A narrative review of psoriasis and multiple sclerosis: links and risks

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Abstract: The association of psoriasis (PsO) with other autoimmune and autoinflammatory diseases has long been a topic of interest. Although previous studies have attempted to clarify the specific relationship between PsO and multiple sclerosis (MS), it remains obscure, with limited and conflicting evidence regarding a link between the two entities. Herein, we review the etiology, pathogenesis, and treatment of each disease and present the available literature to-date regarding a possible relationship between PsO and MS. We conclude that further study is necessary to discern whether there may be a significant relationship between PsO and MS. In the meantime, clinicians may find it appropriate to screen for MS in patients with PsO, allowing for timely referral to a neurologist should it be necessary.

Keywords: psoriasis, multiple sclerosis, incidence, prevalence, links, risk factors

Introduction
Psoriasis (PsO) has been associated with an increased risk of multiple comorbidities including psoriatic arthritis (PsA), cardiovascular disease, diabetes mellitus, metabolic syndrome, inflammatory bowel disease, and certain malignancies.1,2 Multiple sclerosis (MS) has also been reported as a comorbidity in individuals with PsO, and vice versa.3,4 This link between the two diseases may be somewhat unsurprising as both PsO and MS are inflammatory disorders and exhibit similarities in genetic risk variants and inflammatory pathways. Currently, limited and inconclusive evidence exists regarding the relationship between the two conditions.5–8 This review explores the possible link between PsO and MS and whether each condition serves as a potential risk factor for the development of the other.

Etiology and pathogenesis
Psoriasis
PsO is a T-cell mediated, systemic inflammatory disease that affects the skin and joints. It occurs in approximately 2–4% of the US population with similar estimates in Europe.9,10 Although it can occur at any age, PsO most commonly presents between the ages of 15 and 35 years with a second peak occurring in the late 1950s to early 1960s. It affects both men and women equally but preferentially affects persons of white European ancestry.11,12

PsO is characterized by an excessive and rapid growth of the epidermal skin layer. Clinically, it typically presents as well-demarcated, erythematous plaques with overlying silvery scale, most commonly on the extensor surfaces of the skin.13 An increased risk of developing other chronic diseases also accompanies the
diagnosis of PsO, some of which include PsA, metabolic syndrome, non-alcoholic fatty liver disease, cardiovascular disorders, anxiety, depression, Crohn’s disease, and lymphoma.\textsuperscript{14,15} Approximately one-third of PsO patients will develop concomitant PsA.\textsuperscript{16}

The etiology of PsO is multifactorial with complex feedback loops and cross-talk occurring between the innate and adaptive immune systems. Contributing factors to the development of PsO include a genetic predisposition, a proposed environmental or antigenic trigger, and dysregulation of the innate and adaptive immune systems.\textsuperscript{17} Native immune cells, including T-helper cells (T\textsubscript{h}1 and T\textsubscript{h}17), dendritic cells, and keratinocytes, are thought to be activated by an initial antigenic stimulus, which results in the production of pro-inflammatory cytokines. Activated dendritic cells produce tumor necrosis factor (TNF)-alpha and IL-23, among other cytokines. Antigen-presenting cells in the skin activate T-cells by secreting IL-12 and IL-23, leading to a cascade of various cytokines, which generates the chronic inflammatory state of PsO. This cascade of events, along with the TNF-alpha-governed pro-inflammatory environment, leads to the development of cutaneous psoriatic plaques and augmented inflammation which additionally contributes to the underlying comorbid conditions of PsO.\textsuperscript{18,19}

**Multiple sclerosis**

MS is the most common demyelinating disease of the central nervous system (CNS).\textsuperscript{20–22} It affects young adults, usually between the ages of 20 and 40 years, and has a strong female predominance.\textsuperscript{23,24} It is defined by neurological symptoms that characteristically affect variable locations of the CNS over periods of time.\textsuperscript{25} Typical presenting symptoms include visual disturbances, sensory disturbances (such as paresthesias or hypoesthesia), motor weakness, cognitive deficits, fatigue, and pain.\textsuperscript{24} There is wide variation in the presentation of MS. Symptoms can range from mild, benign symptoms to rapidly progressive, debilitating disease. MS has also been associated with a decreased life expectancy by 7–14 years compared to the general, healthy population.\textsuperscript{25}

The definitive pathogenesis of MS remains elusive, but, similar to PsO, it is thought to be an immune-mediated inflammatory disorder, with both genetic and environmental influences.\textsuperscript{21,25,26} It is hypothesized that an as-of-yet unknown self-antigen, possibly a myelin-associated antigen, is presented by antigen-presenting cells resulting in the production of autoreactive T-helper cells (T\textsubscript{h}1 and T\textsubscript{h}17 cells) that then cross the blood–brain barrier and release proinflammatory cytokines like IL-1, interferon (IFN)-gamma, TNF-alpha, and lymphotoxin, resulting in the early inflammation of MS.\textsuperscript{24,26,27} Furthermore, studies have indicated that there is an absence of T\textsubscript{reg} cells in lesions of MS, which provide protection against inflammatory processes, suggesting a loss of a T-cell suppression mechanism in the CNS.\textsuperscript{20,28} This immune cell-mediated inflammatory environment leads to demyelination, gliosis, macrophage activation, and neuroaxonal degeneration, ultimately resulting in the pathologic plaques in MS, characterized by confluent areas of demyelinated white and gray matter involving the spinal cord and brain. As a result, the typical neurological symptoms seen in MS arise.\textsuperscript{24,25} Later lesions of MS are dominated by infiltration of B cells into the CNS, which are then able to produce IgM and IgG leading to oligoclonal bands that can be detected in the cerebrospinal fluid.\textsuperscript{25}

**Multiple sclerosis and psoriasis: links**

The concomitance of PsO and MS may be related to shared genetic and environmental causes leading to an overactive immune system, or may also be related to general immune system dysregulation, for which each condition is characterized by individual alterations.

**Environmental factors**

A variety of known and unknown environmental factors are also thought to play a role in both PsO and MS. As both are believed to be multifactorial diseases, environmental triggers may play a large role in genetically susceptible individuals. Increased UV radiation exposure, low vitamin D levels, Ebstein-Barr virus infection, and smoking have all been associated with an increased risk of MS.\textsuperscript{26,29} Various infections (e.g., Streptococcus, Staphylococcus aureus, Helicobacter pylori, HIV, and fungal infections) and medications (e.g., lithium, NSAID, anti-malarials, beta-blockers, and angiotensin-converting enzyme inhibitors), smoking, obesity, and increased stress levels have all been associated with an increased risk of PsO.\textsuperscript{30}

**Shared genetic factors and genetic predispositions**

T\textsubscript{h}17 cells and IL-23 receptor (R) polymorphisms are both associated with MS and PsO, along with a number of other autoimmune inflammatory conditions. Multiple studies regarding the association of these polymorphisms and the
development of PsO and MS have been conducted. While separate polymorphisms of the receptor are related to each condition, the two diseases seem to have unique associated polymorphisms.\textsuperscript{6,28,31–34}

**Shared cytokine profiles**

Both MS and PsO are T-cell mediated inflammatory conditions involving similar cytokines. The IL-23/IL-17 axis is central to the pathogenesis of both MS and PsO.\textsuperscript{35} IL-23 plays a role in both PsO and MS by reinforcing the $T_{h17}$ population expansion, serving as a pro-inflammatory cytokine in both diseases.\textsuperscript{20,35,36} The inflammatory response in PsO is promoted by $T_{h17}$ cells, and similarly, CNS infiltration of $T_{h17}$ cells with the production of IL-17 occurs in MS patients.\textsuperscript{6,32}

Additionally, TNF-alpha is a key cytokine in both diseases. As with IL-17, increased levels of TNF-alpha are found in both PsO and MS plaques, underlining the central role of these inflammatory mediators in both diseases.\textsuperscript{6,37,38}

IL-27 is an additional cytokine involved in both MS and PsO, although in contrasting roles. IL-27 acts to promote the differentiation of $T_{h1}$ cells and inhibit the differentiation of $T_{h17}$ cells. In MS, the levels of IL-27 are significantly lower when compared to patients without MS, resulting in relative lack of inhibition of $T_{h17}$ differentiation. In contrast, patients with PsO have higher levels of IL-27 relative to healthy patients, increasing the representation of the $T_{h1}$ profile. This is thought to act to prevent the progression of inflammation in PsO. In the population of patients with comorbid MS and PsO, there is evidence of slower progression of MS. It is hypothesized that the higher expression of IL-27/$T_{h1}$ seen in PsO that results in decreased $T_{h17}$ differentiation and cytokine expression is able to counterbalance the effects of decreased IL-27 expression and increased $T_{h17}$ profile seen with MS.\textsuperscript{39}

**Demyelinating disorders associated with anti-TNF-alpha therapy**

Another link between MS and PsO is illustrated with the use of anti-TNF-alpha therapy. TNF-alpha inhibitors are a well-known treatment option for PsO. However, a potential link between TNF-alpha inhibitors and demyelinating disease has been suggested.\textsuperscript{40–44} Demyelinating diseases with possible association to anti-TNF-alpha therapy include MS, optic neuritis, Guillain–Barre syndrome, transverse myelitis, and other peripheral neuropathies.\textsuperscript{42,45–47} The use of TNF-alpha inhibitors in PsO patients with a personal history of a demyelinating disorder or with a first-degree relative with MS is not recommended. However, one study has suggested that the number needed to treat in patients with PsO and MS is at least an order of magnitude smaller than the number needed to harm across all comparisons of anti-TNF-alpha therapies and first-degree relative relationships, suggesting TNF-alpha-inhibitor therapy could remain a treatment option for these patients after all other systemic treatment classes have been exhausted, in close collaboration with neurology colleagues, and while weighing the risks and benefits with the patient.\textsuperscript{48} After all, based on prior studies, it is unclear whether TNF-alpha inhibitors cause MS in patients who may be predisposed or rather unmask MS that would have presented at a later date. Several theories regarding the argument both for and against a pathogenic relationship between TNF-alpha inhibitors and demyelination have been proposed.\textsuperscript{45}

**Multiple sclerosis and psoriasis: is there an increased risk?**

Although an association between MS and PsO has not been clearly elucidated, studies have attempted to determine if an association does exist and whether having either disease places one at a higher risk of developing the comorbid disease. To date, findings have been conflicting.\textsuperscript{49,50} (Table 1)

**Studies suggesting positive correlation**

Cendrowski was the first to observe an increased prevalence of PsO in Polish MS patients, reported in 1989. He reviewed medical records of 51 patients with clinically probable MS as well as 33 controls, and reported a higher incidence of PsO in the MS group (1 in 17 vs 1 in 33, respectively).\textsuperscript{51} However, he later published a more robust series of three groups of MS patients ($n=285$), including these aforementioned 51 patients, and determined that PsO showed no convincing association with MS.\textsuperscript{52} A small case-control study reported an increased prevalence of PsO in patients with MS as compared to controls (6 of 117 vs 7 of 222, respectively).\textsuperscript{53} First-degree relatives of MS patients were also noted to have an increased prevalence of PsO.

In one large, single-center, retrospective, cross-sectional study, PsO ($n=5097$) and MS ($n=1829$) patients were identified via medical record from 2001 to 2014. Twenty-six patients were found to have concomitant diagnoses of PsO and MS. Five of these patients were diagnosed with PsA, as
| Study                  | Study design                        | Number of controls | Number of MS cases | Results regarding concomitant PsO in MS population | Suggests an increased association with psoriasis? |
|-----------------------|-------------------------------------|--------------------|--------------------|----------------------------------------------------|-----------------------------------------------|
| Cendrowski, 1989       | Case-control                        | 33 controls        | 51 with MS         | 5.88% cases vs 3.03% controls                      | Yes                                           |
| Dobson & Giovannoni, 2013 | Systematic review & meta-analysis | –                  | –                  | OR 1.31 (95% CI 1.09–1.57)                         | Yes                                           |
| Edwards & Constantinescu, 2004 | Cross-sectional; United Kingdom | 252,538 controls from general population | 658 with MS       | OR 1.89 (95% CI 0.98–3.66)                         | No                                            |
| Egeberg et al          | Cohort study; Denmark               | 5,397,122 Danish used as reference population | 44 with MS+PsO   | 68,580 with mild & severe PsO                      | Yes, increased risk of MS in patients with PsO IRR 1.78 for reference population vs 1.84/2.61 for mild/severe PsO |
| Fellner et al, 2014    | Case-control; Israel                | 192 controls with headaches | 214 with MS       | 4.2% cases vs 0.5% controls; OR 8.39 (95% CI 1.05–66.81) | Yes                                           |
| Guido et al, 2017      | Cross-sectional; USA                | 564,293 controls   | 1829 with MS       | OR 1.521 (95% CI 1.01–2.29)                        | Yes                                           |
| Henderson et al, 2000  | Case-control; Australia             | 222 controls who lived on the same street as MS cases | 117 with MS     | 5.12% cases vs 3.15% controls; OR 1.66 (95% CI 0.54–5.06) | No *suggested that those with MS have a genetic predisposition to autoimmunity in general, but not specific to PsO |
| Kwok et al             | Systematic review                   | –                  | –                  | Prevalence ranged from 0.41–7.7%                   | No                                            |
| Laroni et al, 2006     | Case-control; Italy                 | 245 age and sex-matched controls | 245 with MS      | 0.41% cases vs 0.82% controls; OR 0.50 (95% CI 0.05–5.53) | No                                            |
| Liu et al, 2019        | Systematic review & meta-analysis   | 870,149 controls (case-control, cross-sectional controls) | 18,456 with MS (case-control, cross-sectional controls) | OR 1.29 (95% CI 1.14–1.45) HR 1.92 (95% CI 1.32–2.80) | Yes                                           |

(Continued)
A Danish study examined the risk of new-onset MS in patients with mild (n=58,628) or severe (n=9952) PsO using a nationwide registry and found significantly increased incidence rates for MS in both mild and severe PsO compared to the reference population, suggesting that PsO may confer a risk of MS which increases with PsO disease severity. Incidence rates for MS per 10,000 person-years were 1.78 (95% CI for the reference population, 1.74–1.82) and for mild PsO and severe PsO, were 3.22 (95% CI 2.57–4.04), and 4.55 (95% CI 2.52–8.22), respectively. When incidence rates were adjusted for age, gender, socioeconomic status, smoking, medication, comorbidity, and UV phototherapy, an increased risk of MS was also seen (incidence rate ratio [IRR]=1.84, 95% CI 1.46–2.30 in mild PsO; IRR=2.61, 95% CI 1.44–4.74 in severe PsO). When analyses included adjustments for family history of MS, prior TNF-inhibitor treatment, or diagnosis of PsA, similar results were also seen.

Another study investigated various chronic inflammatory diseases and their association with MS by looking at 155 MS patients and 200 controls from 1976 to 1986. MS patients had a significantly increased prevalence of PsO compared to controls (OR=2.01, CI 0.73–5.83). This study also supported prior studies showing that families of MS patients experience no different rates of occurrence for autoimmune diseases when compared to control families.

In 2013, a meta-analysis of autoimmune disease in those with MS was performed. Eight studies that analyzed the risk of PsO in the MS population as well as their families were included. These studies found an overall increased risk for PsO in MS patients (OR=1.31, 95% CI 1.09–1.57, P<0.0001). There was no significantly increased risk for PsO in their first-degree relatives (OR=1.17, 95% CI 0.94–1.46, P=0.16).

A retrospective case-control study in Israel investigated the impact of PsO on the disease activity and progression of MS. This study included 3456 patients with PsO and MS who had been followed in excess of 5 years. Cases were compared to a matched control cohort of patients with only an MS diagnosis. This study found that 1.3% of MS patients had PsO as a comorbid diagnosis, and 78% (35 of 45) of these patients had PsO precede their MS diagnosis. Patients with PsO onset before their relapsing-remitting MS onset had later MS disease onset in life, well. An association between PsO and MS was found to be significant after adjusting for confounding variables such as sex, age, PsA, and prior exposure to TNF-alpha agents (OR=1.521; 95% CI 1.01–2.29; P=0.04).
slower progression of MS disability compared to patients without concurrent PsO, and significantly longer time to both second relapse and until significant neurological disability.

One case-control study investigated whether patients with a diagnosis of MS had higher rates of concomitant PsO. They found that 9 of the 214 MS patients and 1 of the 192 consecutive controls had comorbid PsO. Six of the 9 MS patients with PsO had been diagnosed with PsO prior to their MS diagnosis.

Most recently, a systematic review and meta-analysis of observational studies performed in 2018 reported increased OR and HR of PsO in MS patients (OR 1.29, 95% CI, 1.14–1.45; HR 1.92, 95% CI 1.32–2.80).32

Studies suggesting no correlation

In contrast, there have been several studies to suggest no association between PsO and MS. For example, a prospective study of patients diagnosed with MS in England did not detect an association with PsO. In this study, comorbidities of 658 consecutive patients attending a large MS specialty clinic in Nottingham were recorded during 2002–2003. There were 454 females and 204 males that participated (18–80 years old, median age=45) in the study. The prevalence of PsO in MS patients compared to the general population did not differ significantly.

Similarly, one of the largest published multicenter studies evaluated autoimmune disease risk in MS patients as well as their families, comparing rates of occurrence to their first-degree relatives, as well as in their unrelated spouses. In this study, 5031 MS patients along with 30,529 of their first-degree relatives and spouses (n=2707 spouses) were analyzed. The frequency of PsO in MS patients was found to be no different than for their spousal controls (5.8% of MS population vs 5.4% of controls, P=0.44). No significant difference in genders or in first-degree relatives of MS patients compared to controls was found.

In 2015, a systematic review of published studies to estimate the incidence and prevalence of comorbid autoimmune disease in MS was performed. This study also assessed the quality of these reviewed studies, finding less than half of the available studies to be of high quality. The prevalence of PsO in MS varied widely, ranging from 0.39% to 7.74% in previously published studies. The highest estimate was reported by Midgard et al’s population-based study (7.7% in MS patients vs 4% in controls).

A population-based cohort study utilizing the Danish Health Registration system compared MS patients to the general population, estimating the relative risk of other autoimmune diseases in patients with MS and their first-degree relatives. They reported a small, insignificant, increased risk of PsO in patients with MS and no increased incidence in their first-degree relatives. Laroni et al also failed to show an increased prevalence of PsO in patients with MS when compared to controls (0.41% vs 0.82%, respectively). Similarly, a systematic review of the literature also did not find an increased prevalence of PsO in patients with MS.

Finally, a comorbidity survey conducted by the National Psoriasis Foundation which spanned from 2003 to 2011 did not show an increased incidence of MS in patients with PsO.

Limitations of existing studies

An inherent limitation of most studies regarding the relationship between PsO and MS is a small sample size, and often, an observational or retrospective design. Large patient numbers and a reduction in selection bias have been attained in some studies that use nationwide databases, but these databases often introduce a lack of diversity and therefore, limit the ability to extrapolate results to larger, more ethnically diverse populations. A limitation of nationwide database use or electronic medical record systems is also a reliance on correct coding, introducing the possibility of unverified or incorrect diagnoses. In studies that included patient-reported conditions or histories, the potential for ascertainment or reporting bias is large. Some of the above studies also used prevalence data available in the literature, without age and sex matching, instead of obtaining a control population from the same or a similar environment. Meta-analyses are limited by the quality of the studies included and the manner in which the information was obtained or collected in those studies. Psoriasis patients may also receive increased medical attention compared to patients without the disease which could lead to earlier, more frequent diagnoses of comorbid MS.

Management and treatment

Psoriasis

Most patients with mild-to-moderate PsO can be well controlled on topical medications (i.e., corticosteroids, vitamin D analogs, coal tar, calcineurin inhibitors, retinoids, anthralin) and/or phototherapy. For moderate-to-
severe disease, systemic agents and/or biologic agents are often indicated. Oral systemic therapies for PsO include methotrexate (MTX), acitretin, cyclosporine (CYA), and apremilast. Biological therapies approved for use in PsO include TNF-alpha inhibitors (adalimumab, etanercept, certolizumab pegol, infliximab), an IL-12/23p40 inhibitor (ustekinumab), inhibitors of IL-17A (secukinumab, ixekizumab) the IL-17 receptor inhibitor (brodalumab), and IL-23p19 inhibitors (guselkumab, tildrakizumab).

**Multiple sclerosis**

Treatment of MS varies based on the type of MS being treated and treatment goals. Progressive types of MS are more difficult to treat successfully compared to relapsing forms of MS. Disease-modifying treatment options for relapsing-remitting forms of MS include IFN-beta, glatiramer acetate, dimethyl fumarate, teriflunomide, fingolimod, natalizumab, or alemtuzumab. The treatment of progressive types of MS, with evidence of active inflammation, relies primarily on immunosuppressive therapies, which unfortunately have self-limiting side effects with chronic use. Treatment options for secondary progressive MS in addition to the disease-modifying treatments, although of modest or lacking efficacy, include intravenous (IV) glucocorticoids, IV cyclophosphamide, and MTX. Options for primary progressive MS include ocrelizumab (the only drug approved for this type of MS), along with IV glucocorticoids, MTX, cladribine, mitoxantrone, and IVIg. More recently, the use of IL-17 inhibitors, specifically secukinumab, has shown reduction in the number of active brain lesions on magnetic resonance imaging (MRI) scans in patients with relapsing-remitting MS.

**Treatment of psoriasis in patients with concomitant multiple sclerosis**

As seen above, MS and PsO exhibit overlapping treatments including the use of fumarates (used mainly in Northern Europe), IFN-beta with MTX, and IL-17 inhibitors. MTX and CYA are both indicated for the treatment of PsO, and both also improve MS symptoms and reduce relapse rates. Dimethylfumarate works by downregulating T<sub>h</sub>1 and T<sub>h</sub>17 cells, which are upregulated in PsO and MS. This reduces the production of proinflammatory cytokines, including, but not limited to, IL-12, IL-17 and IL-23, which have been implicated in PsO and MS. In a small study, the addition of MTX to IFN-beta for the treatment of MS showed improvement of MS lesions. On the other hand, PsO outbreaks have been described with IFN-beta treatment for MS.

Secukinumab, an IL-17 inhibitor, is approved for use in PsO and PsA, and appears to be safe in patients with MS. As mentioned above, secukinumab causes significant reduction in MRI lesion activity in MS patients as well. The shared polymorphisms of the IL-23 receptor gene associated with MS and PsO may explain the efficacy of fumarates in both diseases, in addition to the successful use of IL-17A inhibitors in both conditions.

Ustekinumab is an IL-12/23p40 inhibitor approved for use in PsO and PsA. During a Phase II clinical trial, ustekinumab did not improve or worsen relapsing remitting MS, and there are no reports of worsening neurological disease with ustekinumab, allowing ustekinumab to remain as a treatment option in concomitant MS and PsO.

As mentioned above, there is a possible increase in MS exacerbations, and demyelinating disorders in general, with patients on anti-TNF alpha therapies. Phototherapy is not only efficacious in PsO treatment, but also benefits patients with MS, likely due to an increase in vitamin D levels which are deficient in patients with higher risk of MS and increased severity of disease.

**Areas of current and future research (e.g., IL-35)**

The most recently identified potential therapeutic target in inflammatory diseases, including PsO and MS, involves IL-35. IL-35 is a more recently identified member of the IL-12 cytokine family and is secreted primarily by regulatory T cells (T<sub>regs</sub>). IL-35 is also uniquely an immunosuppressive cytokine that plays a pivotal role in the function of T<sub>regs</sub> and their immunoregulatory activity. Both PsO and MS, among other autoimmune inflammatory diseases, have abnormal IL-35 expression, making IL-35 a potential new focus of therapeutic strategies.

Another potential treatment for both MS and PsO in recent literature lies in the properties of mesenchymal stem cells (MSCs). MSCs have the capabilities of modulating immune properties and exerting anti-inflammatory effects making them an alluring potential therapy in autoimmune inflammatory conditions. In a recent study, human embryonic (hE)-MSC transplantation resulted in the dramatic reduction of T<sub>h</sub>1 and T<sub>h</sub>17 cytokines in mice with imiquimod-induced PsO-like dermatitis. There have been a relatively larger number of
studies regarding MSC transplantation in the treatment of MS, many of them also showing promise, especially in comparison to current disease-modifying options, for the effective treatment of MS. Further studies are needed to determine the efficacy of MSC and the most promising cell origin as a therapy for both MS and PsO.

Conclusion
The data regarding the association between PsO and MS are overall inconsistent and conflicting. Smaller studies suggest that there may be an association and the few larger studies that have been conducted report no significant association between PsO and MS. Further study to verify or reject this association is warranted as uncovering the relationship between these two diseases could lead to the discovery of common mechanisms and genetic or environmental causes that could be of substantial value in the diagnosis and management of both diseases. Until then, dermatologists and other treating physicians alike may find it appropriate to screen for MS symptoms in patients with PsO so that timely referral to a neurologist can occur if necessary.

Disclosure
The authors report no conflicts of interest in this work.

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