 and 0.3 to 2.0 per 1000 person years in girls and boys respectively [48]. Tollefson *et al* showed that the number of children diagnosed with psoriasis had increased over a 30 years period in the United States from 29.6 to 62.7 per 100 000 patient years. Proposed reasons for this increase included changes in risk factors such as psychosocial stress, infection and obesity [49].

Studies varied in how cases of psoriasis were ascertained (self-reported, diagnostic codes in health records, physician examination) and potentially how psoriasis was defined; most studies required a 'clinical diagnosis' of psoriasis with no pre-defined criteria.

Gender and age of onset

Forty-two studies provided data on the gender distribution. Thirty-three studies provided data on the percentage of the study population which were male [25,28,30,32,50-78]. Twenty five of these 33 studies found that less than 50% of children with psoriasis were boys (range 35.9-49%).The male to female ratio was provided in 16 studies and varied from 1.14:1 to 1:2.33 [30,32,34,49,52,59,60,70,72,75,79-84]. Matusiewicz *et al* reported that the prevalence of psoriasis in children was lower in boys than girls, 0.35% compared to 0.44% [20], and Farber *et al's* survey of 5600 psoriasis patients found that in childhood onset in boys was less common than girls especially amongst those with an onset under the age of 10 years [73]. This female predominance seen in the prevalence of childhood psoriasis is the opposite of what is commonly observed in adults [85].

Age at onset of psoriasis was reported by 30 studies. The range of age at onset was reported by 17 studies and range included from birth to 18 years [30,32,52,53,55,57-59,63,67,72,74,79,83,86-88]. The average age of onset was reported by 22 studies and ranged from 2.1 months to 10.6 years [28,32,34,49-53,55,58,60,65,69,71,72,74,77,79,80,82,83,89].

Age of onset may vary with psoriasis subtype. An earlier age of onset was reported for pustular psoriasis [53,83]. Popadic *et al* described the 20 year experience of childhood pustular psoriasis at their centre and found 50% of children presented before 1 year old [83]. The average age of onset in plaque psoriasis is less clear. This variation may reflect differences in subtype definition, for example, inclusion of scalp, flexural or napkin psoriasis in the term plaque psoriasis. Leow *et al* reported a case series of 112 children; 91.9% had plaque psoriasis and 37.5% developed psoriasis under 1 year old [34]. However, four studies with predominantly plaque psoriasis reported an average age of onset around 10 years [41,58,60,80]. Only one study contained children predominantly with guttate psoriasis and found a clear peak in age of onset for girls at eight years but possibly three peaks for boys at 5, 10 and 13 years [77].

Reliance on medical documentation and patient/parent recall as well as inconsistencies in subtype definition all contribute to difficulties in accurately understanding age of onset in childhood psoriasis.

Family history

Thirty-eight studies provided data on family history [28,30,32,34,50-65,67,69,70,72,76-84,86,87,89-91]. The percentages of children with a positive history in a first degree relative varied from 6.2% to 54.7% and a positive family history in any family member from 4.5% to 88%. Farber et al found that adolescents with psoriasis (10-19 years) were most likely to have a family member with psoriasis, compared to other age groups of children [86]. The large variation reported in family history of psoriasis may in part be due to genetic differences between ethnic populations. For example, a study comparing Asian and European children found only 13.6% of Singaporean children had a first or second degree relative affected by psoriasis compared with 73.3% of Dutch children [79]. This supports child-onset psoriasis as a genetically heterogeneous condition and further research is needed into gene-environment interactions in different populations.

Clinical presentation

Eleven studies reported the initial body site of presentation in child-onset psoriasis [30,34,55,58,59,69,72,76,80,82,84]. Collectively they included nearly 3000 children. The scalp, limbs and trunk were the most common sites of initial presentation (17.9% to 64.8%, 9.5% to 90%, and 7.8% to 93.3% respectively). The face was a common site of presentation, 3.5% to 56.7%, and facial involvement may be an important clinical sign when differentiating psoriasis from eczema in children [28]. Napkin psoriasis was present in most infants with psoriasis and therefore needs to be considered an important presenting sign in this age group [86].

Twenty-three studies presented data on the frequency of different subtypes in childhood psoriasis in a [28,30,32,34,49,51,52,55,56,58-64,70,72,79,80,84,90,91] . As in the adult population, the commonest subtype in was chronic plaque. The range of frequencies of different subtypes was as follows: plaque psoriasis 9% to 91.9%, guttate psoriasis 1.6% to 48.2%, pustular 0% to 13.1%, erythrodermic 0.1% to 5.8%, palmoplantar 0.9% to 12.8%. Nail psoriasis was also a common subtype or current site of involvement, between 2% and 39.3%, and one study found it to be the sole presentation of psoriasis in 2.3% of children [59].

A few studies have compared the clinical presentation of childhood psoriasis according to ethnicity, gender and age. No clear conclusions can be drawn about the effect of ethnicity [55,79]. The presentation may vary according to gender. A multicentre cross-sectional study from the United States found that in boys nail psoriasis was found more frequently (odds ratio (OR) 3.01 (CI 1.62-5.6)) and scalp psoriasis less frequently (OR) 0.40 (CI 0.19-0.84)) compared to girls [81]. The authors suggested that this may be a result of the Kobener phenomenon.

Age appears to be an important factor influencing presentation. Kwon *et al* reported that guttate, plaqueand generalised pustular psoriasis were significantly more common in children under the age of 12 years [60]. Flexural involvement was found to be more common in pre-pubertal children (OR 2.8, $p<0.05$), especially boys (OR 2.5, $p<0.05$) [61]. Kim *et al* found involvement of the face to be a more common presenting site in children compared to adults [84].

Percentages for the frequency of initial site of presentation and subtype of psoriasis varied widely. Possible explanations include differences in clinic populations studied as well as the definition, assessment and documentation of subtypes and sites of presentation.

What are the genetic and environmental factors associated with the onset of psoriasis in childhood?

Genetic factors

Eight studies reported genetic findings on paediatric-onset psoriasis (Table 2) [61,65,71,72,92-95]. The studies suggest a difference in the genetics of for pre and post pubertal onset psoriasis. Lysell et al (2013) found endoplasmic reticulum aminopeptidase type 1 (ERAP1) was only associated with onset of psoriasis between the ages of 10 and 20 years [94]. In 2015, Lysell *et al* found proportion of HLA-C*06 positive patients was higher amongst those with post-

pubertal onset [61]. Conversely, IL22 promotor and IL12B were only associated with onset of psoriasis under the age of 10 years [65,95].

Nanda et al found no association between psoriasis and HLA-C*06 in Kuwaiti children, unlike similar studies in mostly Caucasian children [72]. This study highlights the need for genetic studies in more diverse populations.

Two studies specifically looked at the genotype-phenotype correlation. HLA-C*06 was associated with guttate psoriasis (OR 3.4, p<0.5) and facial lesions (OR 3.8, P<0.01), after controlling for demographic variables [61], but HLA-C*06 negative patients were found to have greater nail involvement (OR 0.32 (CI 0.14-0.76)) [65]. Whilst there is some data it is evident that further genotype-phenotype correlations in childhood psoriasis are needed.

Environmental factors: Infection, emotional stress, trauma and obesity

Trigger factors for the onset of psoriasis are reported in a large number of studies but often the study design employed did not allow the time relationship between exposure and the onset of psoriasis to be assessed. The data from these 20 studies are presented in Table 3 [18,30,34,51,52,54,57,59,65,67,70,72,76,77,79-82,84,96]. Only one paper, Ozden et al, specifically investigated environmental risk factors for the onset of childhood psoriasis in a case control study [82].

Infection was identified as a potential trigger factor in up to 43.4% of children. The most commonly described infection was an upper respiratory tract infection. Two studies specifically reported streptococcal infection, occurring in 22.1% to 21.3% of children [30,81], and Nyfors *et al* found elevated antistreptococcal titres in 60% of children with psoriasis [77]. Other types of infection identified as triggers were urinary tract infections, chicken pox and otitis media.

Stress was identified as a potential trigger factor in 1% to 66.7% of children; this was mostly defined as emotional or psychological stress. Ozden *et al* found that a stressful life event was a risk factor for the onset of psoriasis (OR 2.94 (CI = 2.28-3.79)) [82].

A history of trauma of all types was identified as a potential trigger factor in 1 to 11.5% of children. Koebnerisation was reported in 20.4% to 49.6% of children but further details about the timing in relation to disease onset were not always reported.

Obesity may be an important risk factor for the onset of psoriasis. Ozden *et al* found that that a BMI >26kg/m^2 was a risk factor for psoriasis in children ((OR of 2.52 (CI = 1.42-4.49)). A small retrospective cohort study found diagnosis of obesity or overweight preceded psoriasis in 93% of children [51]. Boccardi *et al* reported that the OR of being obese at first diagnosis of psoriasis was 2.55 (CI 1.31-4.96) [54].

There is a need for studies to differentiate between risk factors for disease onset and aggravating factors for a disease flare. Details on identification and measurement of potential risk factors are often minimal, making evaluation of their clinical relevance difficult.

What other conditions are associated with psoriasis in children?

Studies investigating diseases associated with psoriasis varied in methodology and only three used a study design which allowed a causal relationship to be assessed. Eighteen studies reported data on associated diseases (Table 4) [11,13,20,24,61,69,80,91,97-106]. Nineteen studies reported data on juvenile psoriatic arthritis and these papers are summarised below.

Eleven studies have provided data on cardiovascular disease and hypertension. Childhood psoriasis may increase the risk of hypertension. In two retrospective cohort studies hypertension was found in 1% (p=0.0005) [101] and up to 0.5% of children following a diagnosis of psoriasis [100]. A significant association with cardiovascular disease has not been shown.

Obesity data are presented in eleven studies, many of which support a significant association between psoriasis and obesity. Kimball *et al* reported the prevalence following a diagnosis of obesity amongst patients under 18 years to be 1.8% (p=0.0007) [101], much lower than large cross-sectional studies such as Mahe *et al* 2015, Lysell *et al* and Paller *et al*, 10% (p=0.001), 15% and 20.2% (p<0.001) respectively [61,91,103]. This may imply that obesity was coexistent at the onset of psoriasis, as reported by Becker et al [51].

Twelve studies have presented data on metabolic disease. A retrospective cohort found following a diagnosis of psoriasis, children were at higher risk of diabetes and hyperlipidaemia [101].

Four studies reported findings on psychological disorders and childhood psoriasis. Kimball *et al* investigated the onset of a psychological disorder following a diagnosis of psoriasis. The hazards ratio was significantly raised for any psychiatric disorder (HR 1.25(CI1.11-1.4)) [101].

<u>Juvenile Psoriatic arthritis</u>

Nineteen studies reported data on juvenile psoriatic arthritis in a paediatric psoriasis population [13,32,51,52,56-59,61,64,79-82,90,91,99,101,103]. In a predominantly plaque or guttate psoriasis population, the prevalence of psoriatic arthritis was reported between 0.7% and 10.5%. In a case series of seven children with pustular psoriasis, two children were found to have psoriatic arthritis [57]. The highest percentage (10.5%) was reported by Mercy *et al*, which was; a secondary/hospital multicentre study of children with plaque psoriasis aged 5 to 17 years [81].

What are the long-term outcomes for patients with child-onset psoriasis?

Twenty-two studies provided data on the natural history and long-term outcomes of child-onset psoriasis [2,3,34,50,52,56,68,69,73,76,77,83,86-89,107-112]. Ten studies reported the percentage of adult psoriasis patients with child-onset disease; this was found to be between 12% and 37.1% and much lower in a study solely on genital psoriasis (5%) [110]. Four studies, either prospectively or retrospectively, followed up infants with psoriasiform napkin disease. In a small cohort of nine infants, seven had recurrent psoriasis [86], whereas the proportion in

larger studies was much lower. Neville *et al* found that 16.9% of 71 infants with psoriasiform changes developed psoriasis in childhood [89], while Andersen *et al* only found that this occurred in only 3% [50]. Continuous disease throughout childhood occurs in 5.4% to 56% [52,77,83].

In terms of long-term severity of child-onset disease, Lombolt reported that 35% of psoriatics with child-onset disease had significant disease and flares compared with 18% of those with onset over the age of 20 years [2]. Two studies investigated quality of life in child-onset psoriasis. De Jager *et al* found that intra-patient rating of quality of life was lower in childhood compared to adulthood in those with persistent disease [68]. Kim *et al* found compared lifetime quality of life scores were lower for those with child-onset disease compared to adult-onset [111]. This supports the theory of a cumulative life-course impairment described by Warren et al [109].

Cohort studies on the natural history of child-onset psoriasis have to date focused on napkin psoriasis and therefore information on the outcomes even within childhood is extremely limited. Data on child-onset psoriasis is often obtained from adults with persistent disease, which introduces recall bias and misses those whose psoriasis resolves.

Discussion

Summary of findings

Over the past 25 years in the field of childhood psoriasis epidemiology there has been a dramatic increase in the volume of published studies; the majority of which have been case series and cross section studies concentrated in Europe, Asia and North America.

The prevalence of childhood psoriasis was found to be higher in European countries, older children and females. Up to 48.8% of children had psoriasis in a first degree relative. The most frequent subtype was plaque psoriasis and initial site of presentation is most commonly scalp, limbs and trunk. Specific genetic differences have been found between the child-onset and adult-onset populations. Case-control studies and cohort studies investigating risk factors for psoriasis onset, comorbidities and long-term health outcomes were extremely limited.

Strengths and limitations

This scoping review is the first paper to search and map epidemiological data on child-onset psoriasis. The search strategy was designed to be extensive and the protocol planned to reduce selection bias in the stages of screening and eligibility assessment of papers. We recognise that a limitation of the review is the absence of structured critical appraisal of individual studies.

Research gaps

This scoping review has demonstrated gaps in our evidence base about childhood psoriasis relating to all four of the questions this review set out to address. Although over 100 studies contain epidemiological data, the choice of study design and heterogeneity in methodology limit the validity and generalisability of the information, consistency of the results and comparability of the studies.

Population-based incidence and prevalence studies are needed, investigating the impact of variables such as geographic location and socioeconomic groups. Specifically designed studies are needed to investigate the impact of age, puberty, gender and ethnicity on the genotype-phenotype of psoriasis. We would suggest that there is a need for case control studies to investigate potential risk factors for the onset of disease. Retrospective, and ideally prospective, cohort studies would provide important data on the development of associated diseases and long-term outcomes.

Standardisation is required to reduce variation in methodology. A clear definition of psoriasis and the subtypes would ensure patients included in studies are confirmed to have the same disease and subtype frequencies could be accurately recorded. Clear definition of potential risk factor and associated diseases as well as standardisation of parameters measured would help the generalisability of the findings and allow a meta-analysis of results.

Conclusions

Energy and focus now needs to be directed to well-designed studies with standardised definitions and methodology. These studies will provide precise and consistent information about the frequency and clinical presentation, risk factors, associated diseases and long-term outcomes in child-onset psoriasis.

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