Pediatric Rheumatology: An Under-recognized Subspecialty in India

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Abstract

Pediatrics in India at the levels of both undergraduate and postgraduate training is often viewed upon as an acute disease specialty with little emphasis on chronic medical musculoskeletal diseases. Pediatric rheumatology is an under-recognized subspecialty of pediatrics which deals specifically with childhood arthritis, noninflammatory joint pains, connective tissue diseases, autoimmune diseases, vasculitis, and other rare inflammatory disorders. This article aims to give a bird’s eye view of the repertoire of commonly encountered problems seen by a pediatric rheumatologist, via a classical case vignette for each topic followed by discussion. There is also mention of some rare diseases managed within pediatric rheumatology to give a flavor of the spectrum of diseases encountered. This is to raise awareness of the importance of pediatric rheumatology as a subspecialty within India and to prompt readers to seek specialist advice when encountering challenging cases. Pediatric rheumatologists network and work collaboratively with many other specialties such as ophthalmology, dermatology, neurology, orthopedics, nephrology, infectious diseases, immunology, and gastroenterology for combined care of diverse conditions. There is an unmet need in India to develop a training program for pediatric rheumatology so that shared care pathways with sensitized pediatricians and other specialists can be developed nationwide, to serve these children better to achieve optimal outcomes.

Keywords: Autoimmune, autoinflammatory disease, childhood arthritis, chronic pain, India, juvenile idiopathic arthritis, pediatric rheumatology, vasculitis

Introduction

Rheumatology is an established specialty of medicine which deals with musculoskeletal problems, including arthritis and other autoimmune diseases in adults. It is a misconception that only adults get arthritis or musculoskeletal diseases. The branch of pediatric rheumatology deals specifically with childhood arthritis and other inflammatory/noninflammatory diseases but unfortunately is less recognized in India. If not recognized in a timely manner, some of these children can sustain disabilities or even life-threatening complications. Prompt diagnosis and adequate multidisciplinary management is fundamental to positive long-term outcomes.

This article is not all-inclusive and only aims to give a bird’s eye view of the repertoire of problems seen by a pediatric rheumatologist via case vignettes, with a brief mention of some of the rarer diseases to give a flavor of the spectrum of diseases encountered. Further reading of specific topics is strongly recommended.[1-3]

Juvenile Idiopathic Arthritis

Case: A 4-year-old female child presents with stiff swollen knees for 2 months. She is systemically well. Blood counts and inflammatory markers are normal. Ultrasound shows knee effusions/synovitis. A specialist detects mild wrist arthritis in addition. A slit-lamp examination of her eyes reveals chronic anterior uveitis.

Juvenile idiopathic arthritis (JIA, previously called juvenile rheumatoid arthritis or juvenile chronic arthritis), the most common chronic rheumatic disease of childhood, is idiopathic inflammatory arthritis for a duration of >6 weeks in a

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Oligoarthritis is arthritis in up to four joints, and polyarthritis involves ≥5 joints. The International League Against Rheumatology Classification enlists seven subtypes: (i) oligoarthritis (a) persistent oligoarthritis (never extends beyond 4 joints) and (b) extended oligoarthritis (>4 joints affected after 6 months of disease), (ii) polyarthritis rheumatoid factor (RF) negative, (iii) polyarthritis RF positive, (iv) enthesitis-related arthritis (ERA), (v) psoriatic arthritis, (vi) systemic JIA, and (vii) undifferentiated arthritis.[9]

JIA remains a clinical diagnosis of exclusion. ARTHRITIS could be a useful mnemonic when considering differentials of JIA: Avascular necrosis/orthopedic causes, Reactive arthritis, Trauma, Hematologic causes, Rickets or metabolic/endocrine causes, Infectious causes, Tumors, Idiopathic (including JIA/idiopathic pain), Systemic lupus erythematosus (SLE)/other autoimmune/connective tissue diseases. Nonaccidental injury needs to be borne in mind in certain social settings.

It is important to be aware that malignancies such as leukemia or neuroblastoma are known to masquerade as arthritis and a low/marginally normal platelet count or falling hemoglobin should prompt further investigations (including bone marrow examination). In the Indian subcontinent, tuberculosis (TB) tests are relevant to establish diagnosis and to guide further therapy, especially with biologics. It is unusual for JIA to present as monoarthritis, especially of a single large joint (e.g., hip), and local lesions/infestions need to be excluded.

Blood tests are not “routinely” indicated but are helpful: (i) to exclude differential pathology including chronic infections/malignancy, (ii) in systemic JIA where high inflammatory markers (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], ferritin) correlate with disease activity, and (iii) for drug monitoring.

Antinuclear antibody (ANA) is useful only if suspecting lupus or other connective tissue diseases. RF is useful after a clinical diagnosis of JIA, mainly for prognostication, as RF-positive polyarthritis can be unremitting, being the adult counterpart of RA.

Among the various subtypes of JIA, ERA merits special mention as it might have a higher prevalence in India.[5] Inflammatory bowel disease (Crohn’s disease/ulcerative colitis) might coexist with ERA. Juvenile spondyloarthropathy is considered to be part of ERA, often starts with sacroileitis, and might progress into ankylosing spondylitis in adulthood. A male preponderance and association with human leukocyte antigen (HLA) B-27 positivity might be seen. Acute anterior uveitis or symptomatic uveitis might occur.

Systemic JIA is an entity distinct to other subtypes and shares similarities with adult-onset Still’s disease. It often presents as pyrexia of unknown origin requiring exclusion of infections and malignancy. Fevers are often high-grade quotidiant, and a transient erythematous maculopapular rash at the height of temperatures is classical. Other extra-articular features such as hepatosplenomegaly, lymphadenopathy, and serositis (e.g., pericarditis) may predominate and can precede the onset of arthritis, making the diagnosis challenging. Lack of awareness might lead to systemic JIA being under-diagnosed with significant consequences.

Medical management of JIA includes steroid instillation into affected joints for arthritis (preferably triamcinolone hexacetonide) or into tendon spaces for tenosynovitis (preferably hydrocortisone); young children often need a general anesthetic to enable this. Regular nonsteroidal anti-inflammatory drugs (NSAIDs) are useful as mild anti-inflammatories whilst definitive therapy is instituted. Systemic steroids are needed for widespread polyarthritis or for systemic JIA. The first-choice steroid-sparing disease-modifying antirheumatic drug is methotrexate (weekly, subcutaneous preferably or oral). Recurrent flares of arthritis or severe drug intolerance often warrant escalation of therapy to biologic drugs. These include antitumor necrosis factor (TNF) agents (etanercept, adalimumab, or infliximab), T-cell blockers such as abatacept or interleukin (IL) antagonists (IL-6 inhibitors, e.g., tocilizumab or IL-1 inhibitors, e.g., anakinra in systemic JIA).

Multidisciplinary team support via specialist nurses, physiotherapists, etc., is important to achieve optimal functional status. Risk factors for poor disease outcomes are constantly being delineated, a prime factor being delayed diagnosis.[6] Standards of care for the management of JIA set forth by the British Society of Paediatric and Adolescent Rheumatology, when audited among the UK pediatric rheumatology centers, have shown delayed access to care even in developed countries.[7]

As for other pediatric rheumatic diseases, optimizing growth is of paramount importance via adequate disease control and minimizing side effects of drugs such as steroids. Studies of adults with poorly controlled JIA show higher disability rates, low health-related quality of life, and higher unemployment rates.[8] Core outcome variables (comprising active and restricted joints, visual analog scores, childhood health assessment questionnaire, and ESR) which link into American College of Rheumatology (ACR)-Pedi scores and composite measures such as juvenile arthritis disease activity score (JADAS) are useful as disease activity/impact measures and as objective measures in clinical trials.[9]

Uveitis is the most common extra-articular manifestation, seen in 11%–30% of JIA, rarely predating the arthritis.[10] Children with JIA need periodic slit-lamp screening for uveitis as it is often asymptomatic in young children and can result in ocular complications/visual loss if not promptly managed. Treatment depends on the grade/complications and involves topical steroids/methotrexate before progressing to stronger immunosuppressants including biologics. Certain anti-TNF agents such as etanercept have been associated with a flare.
of uveitis. Cystoid macular edema is a sight-threatening complication which requires high-dose systemic steroids.

Macrophage activation syndrome (MAS) is a life-threatening complication of rheumatic diseases, especially seen in systemic JIA, with a mortality rate of up to 10%. It can present with unremitting fevers, splenomegaly, very high ferritin, cytopenias, transaminitis, high triglycerides, and low fibrinogen. ESR might be paradoxically low due to dysfibrinogenemia. Bone marrow examination might show evidence of hemophagocytosis. Differentials include disease flares, infectious triggers (especially Epstein–Barr virus), primary/genetic hemophagocytic lymphohistiocytosis, and malignancies. Specific criteria for suspecting MAS in systemic JIA have been set forth which highlights relative, rather than absolute, cytopenias.[11] High-dose systemic steroids (i.e., intravenous [IV] methyl prednisolone) are needed, failing which other therapy includes cyclosporine, IL-1 blockers (e.g., anakinra), etoposide etc. Intensive care support might be needed for fulminant organ failure.

**Noninflammatory Joint Pains**

Case: A 13-year-old female child presents to her primary physician with intermittent joint pains in her knees, ankles, and hands, typically worse after physical activity. There is no arthritis on examination. Joints are hypermobile. She is referred for physiotherapy.

Mechanical or biomechanical joint pains are quite common and can be due to a multitude of factors such as structural causes, hypermobile “bendy” joints, and growing pains.

Multiple joints can be involved, with pain typically worse after physical activity. Prolonged morning stiffness is not seen. Joint swelling is unusual and never persistent. Biomechanical joint pains cause “arthralgia” (as opposed to “arthritis” which indicates actual inflamed joints). Physiotherapy is often helpful, and correction of flat feet or pes planus might be beneficial.

Pain localized to a single joint with red flags such as persistent/nocturnal pain, fevers, and weight loss should be investigated for localized lesions including bone tumors. Localized hip pain with restricted rotation might reveal Perthes disease on magnetic resonance imaging (MRI) scan (typically in a young boy) or slipped upper capitofemoral epiphysis (especially in adolescent girls) and need orthopedic management.

Benign joint hypermobility can affect some or all joints. The degree of hypermobility might not correlate with the degree of symptoms. Hypermobility has been shown to be linked with musculoskeletal pain in a cross-sectional study conducted on Indian school children.[12] This study also mentions the utility of pediatric Gait Arms Legs and Spine (p-GALS), which is widely accepted as a generic screening tool for pediatric musculoskeletal examination.

Regular physiotherapy exercises are often beneficial. If there are dysmorphic or additional features, e.g., eye or cardiac involvement, syndromes such as Stickler’s, Marfan’s vascular Type IV Ehler’s Danlos syndrome etc. need to be considered. These disorders of ligament laxity are often labeled “connective tissue disorders” and should not be confused with “connective tissue diseases” which are systemic inflammatory diseases.

Joint enlargement/restriction without arthritis can also be due to “noninflammatory arthropathies” including mucopolysaccharidoses (urinary glycosaminoglycans is a simple screening tool); skeletal dysplasias (often with a genetic basis); pachydermodactyly.

Extended multiprofessional involvement is often needed for these children.

**Chronic Pain**

Case: A 15-year-old female presents with extreme nonspecific pains. She has stopped attending school, sleeps poorly, is often moody, and avoids sporting activity. She has gained weight and has significant allodynia on examination. Blood tests are unremarkable.

Chronic idiopathic pain is pain which is out of proportion to underlying pathology, if any. Appropriate recognition avoids unnecessary investigations and “over-medicalization” with resultant financial implications.

Chronic pain can be localized/generalized. Functional limitation, fatigue and disorders of mood, sleep, eating, etc. can occur. There might be an inciting factor or a life-event preceding the pain cycle. Heightened sensitivity and allodynia are often characteristic.[13]

Chronic pain might also be nonmusculoskeletal such as recurrent abdominal pain and intractable headache without an exclusive defined organic cause. Diffuse idiopathic pain is sometimes referred to as juvenile fibromyalgia. Chronic pain or pain amplification can coexist with underlying inflammatory conditions. It is important to note in this context that neuropsychiatric symptoms and fatigue might be seen in organic pathology (e.g., neuro lupus).

Complex regional pain syndrome (CRPS type 1, previously called reflex sympathetic dystrophy) is localized pain with autonomic changes. The afflicted area can be cold to touch or edematous with discoloration/mottling. A common scenario is extreme ongoing pain after an injury or fracture despite evidence of adequate healing. Prolonged casting to relieve “pain” in such instances can lead to severe disuse atrophy, skin changes/ulceration, or even necessitate amputation in extreme cases.

Management is principally by explanation of diagnosis and pacing (encouraging activity in a phased or graded manner) with support from clinical psychology and allied health professionals. Analgesics including NSAIDs are unlikely to be helpful and opioids are best avoided. Drugs such as low-dose...
amitriptyline and gabapentin/pregabalin for neuropathic pain might be useful in select cases but are best administered by a specialist.

**Juvenile Systemic Lupus Erythematosus**

Case: A 14-year-old female child presents to her local hospital unwell and breathless. She has been increasingly tired with mouth ulcers and Raynaud’s phenomenon. She looks pale with a malar rash with nasolabial sparing. Renal failure is evident on blood tests, alongside lymphopenia and a high ESR. An immunology panel reveals homogenous ANA (titers 1:640), positive double-stranded DNA [dsDNA], low complements (C3, C4). Chest X-ray/echo heart shows mild pleural effusions/pericardial effusion. Urine albumin: urine creatinine ratio is highly elevated. After stabilization, she undergoes a renal biopsy which shows diffuse proliferative lupus nephritis.

SLE is an autoimmune disorder characterized by multisystem inflammation, which can be protean in manifestation. Classification criteria include rashes, oral ulcers, arthritis, serositis, renal or neurological involvement, cytopenias, and distinctive antibodies.

Juvenile lupus can be more severe than in adults, with more hematological, renal, and neurological involvement. The 1997 revised ACR criteria and the 2012 systemic lupus international collaborating clinics (SLICC) criteria are both being increasingly valid in children. Cytopenias can occur often with luphenopenia. Although ESR can be raised, the CRP is typically not elevated in lupus (except in active arthritis or serositis), and if raised, it is an alert for coexisting infection. Complement (C3, C4) levels are often low. In addition to ANA/dsDNA, antibodies to extractable nuclear antigens such as Smith antigen and nucleosomes and even positive RF might be noted. Anti-Ro is implicated in neonatal lupus/congenital heart block due to transplacental transfer of maternal autoantibody.

Specific complement deficiencies (e.g., C1q) are known to cause lupus and need to be investigated, especially in atypical cases such as young age at presentation or absence of ANA positivity. Antiphospholipid antibody (i.e., antiphospholipid antibodies, anti-beta2 glycoprotein antibodies, lupus anticoagulant) syndrome can coexist with resultant clotting dyscrasias/thrombosis, pulmonary embolism, or multiorgan failure.

There has to be a clinical setting for SLE, not just the mere presence of autoantibodies. False positive ANA can be noted in several situations including infections such as TB. Certain rare diseases such as Kikuchi–Fujimoto disease (histiocytic necrotizing lymphadenitis) might eventually evolve into lupus.

Very minor symptoms can be managed with NSAIDs or hydroxychloroquine, but most patients require systemic steroids to induce remission. Maintenance is with steroid-sparing immunosuppressive drugs (including biologics if needed) depending on severity, such as azathioprine, methotrexate, mycophenolate mofetil (MMF), cyclophosphamide, and rituximab.

Intercurrent infections have to be vigorously managed. A healthy lifestyle/diet including adequate calcium/Vitamin D intake should be encouraged. Appropriate management reduces long-term burden, including premature cardiovascular damage. Other connective tissue diseases include linear scleroderma (managed alongside dermatology); rare autoimmune diseases with specific antibodies such as scleroderma (anti-centromere antibody in limited scleroderma/calcinosis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST) syndrome; anti-Scl-70 in systemic sclerosis), mixed connective tissue disease (anti U1-ribonucleoprotein), Sjogren’s syndrome (anti-Ro/La); and granulomatous diseases such as juvenile sarcoidosis (genetic form being Blau syndrome which is a triad of uveitis, arthritis, and dermatitis), all of which need specialized management. “Overlap syndromes” are diseases which satisfy criteria of more than one autoimmune disease.

**Juvenile Dermatomyositis**

Case: A 4-year-old female child presents with increasing weakness. She has profound proximal muscle weakness (including neck flexors) with a heliotrope vasculitic rash on her eyelids, Gottron’s papules on her knuckles, and calcinosis nodules on her elbows. Blood tests show elevation of muscle enzymes (creatine kinase, aspartate transaminase, and lactate dehydrogenase).

Juvenile dermatomyositis (JDM) is the most common inflammatory myopathy of childhood. Diagnostic criteria by Bohan and Peter can be used, but MRI scan (ultrasound if MRI unavailable) evidence of active myositis/fasciitis is the investigation of choice when characteristic skin/muscle signs are present typically with elevated muscle enzymes. As compared to adult dermatomyositis, malignancy is rarely associated. Atypical cases might need a muscle biopsy. Childhood myositis assessment score is useful to assess muscle strength. Myositis autoantibodies (e.g., anti p155/140, anti-Mi2, anti-SRP i.e. signal recognition particle) might correlate with severity/prognosis.

Management involves high-dose systemic corticosteroids and subcutaneous methotrexate. Oral medication might be ineffective from poor absorption due to concomitant gut vasculitis. IV immunoglobulin (IVIG), cyclophosphamide, anti-TNF agents, cyclosporine, MMF, rituximab, etc. might be required for severe skin, lung, or neurological involvement.

**Kawasaki Disease and Other Primary Systemic Vasculitis**

Case: A 3-year-old female child presents with high fevers/ extreme irritability. She has bulbar conjunctivitis, shotty
asymmetrical cervical nodes, “strawberry tongue,” edematous feet, and a perianal rash. Extensive infectious diseases workup (including cerebrospinal fluid studies) is negative. Peeling of fingertips is subsequently observed. Inflammatory markers are high with hypoalbuminemia and a rising platelet count. An echo heart reveals coronary aneurysms.

Kawasaki disease, a medium-vessel vasculitis, is the second-most common vasculitis in childhood. It is characterized by fever, nonexudative conjunctivitis, extremity changes (erythematous oral mucosa/edema), rashes, and cervical lymphadenopathy. Children <5 years are often affected, but older children have been reported. Reactivation of the Bacillus Calmette–Guérin (BCG) scar is sometimes observed. Gallbladder distension/hydrops might be observed on abdominal ultrasound. Coronary artery aneurysms may develop, which can lead to ischemic heart disease/sudden death.

Treatment of choice is IVIG 2 g/kg, repeated if there is no defervescence of fever after 36 h. Aspirin (high dose followed by low dose, once afebrile) is recommended as is cardiac follow-up. The use of IVIG within the first 10 days of illness significantly reduces coronary aneurysms (<1% vs. 30% in untreated cases), IVIG should not be denied at later stages or in “atypical” /“incomplete” cases. Scores are available (e.g., Kobayashi score, Egami score) to classify severity but might not be universally applicable. IVIG refractory cases often need steroids and/or additional immunosuppression such as infliximab.

Other primary systemic vasculitides

Childhood vasculitis can be broadly classified as (i) large-vessel vasculitis, e.g., Takayasu arteritis; (ii) medium-vessel vasculitis, e.g., Kawasaki disease, polyarteritis nodosa (PAN); (iii) small-vessel vasculitis, e.g., Henoch–Schonlein purpura (HSP) and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, which includes granulomatous polyangiitis (GPA or Wegener’s disease), eosinophilic GPA (EGPA or Churg–Strauss disease), and microscopic polyangiitis. International classification criteria are increasingly being validated.

Takayasu disease is a large-vessel vasculitis involving aorta/major branches and can present with low-grade pyrexia, claudication pain, fatigue, hypertension, or unexplained high inflammatory markers. It especially needs to be considered in children presenting with renovascular hypertension. A strong Mantoux positivity might be observed. With disease progression, fibrosis and resultant stenosis of involved vessels ensues with absent pulses. Diagnosis is by angiography (MR or conventional computed tomography). Doppler ultrasound can also be used for supporting diagnosis/follow-up.

HSP is the most common vasculitis of childhood, which manifests as palpable purpura with abdominal pain, arthralgia, or arthritis. Uncomplicated cases are self-limiting and are often managed by general physicians or pediatricians. However, vigilance is needed for complications, especially involvement of gut or kidneys.

PAN is a necrotizing vasculitis that can present with fevers, myalgia, skin nodules, peripheral neuropathy/mononeuritis multiplex, gangrene, or hypertension. Isolated cutaneous PAN is less aggressive than the systemic form. Genetic disorders such as deficiency of adenosine deaminase (DADA-2 involving CECR1 gene) can often mimic PAN.

GPA (formerly Wegener’s) is a granulomatous inflammatory vasculitis which can manifest as a severe systemic illness with airway and/or renal involvement. It is often characterized by antibodies to c-ANCA and elevated proteinase 3 antibodies. IgG4-related disease, although rare in children, can closely mimic limited GPA or Wegener’s disease and needs specialist assessment (including of histopathology) for differentiation.

Inflammatory brain diseases include nonvasculitic diseases (e.g., N-methyl-D-aspartate receptor encephalitis, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections), and childhood central nervous system vasculitis (primary or secondary). These can cause devastating neurological deficits/neuropsychiatric syndromes in previously healthy children. Appropriate immunosuppression could potentially prevent permanent neurological deficits.

Behcet’s disease is a medium-vessel vasculitis (on the spectrum of autoinflammatory diseases) with orogenital ulcers with or without uveitis, with specific pediatric classification criteria.

General diagnostic modalities for systemic vasculitides, (as appropriate and after excluding infections), include urine tests (first morning urine albumin/urine creatinine ratio is a good screening test), ophthalmological evaluation (for retinal vasculitis), blood tests for inflammatory/renal markers/specific antibodies (e.g., ANCA vasculitis), skin biopsy for unusual/persistent rashes, and angiographic studies (e.g., magnetic resonance angiography).

Treatment of systemic vasculitis involves high-dose corticosteroids and steroid-sparing immunosuppressants. Renal involvement and management of hypertension often need nephrology input. Several therapeutic advances in vasculitis have been made over the last decade and specific reading is recommended.

**Chronic Recurrent Multifocal Osteomyelitis and Other Autoinflammatory Conditions**

Case: A 9-year-old female child presents with chronic ankle pain and diffuse swelling. Blood tests are unremarkable. An X-ray shows a lytic lesion. A bone biopsy is performed and antibiotics commenced for presumed osteomyelitis. Histopathology rules out malignancy, showing chronic inflammation. Microbiological studies are negative. A whole-body MRI scan (WB-MRI) shows osteolytic/sclerotic lesions in the lower tibial metaphysis, clavicle, and high signals in the iliac crest.
**Chronic Recurrent Multifocal Osteomyelitis**

Chronic recurrent multifocal osteomyelitis (CRMO) or chronic nonbacterial osteitis is a noninfective autoinflammatory bone disease. Although termed multifocal, unifocal lesions are well recognized. Nocturnal bone pain can be distressing with significant functional impact. A WB-MRI often reveals occult sites.

Typical sites such as the clavicle or multiple sites with a typical history and benign inflammatory markers might not need a bone biopsy for diagnosis.\[27,28\] Osteomyelitis, malignancy, etc. need to be excluded in case of high inflammatory markers, systemic symptoms, or atypical unifocal site. Children with unrecognized CRMO have unnecessarily continued on long-term antibiotics, had extensive investigations, and eventually developed pathologic fractures. Vertebral lesions can lead to compression fractures.

The adult counterpart of CRMO is synovitis, acne, pustulosis, hyperostosis, ostitis (SAPHO). Psoriasis or HLA-B27 disease can be associated.

Treatment is with regular NSAIDs. Ongoing severe nocturnal bone pain and/or lesions necessitate second line, which involves bisphosphonate therapy (e.g., pamidronate infusions). Failure of bisphosphonates often needs escalation to biologics including TNF inhibitors.

**Autoinflammatory diseases and periodic fever syndromes**

Autoinflammatory diseases are disorders of innate immunity whereas autoimmune disorders are disorders of adaptive immunity.

Periodic fever syndromes are a unique entity, wherein children present repeatedly with recurrent fevers without a clear infectious focus or concurrent immunodeficiency. Fevers can recur in a periodic pattern and can last a few days or be prolonged. Triggers might include vaccination, stress, or cold ambient temperatures. Unusual rashes or severe abdominal pain might occur. The febrile episodes can cause significant functional impact/poor school attendance. The long-term concern from uncontrolled inflammation is secondary amyloidosis, especially of kidneys which can lead to renal failure.\[29\]

The most common periodic fever without a known genetic basis is periodic fevers, apthous stomatitis, pharyngitis, adenitis (PFAPA). It can settle in early adolescence. Recurrent episodes might respond to tonsillectomy.

**Familial Mediterranean fever (FMF)** is the most common monogenic periodic fever. Other subtypes are TNF-receptor-associated periodic fever syndrome, hyper-IgD syndrome or mevalonate kinase deficiency, cryopyrin-associated periodic fever syndrome, etc. Some of these can present in the neonatal period with profound multisystem inflammation (e.g., neonatal-onset multisystem inflammatory disease). Biologic therapy especially with IL-1 blockade is often needed. Colchicine sometimes helps with milder attacks in certain subtypes (e.g., FMF) and can play a role in preventing amyloidosis.

Other novel inflammatory diseases such as “interferonopathies” and monogenic vasculitides including DADA-2, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE), and STING-associased vasculitis of infancy (SAVI)\[26\] need highly specialized management often with novel drugs (e.g., Janus kinase inhibitor) with a futuristic vision for gene therapy. Bone marrow transplantation might need to be considered in select pediatric rheumatic diseases or in those refractory to multiple biologic therapy.

**Training and Continuing Professional Development within India**

Pediatrics in India is often viewed upon as an acute specialty. Childhood medical musculoskeletal diseases are not covered in postgraduate orthopedic or pediatric training. Over the last couple of decades, subspecialties such as neonatology and pediatric cardiology have emerged strongly, establishing themselves as independent branches. Pediatric rheumatology is probably the “youngest kid on the block.” Pediatric rheumatologists network with a multitude of specialists for conditions that have an interface across specialties. The pharmacopeia has broadened from steroids, disease-modifying drugs, and antimetabolites to a wide array of biologics targeting specific cytokines, which are often effective yet expensive.

As of 2017, the population of India is 1.34 billion with more than half being <25 years of age.\[30\] Projection of estimated international incidence of childhood rheumatic diseases (e.g., 10/100,000 – JIA; 0.4/100,000 – juvenile SLE; 0.1/100,000 – JDM) to a population of half a billion gives a sense of the sheer scale of the problem. Accurate epidemiological data for individual diseases in India is unfortunately not available, but many of these diseases are known to be widely prevalent.\[31\] It is likely that substantial numbers of children are undiagnosed due to lack of awareness of these conditions. Due to the lack of a coherent structured healthcare system in India, collaborative studies (linking in with available tertiary pediatric rheumatology centers within India) are required to get a representative epidemiological profile.

It is essential to develop a training program in pediatric rheumatology so that shared care pathways with sensitized pediatricians can be developed nationwide to serve these children better. The challenge in the Indian scenario is to attain remission while trying to minimize the cost of treatment. The skill to balance therapy with disease control, preventing morbidity, as well as minimizing potential side effects of treatment, is the cornerstone of the training process.\[31-33\]

Currently across India, there are approximately 16 centers with pediatric rheumatologists and possibly a few other emerging areas. In 2002, when the national pediatric rheumatology chapter of the Indian Academy of Pediatrics (IAP) was created, there were approximately five centers with around 12 centers reported in 2010 in an editorial in Indian pediatrics. The chapter
actively conducts annual conferences in different venues across the country alongside midterm continuing medical education. Information is disseminated to practicing pediatricians and it enthuses new members.

With regard to training, there are two fellowship opportunities at Mumbai and Delhi under the auspices of the IAP and a DM program in pediatric rheumatology/immunology at PGIMER, Chandigarh, all of which have been initiated within the last 5 years. International collaborative resources including online tools are integral in facilitating adequate training.[34]

There is an unmet need to improve pediatric rheumatology training in India, to highlight with the government for therapeutic/other assistance for these families, to develop national registries, and to actively encourage research to improve understanding of the nature/management of these diseases. A concerted effort is needed from all concerned.

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