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Psoriasis in family members of patients with multiple sclerosis

Olivia Charlton[a,*], Kevin Phan[b], Saxon D Smith[c], John Parratt[d]

[a] Lotus Dermatology, Newcastle, Australia
[b] Department of Dermatology, Liverpool Hospital, Liverpool, Australia
[c] The Dermatology and Skin Cancer Centre, Gosford and St Leonards, Australia
[d] Department of Neurology, Royal North Shore Hospital, Sydney, Australia

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ABSTRACT

Background: It has been noted both anecdotally and in a selection of studies that the incidence of multiple sclerosis (MS) and psoriasis may be related, however the nature of that association is unclear. Clustering among families of multiple autoimmune diseases may be linked to genetic factors. Whether family members of those with MS are at increased risk of psoriasis is not well established.
Methods: A systematic review and meta-analysis was performed according to recommended PRISMA guidelines. Data from studies assessing the proportion or effect size of psoriasis cases reported for families or relatives of MS cases versus families or relatives of control cases without MS were extracted and meta-analysed.
Results: From a pooled unadjusted meta-analysis of 5 studies that met criteria, we found that family members of MS patients were at increased risk of psoriasis (OR 1.45 95% CI 1.07, 1.97).
Conclusion: Family members of those with MS may be at greater risk of developing psoriasis.

1. Background

Psoriasis is a chronic, inflammatory disease with proposed genetic and environmental precipitants. It affects 2–4% of people and therefore the prevalence is forty times higher than MS. The incidence of psoriasis is bimodal with peaks between 15–25 years and 50–60 years of age and although the disease is more frequently found in Caucasians it is prevalent in people of all races. Psoriasis is characterised by symmetrical, erythematous, thickened scaly plaques of the skin. The scalp, elbows and knees are frequently affected. Psoriasis is classified according to phenotypic patterns such as chronic plaque, guttate, palmoplantar, sebpsoriasis and scalp psoriasis. Patients with psoriasis are known to have an increased risk of cardiovascular disease, (Shapiro et al., 2012) uveitis (Chi et al., 2017) and chronic kidney disease (Chi et al., 2015). It is also known to significantly impact quality of life (Augustin and Radtke, 2014).

Psoriasis is an immune mediated, inflammatory disease that develops in genetically predisposed individuals. The cutaneous inflammation is propagated by dendritic cells, neutrophils, T -lymphocytes and cytokines. It is postulated that following activation of innate immune cells such as plasmacytoid and myeloid dendritic cells by antigenic stimuli, proinflammatory cytokines are produced, specifically IL-23 and IL-12, inducing activation of T-cells (Wollenberg et al., 2002). T-cells then produce cytokines, notably IL-17A, which promotes proliferation of keratinocytes and prompts the production of proinflammatory peptides. The corresponding perpetuation of inflammation is therefore a product of cytokines produced by keratinocytes and immune cells, in a positive feedback loop.

MS is an inflammatory demyelinating disease of the central nervous system (CNS). Discrete, demyelinating plaques occur, at different times, in the optic nerves, cerebrum and spinal cord (Montalban et al., 2010). It is classified into three “phenotypes” depending upon the disease course: relapsing remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS). RRMS generally has a better prognosis than progressive MS with respect to the time to specific disability landmarks. After trauma, MS is the most common cause of permanent disability in young adults with a mean age of onset between 28 and 31 years (Ramagopalan and Sadovnick, 2011; Noseworthy et al., 2000). MS affects in excess of two million people worldwide, and both environmental and genetic factors are implicated in the pathogenesis of the disease. A variety of studies report differing rates of familial MS, ranging from 3% to 23% (Nielsen et al., 2005). A Danish study of 8205 participants found that first degree relatives of patients with MS had a 7-fold increase in the chance of developing MS (Nielsen et al., 2005).

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* Corresponding author.
E-mail address: oacharlton@gmail.com (O. Charlton).

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One of the most compelling factors for a strong environmental, aetiological component is the finding that MS varies markedly with geography, and in particular latitude (Simpson et al., 2011).

In animal models of MS it has been demonstrated that defects in self-tolerance result in T-lymphocytes producing proinflammatory cytokines in response to self-antigens. This results in recruitment of leukocytes to the sites of the autoantigen (usually myelin proteins in these models) generation of inflammatory cytokines and chemokines, production of reactive oxygen species and phagocytosis of damaged myelin with secondary axonal damage (Gonsette, 2012; LeVine, 1992). The target of the immune response in humans is unknown although frequently assumed to be myelin proteins.

There have not been any large, prospective studies examining the link between MS and psoriasis, however Lui et al. demonstrated in their meta-analysis of observational studies that MS patients have an increased prevalence and incidence of psoriasis. In their pooled analysis of nine case-control and cross-sectional studies, they found a significant increase in prevalent psoriasis (OR 1.29; 95% CI 1.14–1.45), and an increased risk in two cohort studies (pooled HR 1.92; 95% CI 1.32–2.80) (Liu et al., 2019).

It is established that family members of patients with autoimmune disease have a higher incidence of autoimmune disease, themselves (Cooper et al., 2009). However the studies looking at risk of psoriasis in family members of those with MS have shown conflicting results. The objective of this meta-analysis was to determine if first-degree family members of patients with MS are at increased risk of developing psoriasis.

2. Methods

2.1. Search strategy

This systematic review and meta-analysis was performed according to the recommended PRISMA guidelines (Nielsen et al., 2005). As no human or animal subjects were involved in this study, ethics approval was not required. Electronic searches were performed using Ovid Medline, PubMed, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), ACP Journal Club, Database of Abstracts of Review of Effectiveness (DARE), EMBASE and PsycINFO from their dates of inception to 8th August 2018. To achieve maximum sensitivity of the search strategy and identify all studies, we combined the terms “psoriasis”, “multiple sclerosis”, “family”, “first-degree relative”, “familial multiple sclerosis”, as either key words or MeSH terms. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies, assessed using the inclusion and exclusion criteria.

2.2. Selection criteria

Eligible studies for this systematic review and meta-analysis included those in which the proportion or effect size of psoriasis cases was reported for families or relatives of MS patients versus families or relatives of control cases without MS. When institutions published duplicate studies with accumulating numbers of patients or increased lengths of follow-up, only the most complete reports were included for quantitative assessment at each time interval. All publications were limited to those involving human subjects and in the English language. Abstracts, case reports, conference presentations, editorials, reviews and expert opinions were excluded.

2.3. Data extraction

All data were extracted from article texts, tables and figures. Two investigators independently reviewed each retrieved article (O.C., K.P.). Discrepancies between the two reviewers were resolved by discussion and consensus.

2.4. Statistical analysis

The odds ratio (OR) was used as a summary statistic. In the present meta-analysis, the results using the random-effects model were presented to take into account the possible clinical diversity and methodological variation between studies. χ^2 tests were used to study heterogeneity between trials. I^2 statistic was used to estimate the percentage of total variation across studies, owing to heterogeneity rather than chance, with values greater than 50% considered as substantial heterogeneity. I^2 can be calculated as: $I^2 = =100\% \%\times$ (Q – df)/Q, with Q defined as Cochrane's heterogeneity statistics and df defined as degree of freedom. Specific analyses considering confounding factors were not possible because raw data were not available. All *P* values were 2-sided. All statistical analysis was conducted with Review Manager Version 5.2.1 (Cochrane Collaboration, Software Update, Oxford, United Kingdom).

3. Results

After application of inclusion and exclusion criteria, and filtering titles, abstracts and full texts, a fivestudies were included in the present meta analysis. From pooled unadjusted meta-analysis, we found that family members of MS patients were at increased risk of psoriasis (OR 1.45 95% CI 1.07, 1.97) (Table 1).

4. Discussion

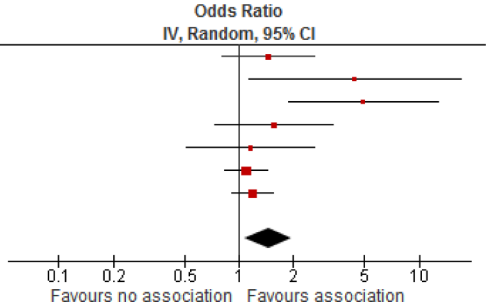
Our results suggest that family members of patients with MS are at greater risk of developing psoriasis, and points to an increased susceptibility to autoimmune disease, in such families.

In an Italian cohort, Annunziata et al. found that psoriasis was the most frequent autoimmune disease occurring in MS patients, followed by thyroid disorders such as Grave's and Hashimoto's disease, and type one diabetes (Annunziata et al., 2003). The prevalence was also significantly higher in fathers of MS patients. In this cohort psoriasis in

Table 1
Forest plot of meta-analysis demonstrating association between MS family members and psoriasis.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Annunziata 2003	0.372	0.303	14.6%	1.45 [0.80, 2.63]
Barcellos 2006	1.482	0.694	4.3%	4.40 [1.13, 17.15]
Deretzi (multiplex families) 2010	1.593	0.49	7.7%	4.92 [1.88, 12.85]
Deretzi (simplex families) 2010	0.445	0.389	10.7%	1.56 [0.73, 3.34]
Henderson 2000	0.148	0.417	9.7%	1.16 [0.51, 2.63]
Roshanisefat (fathers) 2012	0.095	0.137	26.4%	1.10 [0.84, 1.44]
Roshanisefat (mothers) 2012	0.174	0.136	26.5%	1.19 [0.91, 1.55]
Total (95% CI)			**100.0%**	**1.45 [1.07, 1.97]**

Heterogeneity: Tau² = 0.07; Chi² = 12.69, df = 6 (P = 0.05); I² = 53%
Test for overall effect: Z = 2.42 (P = 0.02)



both fathers and mothers accounted for 70% of relatives with psoriasis, lending weight to the theory that autoimmunity is inherited (Bias et al., 1986). Barcellos et al. found that both MS index cases and their family members were at increased risk of psoriasis (Barcellos et al., 2006). Interestingly they noted that a large proportion of patients with both MS and psoriasis were male. In a Greek cohort examining simplex and multiplex MS families, 14.5% and 19.2% of family types respectively had at least one family member with autoimmune disease, compared with 9.3% in control families. However looking at psoriasis specifically, it was only more frequent in multiplex families (Deretzi et al., 2010).

In a Swedish cohort there was no evidence of an elevated risk of psoriasis in family members of those with MS (Roshanisefat et al., 2012). This study, albeit large, was limited by failure to include diagnoses made in the primary care setting. This is naturally relevant as psoriasis is a chronic disease, not commonly warranting hospital admission and acute care. In an Australian cohort, Henderson et al. also did not find an increased risk (Henderson et al., 2000). However in first-degree relatives they noted that there was a significant risk of ankylosing spondylitis. This finding was statistically significant regardless of MS subtype and disease duration.

An overall excess occurrence of psoriasis in family members of those with MS suggests a shared, inherited risk, which may include genes of the human leukocyte antigen (HLA) complex, particularly class II genes, which are associated with inflammatory disorders. A shared immune pathogenesis between psoriasis and MS has been postulated, involving activation of Th-1 and Th-17 cells. In MS it has been proposed that Th-1 cells produce TNF-alpha and interferon gamma, and that Th-17 produces IL 17, 21, 22 and 26 (Yadav et al., 2015). However, there are also notable differences between the immune mechanisms of both diseases perhaps best illustrated by the trial of TNF-alpha inhibition in MS, which led to exacerbation of disease and there are numerous case reports of other TNF-alpha blocking therapies precipitating or exacerbating demyelination (The Lenercept Multiple Sclerosis Study Group, 1999). To the contrary, TNF alpha inhibition in psoriatic arthritis is effective treatment. It is plausible that this pertains to pathogenetic heterogeneity in MS but sub-analysis of the TNF-alpha receptor blocking trials in MS has never been completed to our knowledge.

This meta-analysis indicates that family members of patients with MS are at greater risk of psoriasis and may help to differentiate forms of the two diseases. Both psoriasis and MS are phenotypically and immunologically heterogenous and as such determining the characteristics of the association could prove important for therapeutic interventions, development of guidelines and management. Indeed, some current MS treatments such as Dimethyl Fumerate are active against psoriasis but it is unclear whether particular medications would be more effective for CNS demyelination in psoriatic MS patients or not. Larger prospective studies, examining the link between MS and inflammatory dermatoses are required to understand the association and to elucidate specific phenotypes, identify shared immune mechanisms and probe for amplified, genetic contributors in these defined groups.

Declaration of Competing Interest

None.

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