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ARTICLE TITLE

Early Psoriatic arthritis

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KEY WORDS

4-8 keywords to direct and optimize search results
Psoriatic arthritis, psoriasis, biomarkers, genetic screening

KEY POINTS

List 3 to 5 key points of approximately 25 words each that summarize the main points of the article. Key points appear beneath the article title and authors in print and online

Early psoriatic arthritis is a heterogeneous condition that can make diagnosis difficult and can be confused with nodal osteoarthritis, fibromyalgia and mechanical back pain

Screening questionnaires have highlighted that a significant number of cases are undiagnosed and delay in diagnosis may be associated with poorer long-term outcome

Currently the strongest predictors for the development of psoriatic arthritis in individuals with psoriasis are nail disease, obesity and HLA-
B27

SYNOPSIS

Provide a brief summary of your article (100 to 150 words; no references or figures/tables). The synopsis appears only in the table of contents and is often used by indexing services such as PubMed

Skin psoriasis is a major risk factor for the development of an inflammatory arthritis known as psoriatic arthritis, hence providing a model to study genetic and environmental factors that trigger and perpetuate synovial inflammation, as well an excellent opportunity for early and effective intervention. A number of recent studies have shown that delay in diagnosis is associated with long-term adverse outcome. Screening questionnaires have revealed a potential burden of undiagnosed disease. Lifestyle factors such as smoking and obesity have come under scrutiny as risk factors for the development of psoriatic arthritis as have genetic and soluble biomarkers. Imaging modalities may have an important role in detecting the earliest signs such as entheseal involvement. With the availability of more effective treatments and treatment strategies it may be possible to prevent significant joint damage and associated disability before it happens. However the precise nature of accurate and cost-effective screening strategies remains to be determined.

Early Psoriatic Arthritis

Synopsis

Skin psoriasis is a major risk factor for the development of an inflammatory arthritis known as psoriatic arthritis, hence providing a model to study genetic and environmental factors that trigger and perpetuate synovial inflammation, as well an excellent opportunity for early and effective intervention. A number of recent studies have shown that delay in diagnosis is associated with long-term adverse outcome. Screening questionnaires have revealed a potential burden of undiagnosed disease. Lifestyle factors such as smoking and obesity have come under scrutiny as risk factors for the development of psoriatic arthritis as have genetic and soluble biomarkers. Imaging modalities may have an important role in detecting the earliest signs such as entheseal involvement. With the availability of more effective treatments and treatment strategies it may be possible to prevent significant joint damage and associated disability before it happens. However the precise nature of accurate and cost-effective screening strategies remains to be determined.

Key Indexing terms: Psoriatic arthritis, psoriasis, biomarkers, genetic screening

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Introduction

Psoriatic arthritis is a heterogeneous condition that may present in several different patterns, hence diagnosis and differentiation from other forms of arthritis can often be a challenge. Unlike conditions such as rheumatoid arthritis, systemic lupus erythematosus or systemic vasculitis there are no autoimmune diagnostic markers. Furthermore, once diagnosed the future course may be unpredictable and there is a relative paucity of known risk factors or biomarkers that reliably predict long-term outcome. Whilst there are several national and international guidelines that help guide treatment for patients with persistently active disease, such as those who would benefit from biological therapy, there is less information to guide management of the patient with early or recently diagnosed disease. Yet the most frequently asked question from patients newly diagnosed is what the future will hold.

We now recognise that psoriatic arthritis 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 stage. Skin psoriasis precedes the development of psoriatic arthrtis in the majority of cases and so represents an excellent opportunity for implementing screening strategies. Some of the evidence for the important 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. With the advent of more effective treatment than traditional agents, there has never been such an urgent need to focus much more attention on the natural history of early disease.

Is psoriatic arthritis under-diagnosed?

There have been variable estimates of the incidence and prevalence of psoriatic arthritic, likely due to factors such as historical differences in diagnostic criteria applied, study setting and method of case ascertainment. Whilst a systematic review reported a median incidence of 6.4/100,000 cases per year of psoriatic arthritis in the general population[i](1), a more recent population based study from Norway found 188 incidence cases over an 8 year period giving an incident rate of 41.3/100,000 (2). In studies of psoriasis using information from clinical records there was a 10 year cumulative incidence of 3.1% (3), whereas a prospective cohort study of psoriasis reported an incidence of 1.8% (4).

However both incidence and prevalence are likely to be higher as studies using screening questionnaires have revealed that many patients are undiagnosed. For instance there were 10.9 % of patients from dermatology clinics in Germany with undiagnosed psoriatic arthritis (5) and 29% in a study from Dublin (6). In a German study from 48 centres studying 1511 patients with psoriasis, 21% had psoriatic arthritis and as many as 85% of cases were newly diagnosed following rheumatology assessment (7). In another multinational study of 34 dermatology centres, 949 patients with plaque psoriasis were evaluated and 41% of 285 with psoriatic arthritis had not previously been diagnosed (8). From a large population based telephone survey of households in North America and Europe, 44% of patients with a diagnosis of psoriasis alone reported joint pain (9). However the importance of earlier detection remains uncertain as the natural history of undiagnosed psoriatic arthritis is unknown.

Observational studies of outcome in psoriatic arthritis

Long-term observational studies of psoriatic arthritis such as those from the Toronto cohort and elsewhere have provided valuable information on the natural history. For instance health-related quality of life measures are similar to rheumatoid arthritis (10). There are important comorbidities such as dyslipidaemia and premature atherosclerosis. In one study of early psoriatic arthritis joint erosions were present in 27% of patients at 10 months and in 47% of patients within two years of disease onset (11). Peripheral joint disease is progressive in the majority of patients with the highest rate of progression in the first year of disease (12).

Several more recent studies also suggest that delay in diagnosis is associated with a worse outcome. In the Toronto cohort those patients first seen after two years of diagnosis compared to those seen within two year had a greater rate of joint damage (13). In our own Bath cohort, delay in diagnosis as well as smoking, female gender and older age at onset were associated with a worse physical function measured by the Health Assessment Questionnaire (HAQ) after 10 years (14). Similar observations were reported in a Dublin cohort with late consulters having greater peripheral joint erosion and worse physical function (15). Finally results from the Swedish Early Psoriatic Arthritis Register showed that shorter duration of symptoms and lower HAQ scores were independent predictors of reaching a state of minimal disease activity at 5 years (16). Therefore there is some indirect

evidence to suggest that early intervention may be important in reducing the burden of disease.

Some further evidence in support of early intervention comes from clinical trials. In the PRESTA study patients receiving etanercept 50 mg once weekly and having PsA for less than 2 years had greater improvement in efficacy measures than those with longer disease duration (17).

Detection of early disease

The development of the CASPAR classification criteria has helped standardise the characteristics of patients in cohort studies and entry into clinical trials (18). CASPAR also performs well in patients with early psoriatic arthritis (19). However CASPAR is mainly designed for use in rheumatology settings hence other mechanisms for identifying patients who may have psoriatic arthritis are required.

i. Screening questionnaires

There have been several questionnaires developed to screen for patients with psoriatic arthritis in various settings. Studies to compare the performance of the questionnaires have also been performed, such as two comparing the Psoriatic Arthritis Screening Evaluation (PASE), the Toronto Psoriatic Arthritis Screen (ToPAS) and the Psoriasis Epidemiology Screening Tool (PEST) (6, 20) and another the Psoriasis and Arthritis Screening Questionnaire (PASQ) with ToPAS and PEST (21). In general the screening tools have not

performed as well as in the setting where they were derived although have identified both undiagnosed psoriatic arthritis and patients who may benefit from rheumatology review. More recently another questionnaire (CONTEST) has been derived combining optimal questions from existing tools and needs further evaluation (22). The place of screening questionnaires in various health care settings including the frequency of use and characteristics of the target population to which they are applied still needs to be determined.

ii. imaging

Imaging modalities such as ultrasound have the potential for detecting preclinical disease. Gisondi et al were able to demonstrate entheseal abnormalities by ultrasonography in clinically asymptomatic patients with psoriasis (23). Power Doppler may detect vascular changes that herald the development of arthritis (24). Also of much interest psoriasis patients with nail changes were shown to higher enthesitis scores at remote sites than patients with normal nails, consistent with observations that patients with psoriatic arthritis have a greater frequency of nail disease than psoriasis patients alone (25). MRI scanning may reveal subclinical synovitis and enthesitis inpatients with psoriasis without arthritis symptoms (26).

Ultrasound may also be helpful with good specificity for documenting joint and tendon involvement in early psoriatic arthritis. Furthermore persistent change on grey scale or power Doppler ultrasound may be a risk factor for disease progression (27).

Risk factors for psoriatic arthritis in psoriasis (Table one)

i. Clinical and lifestyle

There may be certain types of psoriasis that put those individuals at greater risk of developing psoriatic arthritis such as scalp and intergluteal psoriasis and nail disease (3). Certainly nail disease has consistently been found to be a major risk factor (28). Evidence for smoking is more conflicting with at least two studies finding smoking a positive risk factor (14, 29) and another reporting that smoking is protective (30). A population based study using The Health improvement Network (THIN) database reported a greater incidence rate of psoriatic arthritis in a psoriasis population with increasing BMI (31). Severity of psoriasis seems unlikely to be a major risk factor for developing psoriatic arthritis, as most patients with psoriatic arthritis have low Psoriasis Area Severity Index (PASI) scores. However meta-analysis from a recent systematic literature review did show a trend between PASI score and risk of psoriatic arthritis (32). Although it has been commonly held that psoriatic arthritis most commonly develops within 10 years of onset of psoriasis, notably one study of European dermatology centres found the incidence rate of PsA remained constant with time following the diagnosis of psoriasis (33).

ii. Genetic factors

There are likely to be genetic factors that make individuals with psoriasis susceptible to psoriatic arthritis. HLA-Cw6 is strongly associated with psoriasis and more so in younger onset but is less frequent in psoriatic arthritis suggesting that there are independent

susceptibility genes for psoriatic arthritis (34). Two such loci appear to be IL-13 and HLA-B27 (35). The presence of HLA-B27 is associated with a shorter interval between the onset of psoriasis and the onset of psoriatic arthritis (34). Furthermore it would appear that there are combinations of HLA-B and C alleles/haplotypes that confer susceptibility to phenotypes and severity. In an Irish population a HLA*B27:05:02 haplotype was associated with enthesitis, dactylitis and symmetrical sacroiliitis, whereas a HLA*08:01:01 haplotype was associated with a synovial-based pathology including joint fusion and deformities, asymmetrical sacroillitis and also dactylitis (36).

iii. Other Biomarkers

Osteoclast precursors identified with by cellular markers are upregulated in psoriatic arthritis and include dendritic cell specific membrane protein (DC-STAMP). There is data to suggest that patients with psoriasis who develop arthritis show increased DC-STAMP expression on peripheral blood mononuclear cells (37). 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 review (38). Markers that appear to differentiate psoriatic arthritis from psoriasis include matrix metalloproteinase-3 (MMP-3), dickkopf 1 (DKK-1) macrophage colony stimulating factor (M-CSF), a ratio of type II collagen synthesis to degradation (CPII:C2C) and possibly osteoprotegerin. Increased levels of highly sensitive CRP (hsCRP) may also be discriminatory (39). These markers need further study in a prospective cohort of patients with psoriasis to test their predictive value.

Clinical presentation of early disease

The distribution of the classical five subgroups of psoriatic arthritis as reported by Moll and Wright has varied in cohort studies, to some extent dependent on mean disease duration as subgroups may overlap and evolve (40). Nonetheless oligoarthritis of peripheral joints in a patient with plaque psoriasis and nail disease remains a common presenting scenario. However, the early stages of other forms of psoriatic arthritis may be difficult to distinguish not only from other inflammatory joint disease such as rheumatoid arthritis, but even more so from osteoarthritis, fibromyalgia and mechanical back pain. The bony proliferation that is a characteristic feature of PsA and contributes to the CASPAR classification criteria may yield a clinical phenotype that resembles nodal osteoarthitis when affecting the small joints of the hand. Likewise pain and tenderness secondary to entheseal disease may be attributed to other conditions such as fibromyalgia. Enthesitis, inflammatory axial disease and oligoarthritis contributed to 69% of undiagnosed PsA in a screening study of dermatology practice (15). In a study of early psoriatic arthritis, the presence of enthesitis, inflammatory low back pain and dactylitis were helpful diagnostic features (41). Given the considerable heterogeneity of early psoriatic arthritis the development of treatment algorithms can be major challenge (42).

Conclusions

We know that left unchecked the long term outcome of psoriatic arthritis carries a high disease burden. The estimated mean health cost is high especially in those with severe loss of physical function (43). There are high levels of unemployment and loss of productivity that may be more readily reversible with early intervention (44). The availability of more effective treatments with several also in the pipeline make the case for early intervention 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 establishment of more robust bioprofiles are needed in order stratify patients into appropriate treatment pathways and to implement effective screening strategies.

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Table one: Possible risk factors for developing psoriatic arthritis in individuals with psoriasis

Lifestyle	
	Obesity*
	Smoking?
Clinical	
	Severity of psoriasis
	Pattern of psoriasis (scalp, intergluteal)
	Nail psoriasis*
Imaging	
	Ultrasound evidence of enthesitis
Biomarkers	
	HLA-B27*
	IL-13
	hsCRP
	DC-STAMP
	MMP-3
	DKK-1
	M-CSF
	CPII:C2C

- Denotes factors where there is strongest evidence

[i]