

Psoriatic Arthritis: The Need for Early Intervention

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ABSTRACT. About 30% of individuals with skin psoriasis will develop an inflammatory disease of the peripheral or axial skeleton involving synovial and/or enthesal tissue termed psoriatic arthritis (PsA). In most cases psoriasis will precede PsA by several years. Hence skin psoriasis provides an opportune model to investigate genetic and environmental factors that interact and contribute to the development of a common form of inflammatory arthritis. Further, the preexisting presence of psoriasis represents a unique opportunity for the early detection of arthritis and the potential for more effective intervention. However, despite the presence of psoriasis, there may be delay in the diagnosis of PsA that is associated with adverse longterm outcome. Undiagnosed disease is not uncommon, as demonstrated by studies applying screening questionnaires to primary care and dermatology clinic populations. Other potential risk factors, such as obesity and smoking, the presence of certain genetic and biomarker profiles, combined with accurate imaging modalities, offer the potential for more targeted screening. So in future it should be possible to detect PsA at a much earlier stage and prevent significant joint damage and associated disability before it happens. (J Rheumatol Suppl. 2015 Nov; 93:10–13; doi:10.3899/jrheum.150625)

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Verna Wright Lecture

The concept of psoriatic arthritis (PsA) owes much to the insightful studies of Verna Wright. In one of his earliest studies 42 cases of psoriasis with arthritis were described and compared with 55 unselected patients with rheumatoid arthritis and 310 patients with psoriasis alone¹. He concluded that most of the 42 cases comprised a distinct entity. Of interest he was surprised by finding nail changes in 4 male patients with osteoarthritis, although possibly he may have been witnessing the bony proliferative element of PsA we recognize today. Notwithstanding he was the first to document the topographical association between nail disease and distal interphalangeal joint disease. In a later article he demonstrated many of the characteristic radiological features of PsA such as osteolysis and a greater incidence of sacroiliac joint change². His conclusion that PsA was “less severe than rheumatoid arthritis” is somewhat more contentious, but most certainly his observations of the different phenotypes of PsA were landmark findings.

We now recognize that PsA is not a benign condition, and with more effective treatments available there may never be a better opportunity for preventing its development from an early stage³. Skin psoriasis precedes the development of PsA in the majority of cases and so represents an excellent oppor-

tunity for implementing screening strategies. Some of the evidence for the importance of early detection will be reviewed, as will recent epidemiological findings, the development of screening questionnaires, and identification of high-risk groups where screening should be applied. The review is not comprehensive and concentrates on selective recent findings.

Is PsA Underdiagnosed?

Published estimates of the incidence and prevalence of PsA have varied, most likely due to the type of study setting, differences in the method of case ascertainment, and developments in diagnostic or classification criteria, such as the more recent adoption of the CASPAR (CLASSification for Psoriatic Arthritis criteria)⁴. A systematic review reported a median incidence of 6.4/100,000 cases per year of PsA in the general population⁵, yet a more recent population-based study from Norway found 188 incidence cases over an 8-year period giving an incident rate of 41.3/100,000⁶. In a longitudinal retrospective population-based study of psoriasis using a medical records-linked system, there was a 10-year cumulative incidence of 3.1% in Olmsted County, Minnesota, USA⁷. In contrast, a prospective cohort study of psoriasis in Toronto, Canada, reported a higher incidence of 1.8%⁸. However, both incidence and prevalence of PsA may be even higher. Studies using screening questionnaires applied to psoriasis populations in dermatology and primary care settings have revealed that many patients are undiagnosed. In a German study there were 10.9% of patients from dermatology clinics with undiagnosed PsA⁹ and as many as 29%

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in a study from Dublin¹⁰. Although retrospective studies do point to the potential importance of early diagnosis, it is important to note that the natural history of undiagnosed PsA is unknown.

Observational Studies of Outcome in PsA

Longterm observational studies of PsA have provided valuable information on the natural history of PsA. Health-related quality of life measures are affected in a degree similar to rheumatoid arthritis¹¹. An atherogenic lipid profile is associated with active PsA¹², there is an increased incidence of subclinical atherosclerosis^{13,14}, and an increased risk of cardiovascular disease¹⁵. Joint damage occurs in 47% of patients within 2 years of disease onset¹⁶.

Several studies of longitudinal disease cohorts suggest that delay in diagnosis is associated with a worse outcome. In the Toronto cohort a greater rate of joint damage was reported in those patients first seen after 2 years of diagnosis compared to those seen within 2 years¹⁷. In our own Bath cohort, delay in diagnosis, smoking, female gender, and older age at onset were associated with a worse physical function measured by the Health Assessment Questionnaire (HAQ) after 10 years¹⁸. Similar observations were reported in a Dublin cohort with late consulters having greater peripheral joint erosion and worse physical function¹⁹. In a prospective study from the Swedish Early PsA Register a shorter duration of symptoms and lower HAQ scores were independent predictors of reaching a state of minimal disease activity at 5 years²⁰. Therefore there is increasing evidence that early intervention may be important in reducing the burden of disease, although further prospective studies are needed.

Detection of Early Disease

Screening questionnaires. There have been several questionnaires available to screen for patients with PsA in various settings. The performance of the questionnaire has been compared in several studies, such as 2 comparing the PASE (Psoriatic Arthritis Screening Evaluation): the Toronto Psoriatic Arthritis Screen (ToPAS) and the Psoriasis Epidemiology Screening Tool (PEST)^{10,21}; and another: PASQ (Psoriasis and Arthritis Screening Questionnaire) with ToPAS and PEST²². In general the screening tools help identify a substantial number of patients with undiagnosed PsA and patients who may benefit from rheumatology review. A further questionnaire [Comparison of Three Screening Tools for psoriatic arthritis (CONTEST)] has been derived, combining optimal questions from existing tools, and needs further evaluation²³. Questions remain regarding the appropriate healthcare setting in which to apply the questionnaires, the frequency of their use, and the characteristics of the target population. Also patients with PsA may have mild psoriasis that never comes to healthcare attention until after PsA is diagnosed and so they may not be captured by screening.

Imaging. Imaging studies have revealed preclinical disease

in patients with psoriasis alone. Indeed patients with psoriasis clinically asymptomatic for musculoskeletal disease have a higher prevalence of enthesal abnormalities on ultrasound than age- and sex-matched controls²⁴. Power Doppler may detect vascular changes that distinguish PsA from psoriasis alone and offers the potential for detecting early development of arthritis²⁵. Psoriasis patients with nail changes had higher enthesitis scores at remote sites than patients with normal nails, consistent with observations that patients with PsA have a greater frequency of nail disease than psoriasis patients alone²⁶. MRI scanning may reveal subclinical synovitis and enthesitis in patients with psoriasis without arthritis symptoms²⁷.

Risk Factors for PsA in Psoriasis

Clinical and lifestyle. There are relatively few studies addressing the pattern of psoriasis as a risk factor for PsA. One such study found that scalp and intergluteal psoriasis and nail disease put those individuals at risk of developing PsA⁷. Nail disease is more common in patients with PsA compared to psoriasis and has been confirmed as a risk factor in a more recent study²⁸. Evidence for smoking as a risk factor is more conflicting, with at least 2 studies finding smoking a positive risk factor^{18,29} and another reporting that smoking is protective³⁰. A population-based study using The Health Improvement Network (THIN) database reported a greater incidence rate of PsA in a psoriasis population with increasing body mass index³¹. At least 1 study has reported the prevalence of PsA to be associated with greater extent of psoriasis³² albeit most patients with PsA have mild psoriasis and low PASI scores. Although the median time of onset of PsA is within 10 years of onset of psoriasis³², notably 1 study of European dermatology centers found the incidence rate of PsA remained constant with time following the diagnosis of psoriasis³³.

Genetic factors. There are genetic susceptibility factors common to both psoriasis and PsA. However, some known genetic factors such as presence of the HLA-Cw6 allele are strongly associated with psoriasis and more so in younger patients than in PsA itself. Therefore, there likely exist genetic factors associated with susceptibility to PsA other than those for skin psoriasis alone. Three such loci appear to be interleukin 13, HLA-B27, and PTPN22^{34,35}. The presence of HLA-B27 is associated with a shorter interval between the onset of psoriasis and the onset of PsA³⁶. Further, different combinations of HLA-B and HLA-C alleles and haplotypes may be associated with particular phenotypes and disease severity³⁷.

Other biomarkers. Osteoclast precursors are upregulated in PsA and can be identified by cellular markers such as dendritic cell-specific transmembrane protein (DC-STAMP). There are data to suggest that patients with psoriasis who develop arthritis show increased DC-STAMP expression on peripheral blood mononuclear cells³⁸. Measurement requires freshly isolated cells and access to flow cytometry and so is

not at present a feasible strategy for screening. Other soluble biomarkers that can be more readily measured are of interest, and bone turnover markers have been the subject of a recent systematic review³⁹. Markers that appear to differentiate PsA from psoriasis include matrix metalloproteinase-3, dickkopf 1, macrophage colony stimulating factor, a ratio of type II collagen synthesis to degradation, and possibly osteoprotegerin. Increased levels of highly sensitive C-reactive protein may also be discriminatory⁴⁰. These markers need further study in a prospective cohort of patients with psoriasis to test their predictive value.

In conclusion, the longterm outcome of PsA in those patients referred to a rheumatology service carries a high disease burden. Less is known of the outcome in patients who do not seek medical attention or who remain undiagnosed. The estimated mean health cost is high, especially in those with severe loss of physical function⁴¹. There are high levels of unemployment and loss of productivity that may be more readily reversible with early intervention⁴². With the development of treat-to-target regimes using more effective therapies the case for early intervention is even stronger. Individuals with psoriasis who would appear to be at most risk are those who are obese, have nail disease, and carry the HLA-B27 allele. However, more knowledge is needed to create robust bioprofiles that can be applied to clinical phenotypes that stratify patients into appropriate treatment pathways and help implement effective screening strategies.

REFERENCES

1. Wright V. Psoriasis and arthritis. *Ann Rheum Dis* 1956;15:348-56.
2. Wright V. Psoriatic arthritis. A comparative radiographic study of rheumatoid arthritis and arthritis associated with psoriasis. *Ann Rheum Dis* 1961;20:123-32.
3. McHugh N. Early psoriatic arthritis. *Rheum Dis Clin North Am*; in press.
4. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006;54:2665-73.
5. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of psoriatic arthritis: a systematic review. *J Rheumatol* 2008; 35:1354-8.
6. Hoff M, Gulati AM, Romundstad PR, Kavanaugh A, Haugeberg G. Prevalence and incidence rates of psoriatic arthritis in central Norway: data from the Nord-Trøndelag health study (HUNT). *Ann Rheum Dis* 2015;74:60-4.
7. Wilson FC, Icen M, Crowson CS, McEvoy MT, Gabriel SE, Kremers HM. Incidence and clinical predictors of psoriatic arthritis in patients with psoriasis: a population-based study. *Arthritis Rheum* 2009;61:233-9.
8. Eder L, Chandran V, Shen H, Cook RJ, Shanmugarajah S, Rosen CF, et al. Incidence of arthritis in a prospective cohort of psoriasis patients. *Arthritis Care Res* 2011;63:619-22.
9. Henes JC, Ziupa E, Eisfelder M, Adamczyk A, Knaudt B, Jacobs F, et al. High prevalence of psoriatic arthritis in dermatological patients with psoriasis: a cross-sectional study. *Rheumatol Int* 2014;34:227-34.
10. Haroon M, Kirby B, FitzGerald O. High prevalence of psoriatic arthritis in patients with severe psoriasis with suboptimal performance of screening questionnaires. *Ann Rheum Dis* 2013;72:736-40.
11. Husted JA, Gladman DD, Farewell VT, Cook RJ. Health-related quality of life of patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis. *Arthritis Rheum* 2001;45:151-8.
12. Jones SM. Lipoproteins and their subfractions in psoriatic arthritis: identification of an atherogenic profile with active joint disease. *Ann Rheum Dis* 2000;59:904-9.
13. Eder L, Zisman D, Barzilai M, Laor A, Rahat M, Rozenbaum M, et al. Subclinical atherosclerosis in psoriatic arthritis: A case-control study. *J Rheumatol* 2008;35:877-82.
14. Tam LS, Shang Q, Li EK, Tomlinson B, Chu TT, Li M, et al. Subclinical carotid atherosclerosis in patients with psoriatic arthritis. *Arthritis Rheum* 2008;59:1322-31.
15. Tam LS, Tomlinson B, Chu TT, Li M, Leung YY, Kwok LW, et al. Cardiovascular risk profile of patients with psoriatic arthritis compared to controls—the role of inflammation. *Rheumatology* 2008;47:718-23.
16. Kane D, Stafford L, Bresnihan B, FitzGerald O. A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. *Rheumatology* 2003;42:1460-8.
17. Gladman DD, Thavaneswaran A, Chandran V, Cook RJ. Do patients with psoriatic arthritis who present early fare better than those presenting later in the disease? *Ann Rheum Dis* 2011;70:2152-4.
18. Tillett W, Jadon D, Shaddick G, Cavill C, Korendowych E, de Vries CS, et al. Smoking and delay to diagnosis are associated with poorer functional outcome in psoriatic arthritis. *Ann Rheum Dis* 2013;72:1358-61.
19. Haroon M, Gallagher P, FitzGerald O. Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. *Ann Rheum Dis* 2015;74:1045-50.
20. Theander E, Husmark T, Alenius GM, Larsson PT, Telemann A, Geijer M, et al. Early psoriatic arthritis: short symptom duration, male gender and preserved physical functioning at presentation predict favourable outcome at 5-year follow-up. Results from the Swedish Early Psoriatic Arthritis Register (SwePsA). *Ann Rheum Dis* 2014;73:407-13.
21. Coates LC, Aslam T, Al Balushi F, Burden AD, Burden-Teh E, Caperon AR, et al. Comparison of three screening tools to detect psoriatic arthritis in patients with psoriasis (CONTEST study). *Br J Dermatol* 2013;168:802-7.
22. Mease PJ, Gladman DD, Helliwell P, Khraishi MM, Fuiman J, Bananis E, et al. Comparative performance of psoriatic arthritis screening tools in patients with psoriasis in European/North American dermatology clinics. *J Am Acad Dermatol* 2014;71:649-55.
23. Coates LC, Walsh J, Haroon M, FitzGerald O, Aslam T, Al Balushi F, et al. Development and testing of new candidate psoriatic arthritis screening questionnaires combining optimal questions from existing tools. *Arthritis Care Res* 2014;66:1410-6.
24. Gisondi P, Tinazzi I, El-Dalati G, Gallo M, Biasi D, Barbara LM, et al. Lower limb enthesopathy in patients with psoriasis without clinical signs of arthropathy: a hospital-based case-control study. *Ann Rheum Dis* 2008;67:26-30.
25. Aydin SZ, Ash ZR, Tinazzi I, Castillo-Gallego C, Kwok C, Wilson C, et al. The link between enthesitis and arthritis in psoriatic arthritis: a switch to a vascular phenotype at insertions may play a role in arthritis development. *Ann Rheum Dis* 2013;72:992-5.
26. Ash ZR, Tinazzi I, Gallego CC, Kwok C, Wilson C, Goodfield M, et al. Psoriasis patients with nail disease have a greater magnitude of underlying systemic subclinical enthesopathy than those with normal nails. *Ann Rheum Dis* 2012;71:553-6.
27. Emad Y, Ragab Y, Gheita T, Anbar A, Kamal H, Saad A, et al. Knee enthesitis and synovitis on magnetic resonance imaging in patients with psoriasis without arthritic symptoms. *J Rheumatol* 2012;39:1979-86.

28. Langenbruch A, Radtke MA, Krensel M, Jacobi A, Reich K, Augustin M. Nail involvement as a predictor of concomitant psoriatic arthritis in patients with psoriasis. *Br J Dermatol* 2014;171:1123-8.
29. Li W, Han J, Qureshi AA. Smoking and risk of incident psoriatic arthritis in US women. *Ann Rheum Dis* 2012;71:804-8.
30. Eder L, Shanmugarajah S, Thavaneswaran A, Chandran V, Rosen CF, Cook RJ, et al. The association between smoking and the development of psoriatic arthritis among psoriasis patients. *Ann Rheum Dis* 2012;71:219-24.
31. Love TJ, Zhu Y, Zhang Y, Wall-Burns L, Ogdie A, Gelfand JM, et al. Obesity and the risk of psoriatic arthritis: a population-based study. *Ann Rheum Dis* 2012;71:1273-7.
32. Gelfand JM, Gladman DD, Mease PJ, Smith N, Margolis DJ, Nijsten T, et al. Epidemiology of psoriatic arthritis in the population of the United States. *J Am Acad Dermatol* 2005;53:573.
33. Christophers E, Barker JN, Griffiths CE, Dauden E, Milligan G, Molta C, et al. The risk of psoriatic arthritis remains constant following initial diagnosis of psoriasis among patients seen in European dermatology clinics. *J Eur Acad Dermatol Venereol* 2010;24:548-54.
34. Bowes J, Eyre S, Flynn E, Ho P, Salah S, Warren RB, et al. Evidence to support IL-13 as a risk locus for psoriatic arthritis but not psoriasis vulgaris. *Ann Rheum Dis* 2011;70:1016-9.
35. Bowes J, Loehr S, Budu-Aggrey A, Uebe S, Bruce IN, Feletar M, et al. PTPN22 is associated with susceptibility to psoriatic arthritis but not psoriasis: evidence for a further PsA-specific risk locus. *Ann Rheum Dis* 2015; Apr 28 (E-pub ahead of print).
36. Winchester R, Minevich G, Steshenko V, Kirby B, Kane D, Greenberg DA, et al. HLA associations reveal genetic heterogeneity in psoriatic arthritis and in the psoriasis phenotype. *Arthritis Rheum* 2012;64:1134-44.
37. Haroon M, Winchester R, Giles JT, Heffernan E, FitzGerald O. Certain class I HLA alleles and haplotypes implicated in susceptibility play a role in determining specific features of the psoriatic arthritis phenotype. *Ann Rheum Dis* 2014; Sept 26 (E-pub ahead of print).
38. Ritchlin C. Biomarker development in psoriatic arthritis. *J Rheumatol Suppl.* 2012 Jul;89:57-60.
39. Jadon DR, Nightingale AL, McHugh NJ, Lindsay MA, Korendowych E, Sengupta R. Serum soluble bone-turnover biomarkers in psoriatic arthritis and psoriatic spondyloarthropathy. *J Rheumatol* 2015;42:21-30.
40. Chandran V. Soluble biomarkers may differentiate psoriasis from psoriatic arthritis. *J Rheumatol Suppl.* 2012 Jul;89:65-6.
41. Poole CD, Lebmeier M, Ara R, Rafia R, Currie CJ. Estimation of health care costs as a function of disease severity in people with psoriatic arthritis in the UK. *Rheumatology* 2010;49:1949-56.
42. Tillett W, Shaddick G, Askari A, Cooper A, Creamer P, Clunie G, et al. Factors influencing work disability in psoriatic arthritis: first results from a large UK multicentre study. *Rheumatology* 2015;54:157-62.