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Psoriatic Arthritis: Gender and Age-based Insights into Diagnosis and Treatment

Overview of psoriatic arthritis (PsA)

PsA is a progressive inflammatory musculoskeletal disease occurring where tendons and ligaments are attached to bones (entheses), in synovial joints, and in the spine

The immune system overreacts, creating pain, inflammation, and swelling

Develops in many patients diagnosed with psoriasis, a disease affecting the skin

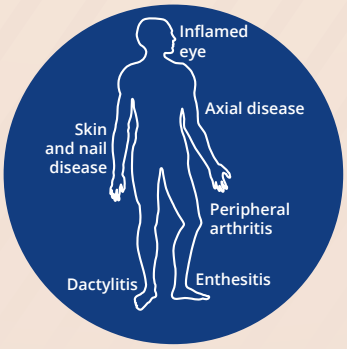
There is no cure for PsA; however, awareness of the condition and new treatments can slow progression, lessen pain, and protect joints

Causes of PsA

Patients with a family history can develop PsA

Some molecular markers have been identified, such as tumour necrosis factor (TNF)-α, interleukin (IL)-17, IL-6, IL-21, IL-22, IL-23, and interferon (IFN)-γ

Environmental factors, obesity, infection, stress, and injury may trigger the onset



PsA symptoms and manifestations

Symptoms, although highly variable between individuals, may include:

- Peripheral arthritis
- Tenderness in entheses
- Swelling of digits
- Inflammation of the eyes and uveitis
- Axial disease
- Inflammatory bowel disease
- Skin and nail disease
- Dactylitis

Disease classification

Moll and Wright criteria

- Inflammatory arthritis
- Presence of psoriasis
- Absence of serological tests for rheumatoid factor

ClASsification of Psoriatic ARthritis (CASPAR criteria)

- Presence of inflammatory articular disease (in the joints, spine, or entheses)
- ≥3 points scored based on specific criteria

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Mechanism and pathophysiology of PsA

1. Dysregulated cytokine expression

- Pro-inflammatory cytokine expression most pronounced at joints/synovia
- TNF-α, IL-17, IL-6, IL-21, IL-22, IL-23, and IFN-γ involved

2. Immune cell dysregulation

- Dendritic cells (DCs) play a key role in PsA pathogenesis
- DC stimulate T helper (Th) 17, gamma delta T (γδT) cells, innate lymphoid cells (ILC3), and Th1 cells
- Excessive production of inflammatory cytokines

3. Genetic factors

- Genetic links to the Human Leukocyte Antigen (HLA) cluster
- *IL12B* (5q31.1eq33.1), *IL23A* (12q13.3), *TYK2, STAT3,* and *TRAF3IP2* genes enhance T cell activation and cytokine signalling pathways tied to the IL-23/-17 axis
- How genetically susceptible individuals develop the disease is largely unknown

4. Epigenetic alterations

- Heritable but reversible modifications that affect gene expression
- Do not alter the underlying DNA sequence
- Include DNA methylation, histone modifications, and non-coding RNAs (micro-RNAs)

5. Environment and microbiome

- Stress, trauma, diet, and the microbiome can trigger the immune system
- Important in genetically predisposed individuals
- Dysbiosis and gut bacterial species may play an important role

Available treatments and therapies under investigation

- Goals are to minimise disease activity, prevent structural damage, and improve quality of life
- Conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) work for symptom relief
- DMARDs do not help with axial symptoms, slow radiographic progression, or relieve uveitis, enthesis, and dactylitis
- TNF inhibitors (TNFi), available since the 2000s, are effective in treating multiple domains of the disease
- Several therapies including anti-TNFs, anti-IL-12/23, anti-IL-17, and anti-IL-23 therapeutics are available
- Additional agents under investigation

Agent	Study	Mechanism of action	Status
Certolizumab	RAPID-PsA	Anti-TNFα antigen	Available therapy
Adalimumab	ADEPT	Binds to TNFα	Available therapy
Ixekizumab	SPIRIT-P1	Il-17 inhibitor	Available therapy
Apremilast	PALACE 3	Phosphodiesterase-4 inhibitor	Available therapy
Abatacept	ASTRAEA trial	CTLA4Ig* inhibitor	Available therapy
Tofacitinib	OPAL BROADEN	JAK3-1* inhibitor	Available therapy
Adalimumab	GENOVESE		Available therapy
Etanercept	Mease 2000	Fusion protein	Available therapy
Infliximab	IMPACT	Binds to TNF-α	Available therapy
Golimumab	GO-REVEAL	Binds to TNF-α	Available therapy
Ustekinumab	PSUMMIT -1/-2	Binds to IL-23 and IL-12	Available therapy
Apremilast	PALACE 4, DMARD-naive		Available therapy
Secukinumab	FUTURE 2	IL-17 inhibitor	Available therapy
Guselkumab	DISCOVER -1/-2	IL-23 inhibitor	Under investigation
Risankizumab		IL-23 inhibitor	Under investigation
Filgotinib		JAK1* inhibitor	Under investigation
Upadacitinib		JAK1* inhibitor	Under investigation

*CTLA4Ig: cytotoxic T lymphocyte-associated antigen-4 immunoglobulin; JAK: Janus tyrosine kinase

Barriers to effective PsA treatment

- Well-characterised disease markers and definitive screening procedures are lacking
- Many available PsA screening tools have not been validated for clinical use
- Delay in referring patients for specialist (dermatologist/rheumatologist) evaluation
- Lack of awareness about the clinical spectrum of PsA presentation
- Approaches to patient care might differ based on geographic region and availability of specialists
- Patient non-adherence to the treatment regimen
- Infrequent and unclear communication between patients and physicians
- Poor patient knowledge about PsA and standards of care for treatment
- Poor coordination between patients, primary care physicians, and specialists

Gender differences in PsA

Differences in clinical features

- Onset of PsA in men and women may be influenced by age
- Differences in musculoskeletal and extra-articular manifestations are evident between men and women
- Men have more axial involvement; women frequently have peripheral joint involvement
- Women develop less structural damage in axial and peripheral joints

Differences in treatment

- Women have a greater tendency to seek healthcare
- Men are more likely to ignore symptoms, self-medicate, and seek help only after intolerable symptoms develop
- Women are better able to navigate the health system
- Pain and fatigue are misinterpreted/related to mental health disorders in women
- Men respond better to advanced therapy and are more likely to experience sustained remission/low disease activity
- Women have a poorer response to medications and more frequently discontinue therapy

Differences in quality of life

- Women have poorer quality of life and functional status

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Age in PsA

Age naturally influences the onset of comorbidities and aspects like mental health and social determinants, which affect the manifestations of PsA and its outcomes

Late-onset PsA

- More common in women
- HLA-C*06 less common in patients
- Psoriasis presents for longer

Late-onset PsA is more aggressive and shows:

- Elevated inflammatory marker levels
- Mortality
- Patient body mass index
- Dactylitis
- Involvement of nails
- Psoriasis Severity Index (PASI) scores

Summary

1. PsA is a progressive inflammatory disease occurring where tendons and ligaments are attached to bones (entheses) in synovial joints, and in the spine, resulting in enthesitis, peripheral arthritis, and spondylitis
2. Immune cell dysregulation, altered cytokine expression, genetic factors, epigenetic regulation, and environment contribute to disease expression
3. Several treatments are available and more are under investigation
4. Gender and age of patients influence clinical features, quality of life, and treatment outcomes

References

1. Nancy Garrick, D. D. (2017). *Psoriatic Arthritis.* National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIAMS.
2. Van den Bosch, F., & Coates, L. (2018). Clinical management of psoriatic arthritis. *The Lancet, 391*(10136), 2285-2294.
3. Helliwell, P., & Taylor, W. (2005). Classification and diagnostic criteria for psoriatic arthritis. *Annals of the Rheumatic Diseases, 64*(suppl 2), ii3–ii8.
4. Tillett, W., Costa, L., Jadon, D., Wallis, D., Cavill, C., McHugh, J., ... & McHugh, N. (2012). The ClASsification for Psoriatic ARthritis (CASPAR) criteria–a retrospective feasibility, sensitivity, and specificity study. *The Journal of Rheumatology, 39*(1), 154–156.
5. Carvalho, A. L., & Hedrich, C. M. (2021). The molecular pathophysiology of psoriatic arthritis—the complex interplay between genetic predisposition, epigenetics factors, and the Microbiome. *Frontiers in Molecular Biosciences, 8.*
6. Ocampo D, V., & Gladman, D. (2019). Psoriatic arthritis. *F1000Research, 8,* F1000 Faculty Rev-1665.
7. Visalli, E., Crispino, N., & Foti, R. (2019). Multidisciplinary management of psoriatic arthritis: The benefits of a comprehensive approach. *Advances in Therapy, 36*(4), 806–816.
8. Tarannum, S., Leung, Y.-Y., Johnson, S. R., Widdifield, J., Strand, V., Rochon, P., & Eder, L. (2022). Sex-and gender-related differences in psoriatic arthritis. *Nature Reviews Rheumatology, 18*(9), 513–526.
9. Fragoulis, G. E., Nikiphorou, E., McInnes, I. B., & Siebert, S. (2022). Does age matter in psoriatic arthritis? A narrative review. *The Journal of Rheumatology, 49*(10), 1085–1091.

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