

Review Article

Primary Immunodeficiency Disorders (PIDs) and its Rheumatologic Manifestations

Mohammad Imnul Islam

Abstract

The hallmark of Primary Immunodeficiency Disorders (PIDs) is increased susceptibility to recurrent infections, which are often poorly responsive to therapy, prolonged and life-threatening. The infections can involve bones and joints. PIDs may also predispose to allergic, autoimmune, autoinflammatory and malignant disorders. Arthritis is the most common rheumatological manifestation of PIDs. Recurrent septic arthritis, arthritis with increased susceptibility to infection, skeletal changes, autoimmune disease or systemic lupus erythematosus with negative antinuclear antibody (ANA) are the essential clinical clues that could be considered rheumatologic manifestations of PIDs. This is considerable concern that early detection of PIDs patients invariably improves the quality of life and life expectancy through the prompt implementation of appropriate medical intervention.

Key Words: Primary Immunodeficiency Disorders (PIDs)

DOI: <https://doi.org/10.3329/bjch.v46i2.72121>

Background

Primary immunodeficiency disorders (PID) or in born errors of immunity (IEI) are a heterogeneous group of diseases resulting from inherited defect of both innate and adaptive immunity. These result from intrinsic defects in immune cells, including T cells, B cells, complement components, phagocytes and others.¹ PIDs are associated with increased susceptibility to infections determined by affected component of immune system. Autoimmune complications of PID are often independent of any known infection, and as per evidences from animal models, immunodeficiency can directly predispose to rheumatic, autoimmune or autoinflammatory disease by disrupting mechanisms that normally negatively regulate immune responses.² The field of PIDs is growing fast as a consequence of educational initiatives, scientific activities, supporting agencies, and patient organizations awareness program though it is not well developed in our country. Here in this

review the rheumatic and autoimmune presentations of PIDs will be highlighted with an aim to enrich knowledge with updated information among the physicians which would potentiate early diagnosis and effective treatment of these patients. The overall incidence of PIDs is around 1:10,000 and they are more prevalent in children.³ Within the context of epidemiology, several papers are there presenting international cohorts. In Korea, the prevalence was 11.25 per million children.⁴ Sweden carried out a study during the period 1974 through 1979 and resulted in 201 reported cases.⁵ In a Taiwan tertiary hospital from January 1985 to October 2004, 37 patients with PIDs were identified.⁶ Similarly, in Singapore between 1990 and 2000, thirty-nine patients with PID were identified.⁷ In a Indian study after screening of suspected 528 patients they found 12% of PID cases in their study.⁸ Though there is no concrete data regarding prevalence of PIDs in Bangladesh, but raising awareness among the physicians with essential laboratory (flow cytometry analysis) facility in some limited centers number of PIDs cases are increasing gradually across the countries.

Correspondence: Mohammad Imnul Islam, Professor of Pediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. Cell: 01711393049, email: imon27@gmail.com

Received: 10/06/2022

Pathophysiology

Disorders of innate immunity: Innate immunity is the first line of defense against potential pathogens. Numerous cells and proteins are involved in the innate immune response including phagocytes (neutrophils and macrophages), dendritic cells, and complement proteins. Defects in the development and function of any of these elements of innate immunity may lead to PIDs. Innate immunity also plays a key role in helping B and T lymphocytes to accomplish their fundamental functions.⁹

Disorders of adaptive immunity: T cells and B cells are the primary cells of the adaptive immune system. B cells mediate antibody production and, therefore, play a major role in humoral immunity. T cells, on the other hand, are responsible for cell-mediated immune responses. Defects occurring at any stage of T-cell development, differentiation and maturation lead to T-cell (cellular) immunodeficiency disorders, while defects relating to B-cell development and/or maturation result in B-cell (antibody-deficiency) disorders. Since B-cell-mediated antibody production requires intact T-cell function, most T-cell defects lead to combined (B- and T-cell) immunodeficiency disorders (CIDs).^{10,11}

Inborn errors of immunity (IEI) are caused by damaging germline variants in single genes. Mechanisms of disease in IEI depend on the nature of the variant as well as the mode of inheritance, though most immunodeficiencies are congenital and have an X-linked or autosomal recessive inheritance pattern.⁹

Rheumatic manifestations of PIDs: Though the main characteristic of a PID is an increased susceptibility to infections, some forms can present with immune dysregulation leading to autoimmune and rheumatological conditions.² This can arise from a variety of mechanisms and occur chiefly in antibody deficiency disorder of PIDs. Joint manifestations are more common than bone involvement and usually presented as arthralgia, although arthritis is relatively frequent.¹² When a child presents with an atypical presentation or rare features of a common rheumatological illness before a diagnosis of immunodeficiency could give us a clue to conclude the diagnosis as PIDs.

Septic arthritis: These are commonly seen in children with predominantly antibody deficiency like common variable immunodeficiency (CVID) and X-linked agammaglobulinaemia.¹² Patients with Chronic

granulomatous disease (CGD), Wiskott–Aldrich syndrome, autosomal dominant Hyper Ig E Syndrome (HIES) and combined immunodeficiency syndromes have also been reported to develop septic arthritis.¹³ Septic arthritis was documented more frequently in a cohort of CVID patients with rheumatologic disorders, and they also detected an association between history of septic arthritis and RA/JIA in their study.¹⁴ Septic arthritis has been found in several case reports of SLE patients. The non-typhoid Salmonella (NTS) infections and their subsequent complications in these patients have been reported in this reports.¹⁵ Complement deficiency disorders have also septic arthritis like presentation. There are case report of septic arthritis in a patient with C5, C6, C7 deficiency and properdin deficiency.¹² The organisms most commonly isolated are *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Mycoplasma* spp. and *Ureaplasma urealyticum*.^{16,17}

Aseptic arthritis: Aseptic arthritis is the term used when no organism can be isolated from the synovial fluid or the synovial biopsy. Polyarthritis is the usual presentation. The aseptic arthritis could be sequelae of recurrent bacterial and parasitic infections in patients with PIDs or could be part of the autoimmune spectrum of disease. In XLA patients caused by mutation in the Bruton Tyrosine kinase (BTK) gene found aseptic JIA in different studies.¹² Cunningham Rundles et al. study of a cohort of CVID patients had found 2% had rheumatoid arthritis, 1.6% juvenile idiopathic arthritis. Rheumatoid arthritis has been reported in CVID patients with Inducible costimulator (ICOS) deficiency.¹⁸ Intravenous immunoglobulin is effective in most cases. Tumor necrosis factor- α receptor antagonist, etanercept, has also been found efficacious in CVIDs. The role of etanercept seems to be more in patients with granulomatous disease.^{12,19}

Lupus manifestations: Lupus and SLE-like manifestations were recognized in complement deficiency disorders. Generally, complement deficiencies cluster into two main categories of disease: i) recurrent encapsulated bacterial infections with or without rheumatic disorders ii) recurrent *Neisseria* infections. Early classical complement deficiencies are specifically associated with systemic lupus erythematosus.²⁰ Suliaman et al. found mucocutaneous lesions, arthritis and lung involvement were the clinical features in their PIDs cohort. C1q deficiency was the most frequent complement

deficiency followed by C3 and C4 deficiency.²¹ C1q and C4 deficiency has been associated with lupus arthritis in 50% and 4% of cases respectively.^{22,23} There is a case report of C1s deficiency also having lupus arthritis.²⁴

Table-I:

*When to suspect underlying immunodeficiency in a child with rheumatological disorders*²⁵

Atypical presentation
Early age of presentation
Septic arthritis with atypical organism or recurrence
Recurrent septic arthritis
Dysmorphic facies
Eczema and bleeding
Hepatosplenomegaly
Autoimmune diseases
Recurrent infection in childhood
Family history
Early sibling deaths
Consanguinity

Skeletal manifestations: Bloom syndrome is another DNA repair defects presented with dolicocephaly and short stature. Thymic defects with other congenital anomalies were observed in DiGeorge syndrome also associated with bone anomalies.²⁵ Nijmegen breakage syndrome (NBS) is a rare autosomal recessive disorder due to disturbance of DNA repair mechanism. Essential features found in NBS were microcephaly, typical facial appearance, immunodeficiency, chromosomal instability, and predisposition to malignancy. Important additional features were skin abnormalities, particularly café au lait spots and vitiligo, and congenital malformations, particularly clinodactyly and syndactyly.²⁶

In Severe Combined Immunodeficiency Disorder (SCID), reticular dysgenesis AK2 deficiency had unique skeletal defects. Chest radiography showed squaring of the scapular tips and cupping and fraying of the rib costo-chondral junctions anteriorly.²⁷ Characteristic skeletal changes of anterior rib junction, metaphyseal changes, and scapular squaring have been reported in SCID due to adenosine deaminase

deficiency.²⁸ The hyper-IgE syndromes (HIES) exhibit markedly elevated IgE levels, recurrent staphylococcal skin abscesses, eczema and pulmonary infections. Patients with autosomal dominant HIES also exhibit distinct dental, skeletal and connective tissue abnormalities. Musculoskeletal abnormalities found in AD-HIES include minimal trauma fractures, osteopenia, scoliosis and joint hyperextensibility.²⁹ Autosomal recessive Hyper-IgE Syndrome, caused by DOCK8 mutations, presented with Systemic Lupus Erythematosus (SLE) with purpuric and necrotic skin lesions diffuse arthritis, and glomerulonephritis.³⁰ Neonatal onset multi-inflammatory disease (NOMID) may present with skeletal abnormalities like frontal bossing, delayed closure of the anterior fontanelle, abnormalities of the metaphysis and epiphysis, irregular bony trabeculations, epiphyseal overgrowth in the form of a large patella.^{31,32}

Osteomyelitis of the long and small bones is common, especially in patients with CGD. The US and Italian registries report showed 16-25% patients of CGD had osteomyelitis. The common organisms are *S. aureus*, *Aspergillus*, *Candida* spp., *Serratia* spp., *Klebsiella* spp. and *Salmonella*.^{33,34} Ataxia Telangiectasia has been associated with rickets where all three members of a family had rickets.²⁵

Conclusion:

Besides recurrent infections, PID patients may present with autoimmune and rheumatologic manifestations due to immune dysregulation. Arthritis is the most common rheumatological manifestation of PIDs. This study concluded that patient with rheumatologic manifestations and early onset disease, family history of rheumatic disease or recurrent infections should undergo immunological work-up and genetic testing to rule out PID. A high level of suspicion and awareness is mandatory for the physicians to detect specific rheumatologic condition and underlying PIDs.

References

1. Nima Rezaei, Asghar Aghamohammadi, Notarangelo LD, Springerlink (Online Service. Primary Immunodeficiency Diseases: Definition, Diagnosis, and Management. Berlin, Heidelberg: Springer Berlin Heidelberg; 2008.
2. Goyal R, Bulua AC, Nikolov NP, Schwartzberg PL, Siegel RM. Rheumatologic and autoimmune manifestations of primary immunodeficiency disorders. Current Opinion in Rheumatology. 2009 Jan;21:78-84.
3. Van Zelm MC, Condino-Neto A, Barbouche MR. Editorial:

- Primary Immunodeficiencies Worldwide. *Frontiers in Immunology*. 2020 Jan 22;10.
4. Rhim JW, Kim KH, Kim DS, Kim BS, Kim JS, Kim CH, et al. Prevalence of Primary Immunodeficiency in Korea. *JKorean Med Sci*. 2012; 27(7):788-93. Available from: <http://dx.doi.org/10.3346/jkms.2012.27.7.788>
 5. Fath A. Primary immunodeficiency disorders in Sweden: Cases among children, 1974-1979. *J Clin Immunol*. 1982;2:86-92.
 6. Lee W-I, Kuo M-L, Huang J-L, Lin S-J, Wu C-J. Distribution and Clinical Aspects of Primary Immunodeficiencies in a Taiwan Pediatric Tertiary Hospital during a 20-year period. *J Clin Immunol*. 2005;25:162-73.
 7. Naidoo R, Ungerer L, Cooper M, Pienaar S, Eley BS. Primary Immunodeficiencies: a 27-year review at a tertiary paediatric hospital in Cape Town, South Africa. *J Clin Immunol*. 2011;31:99-105.
 8. Gupta D, Thakral D, Kumar P, Kabra SK, Lodha R, Kumari R, et al. Primary Immunodeficiency Disorders Among North Indian Children. *Indian J Pediatr*. 2019; 86:885-91.
 9. Justiz Vaillant AA, Qurie A. Immunodeficiency [Internet]. PubMed. Treasure Island (FL): Stat Pearls Publishing; 2020. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK500027/s>
 10. Notarangelo LD. Primary T-Cell Immunodeficiencies. *J Allergy Clin Immunol*. 2010;125(2):s120-94.
 11. Bonilla FA, Khan DA, Ballas ZK, Chinen J, Frank MM, Hsu JT, et al. Practice Parameters for Diagnosis and Management of Primary immunodeficiency. *J Allergy Clin Immunol*. 2015;136:1186-05.
 12. Agarwal M, Jariwala M. Rheumatic Manifestations of Primary Immunodeficiencies in Children. *Indian J Rheumatol*. 2012;7:52-56.
 13. Lee AH, Levinson AI, Schumacher HR Jr. Hypogammaglobulinemia and Rheumatic Disease. *Semin Arthritis Rheum*. 1993;22:252-64.
 14. Azizi G, Kiaee F, Hedayat E, Yazdani R, Dolatshahi E, Alinia T, et al. Rheumatologic Complications in a Cohort of 227 Patients with Common Variable Immunodeficiency. *Scand J Immunol*. 2018;87(5):e12663.
 15. Marzouk S, El Aoud S, Hriz H, Jallouli M, Zribi W, Bahloul Z. Salmonella Enteritidis Arthritis Complicating Systemic Lupus Erythematosus. *Chir Main*. 2013;32:420-3.
 16. Hansel TT, Haeney MR, Thompson RA. Primary Hypogammaglobulinaemia and Arthritis. *Br Med J (Clin Res Ed)*. 1987;295(6591):174-5. Available from: <http://dx.doi.org/10.1136/bmj.295.6591.174>
 17. Furr PM, Taylor-Robinson D, Webster AD. Mycoplasmas and Ureaplasmas in Patients with Hypogammaglobulinaemia and their role in Arthritis: Microbiological Observations over Twenty Years. *Ann Rheum Dis*. 1994;53(3):183-87.
 18. Schepp J, Chou J, Skrabl-Baumgartner A, Arkwright PD, Engelhardt KR, Hambleton S, et al. 14 years after discovery: Clinical follow-up on 15 patients with Inducible Co-stimulator deficiency. *Front Immunol*. 2017;8 :964.
 19. Smith KJ, Skelton H. Common Variable Immunodeficiency Treated with a Recombinant Human IgG, Tumour necrosis factor-alpha receptor fusion protein. *Br J Dermatol*. 2001;144:597-600.
 20. Ana Catarina Lunz Macedo, Lourdes Isaac Systemic Lupus Erythematosus and Deficiencies of Early Components of the Complement Classical Pathway. *Front Immunol*. 2016;7:55.
 21. Al-Mayouf SM, Alreefi HA, Alsinan TA, AlSalmi G, AlRowais A, Al-Herz W, et al. Lupus Manifestations in children with Primary Immunodeficiency Diseases: Comprehensive Phenotypic and Genetic features and outcome. *Mod Rheumatol*. 2021;31(6):1171-78.
 22. Higuchi Y, Shimizu J, Hatanaka M, Kitano E, Kitamura H, Takada H, et al. The Identification of a Novel Splicing Mutation in C1qB in a Japanese Family with C1q Deficiency: a Case Report. *Pediatr Rheumatol Online J*. 2013;11:41.
 23. Pettigrew HD, Teuber SS, Gershwin ME. Clinical Significance of Complement Deficiencies. *Ann N Y Acad Sci*. 2009;1173:108-23.
 24. Dragon-Durey MA, Quartier P, Frémeaux-Bacchi V, Blouin J, de Barace C, Prieur AM, et al. Molecular Basis of a Selective C1s Deficiency Associated with Early Onset Multiple Autoimmune diseases. *J Immunol*. 2001;166: 7612-6.
 25. Gharib A. Skeletal and Joint Manifestations of Primary Immunodeficiency Diseases. *SOJ Immunol*. 2016;4:1-13.
 26. Deripapa E, Balashov D, Rodina Y, Laberko A, Myakova N, Davydova NV, et al. Prospective Study of a Cohort of Russian Nijmegen Breakage Syndrome patients Demonstrating Predictive Value of Low kappa-deleting Recombination Excision Circle (KREC) Numbers and Beneficial Effect of Hematopoietic Stem Cell Transplantation (HSCT). *Front Immunol*. 2017;8:807.
 27. Ghaloul-Gonzalez L, Mohsen A-W, Karunanidhi A, Seminotti B, Chong H, Madan-Khetarpal S, et al. Reticular Dysgenesis and Mitochondriopathy induced by Adenylate kinase 2 deficiency with atypical presentation. *Sci Rep*. 2019;9:15739.
 28. Sordet C, Cantagrel A, Schaefferbeke T, Sibilia J. Bone and Joint Disease Associated with Primary Immune Deficiencies. *Joint Bone Spine*. 2005;72:503-14.
 29. Yong PFK, Freeman AF, Engelhardt KR, Holland S, Puck JM, Grimbacher B. An update on the Hyper-IgE syndromes. *Arthritis Res Ther*. 2012;14:228.
 30. Aydin SE, Kilic SS, Aytakin C, Kumar A, Porras O, Kainulainen L, et al. DOCK8 Deficiency: Clinical and Immunological Phenotype and Treatment options - a Review of 136 patients. *J Clin Immunol*. 2015;35:189-98.
 31. Torbiak RP, Dent PB, Cockshott WP. NOMID—a Neonatal Syndrome of Multisystem Inflammation. *Skeletal Radiol*. 1989;18:359-64.
 32. Breuton LA, Sanderson IR, Jadresic L, Harper JI, Savage MO, Ansell BM. An Infant with Chronic Articular and Cutaneous Manifestations: a New Syndrome? *J R Soc Med*. 1989;82:223-5.
 33. Martire B, Rondelli R, Soresina A, Pignata C, Broccoletti T, Finocchi A, et al. Clinical Features, Long-Term Follow-up and Outcome of a Large Cohort of patients with Chronic Granulomatous Disease: an Italian Multicenter Study. *Clin Immunol*. 2008;126:155-64.
 34. Johnston RB Jr. Clinical aspects of chronic granulomatous disease. *Curr Opin Hematol*. 2001;8:17-22.