PERSPECTIVE

Sensing the Simmering Inflammation: Clues for Diagnosis of Underlying Rheumatic Disorder

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ABSTRACT

Diagnosing pediatric rheumatic diseases can be challenging, as they often mimic common conditions such as infections and, less commonly, malignancies. Characteristic pattern recognition, guided by a detailed history and clinical examination, often helps in making the correct diagnosis. A delay in diagnosing these disorders can lead to disease-related damage, such as joint disabilities in juvenile idiopathic arthritis, and life-threatening organ involvement in conditions like childhood vasculitis and lupus. Easily accessible laboratory investigations can guide towards the underlying diagnosis. In the current era, early diagnosis helps achieve favorable outcomes with the use of effective therapeutic options. This article aims to highlight important clinical and laboratory features that would assist the primary care pediatricians in the early diagnosis of rheumatic disorders.

Keywords: *Childhood lupus, Juvenile idiopathic arthritis, Rheumatic diseases, Vasculitis*

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Rheumatic disorders in children pose unique challenges for clinicians with their diverse clinical manifestations and resemblance to other common childhood diseases. Often underdiagnosed or overlooked, these conditions can result in persistent inflammation, worsening morbidity, and in severe cases, mortality. Rheumatic diseases may be perceived to be rare in children, such that they may not be considered in the initial differential diagnosis unless distinctive symptoms are evident. Unlike organ-specific disorders, rheumatic diseases can affect multiple organ systems, thereby complicating appropriate and timely referrals [1].

COMMON CLINICAL MANIFESTATIONS OF RHEUMATIC DISEASES

Constitutional symptoms: Prolonged or recurrent fever is a common presenting symptom in children with rheumatic diseases [2]. In systemic onset juvenile idiopathic arthritis (sJIA), fever typically presents as quotidian, with 1-2 spikes per day [3]. Children with systemic lupus erythematosus (SLE) may experience fevers associated with disease flares or concurrent infections [4]. Fever of more than 5 days duration with typical muco-cutaneous involvement is characteristic of Kawasaki disease (KD) [5]. Those with periodic fever syndromes exhibit recurrent episodes of fever at regular intervals, interspersed with symptom-free periods [6].

Although non-specific, fatigue is a widely prevalent debilitating symptom in children with inflammatory diseases. Chronic inflammation, pain, disrupted sleep patterns, medication side effects, or the emotional burden of coping with chronic illness can result in overwhelming fatigue [4].

Musculoskeletal manifestations: Arthralgia or arthritis is a hallmark feature of various pediatric rheumatic disorders. Arthritis is defined as the presence of joint swelling or effusion, increased warmth, and/or painful restricted movement, with or without joint line tenderness. Pediatric Gait, Arms, Legs, and Spine (pGALS) is a valuable clinical assessment tool that can be used in busy clinical settings. It involves a structured examination of the musculoskeletal system in children [7]. Juvenile idiopathic arthritis (JIA) presents with joint inflammation that has a predilection for particular joints depending on the subtype for eg. sacroiliac joint involvement is a characteristic feature of juvenile spondyloarthropathy [3,8]. In addition

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to arthritis, enthesitis i.e. inflammation at the site of attachment of tendons and ligaments (e.g. heel pain secondary to tendoachilles enthesitis), is a key feature of enthesitis-related arthritis. Arthritis can be anaccompanying feature of various other rheumatic disorders such as SLE, juvenile dermatomyositis (JDM), and childhood vasculitides. A simplified approach to joint pain in children has been illustrated in **Fig. 1**.

Myositis *r*esults from the inflammatory process in JDM that primarily targets the muscles and presents with proximal muscle weakness. Additionally, weakness of the muscles involved in swallowing and breathing can lead to dysphagia and respiratory compromise, posing significant risks of mortality [9,10]. Myositis can also be a feature of other rheumatic disorders such as SLE, mixed connective tissue disorder or overlap syndrome, but usually, it is less profound than JDM.

Dermatological features: Cutaneous manifestations provide valuable clues in suspecting rheumatic diseases. Children with rheumatoid factor positive JIA may develop erythematous, raised, tender nodules over extensor surfaces, known as rheumatoid nodules. Psoriatic JIA may have a dry, itchy, red, scaly rash and/or nail pitting, while systemic onset JIA (sJIA) is characterised by a distinctive fleeting salmon-coloured rash [3,8]. However, it may be difficult to appreciate this rash in dark-skinned individuals. Children with SLE may present with a malar rash, discoid lesions, photosensitive rash, and/ or vasculitic lesions, which often mirror systemic disease activity and aid in diagnosis [4]. JDM typically presents with Gottron's papules (erythematous to violaceous papules over the extensor surfaces), heliotrope rash (violaceous rash on the upper eyelids), and mechanic's hands (cracked and hyperkeratotic skin over the palmar surfaces) [11]. Juvenile systemic sclerosis is characterised by the presence of sclerodactyly (thickening and tightening of the skin over the fingers and toes), Raynaud's phenomenon (digital colour changes upon exposure to cold or stress), and skin thickening over the extremities and face [12]. Dermatological manifestations of vasculitis syndromes in children can vary widely but often include palpable purpura in IgA vasculitis (small, palpable, purpuric lesions), livedo reticularis (mottled reticulated discolouration of the skin), digital tip gangrene and cutaneous ulcers in polyarteritis nodosa [13]. KD can present with any rash except for vesiculobullous lesions. The other mucocutaneous manifestations of KD include oropharyngeal changes, strawberry tongue and non-purulent conjunctivitis [5]. **Web Fig. 1** depicts the characteristic cutaneous findings in rheumatic disorders.

Renal manifestations: Renal involvement of varying severity is seen in several rheumatic disorders like SLE, systemic vasculitides such as IgA vasculitis and antineutrophil cytoplasmic antibodies (*ANCA*)-associated vasculitis [11,12]. Immune complex deposition within the glomeruli can lead to glomerulonephritis, proteinuria, hematuria, and renal insufficiency. Without prompt diagnosis and treatment, progressive renal damage and end-stage renal disease can occur with, the need for renal

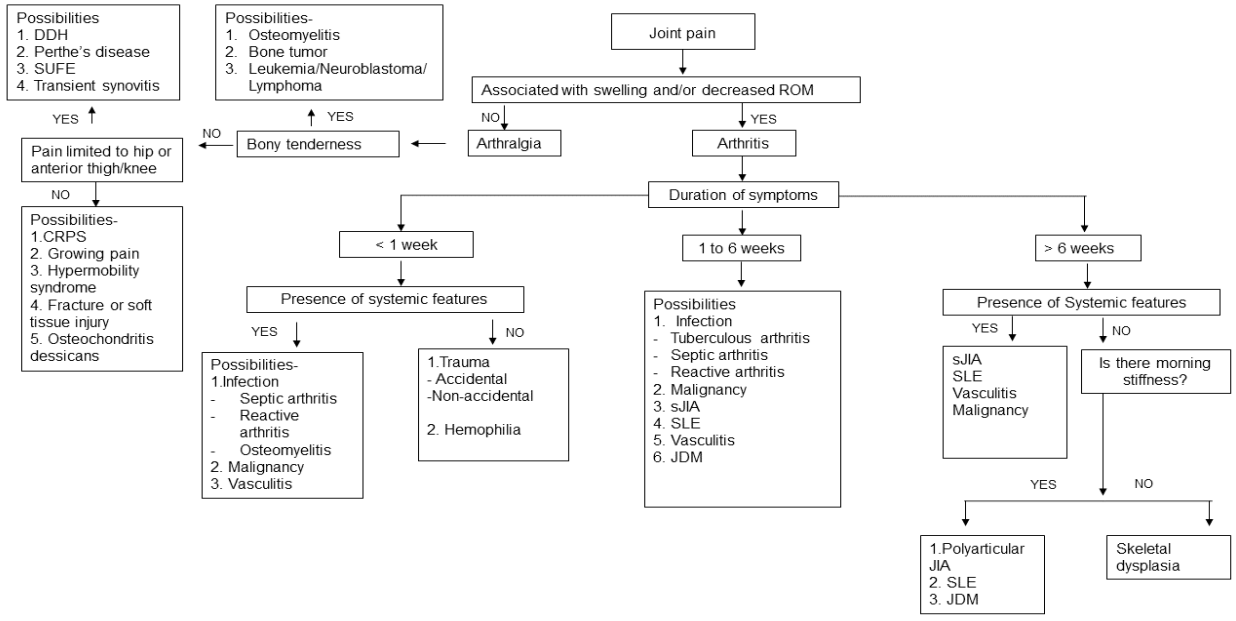

Fig. 1 Approach to a child with joint pain

replacement therapy [13-15]. Children at risk of renal involvement should be periodically screened through blood pressure monitoring, urine examination and renal function tests.

Neurological manifestations: These can be diverse and range from peripheral neuropathy in polyarteritis nodosa (PAN) to central nervous system vasculitis characterized by early-onset stroke in deficiency of adenosine deaminase 2 (DADA-2) [16]. Neuropsychiatric lupus can manifest as seizures or cognitive decline [15, 16].

Cardiopulmonary manifestations:Interstitial lung disease (ILD) and pulmonary arterial hypertension are an important cause of morbidity and mortality in juvenile systemic sclerosis and some phenotypes of JDM that are associated with anti melanoma differentiation-associated protein (MDA) -5 antibodies [17]. Parenchymal lung disease associated with sJIA is associated with a high mortality [18]. Children with granulomatosis with polyangiitis (GPA), also known as Wegener's gramulomatosis, and lupus can develop a devastating complication of diffuse alveolar haemorrhage (DAH). Other cardiopulmonary manifestations of lupus include pleurisy and myocarditis. Bronchial asthma is an important feature of eosinophilic granulomatosis with polyangiitis (EGPA) [19]. Up to 25% of untreated children with KD can develop coronary aneurysms. Coronary artery aneurysms can also be seen in PAN. Other cardiac manifestations such as pericarditis are often seen in sJIA and SLE. Aortic root insufficiency, cardiac tamponade and arrhythmias are uncommon complications of pediatric rheumatic diseases [5].

Ocular manifestations: Uveitis is one of the primary ocular concerns, prevalent in diseases like antinuclear antibody (ANA)-positive oligoarticular JIA, early-onset sarcoidosis (Blau syndrome) and Behçet's disease [20,21]. Chronic anterior uveitis is most commonly associated with ANA positive oligoarticular JIA, while acute anterior uveitis is commonly associated with enthesitis – related arthritis (ERA). Chronic anterior uveitis is usually asymptomatic but may be sight-threatening. Other inflammatory conditions such as keratitis, conjunctivitis, episcleritis, and scleritis can also manifest with symptoms like eye pain, redness, and vision disturbances. Optic neuritis secondary to SLE or vasculitis, retinal vasculitis, and cataracts further contribute to the spectrum of ocular involvement in rheumatic disorders [22].

Hematological manifestations: These are commonly seen in conditions such as sJIA, SLE, and childhood vasculitis. These include anemia attributed to chronic inflammation or medication-induced effects (e.g., methotrexate). Autoimmune anemia, leukopenia, lymphopenia and thrombocytopenia can be observed in SLE. A prothrombotic state leading to complications such as early onset stroke can be seen in children with antiphospholipid antibody (APLA) syndrome [23]. **Table I** summarises the key clinical and laboratory features of common rheumatic disorders.

DIAGNOSIS OF RHEUMATIC DISEASES

In pediatric rheumatic diseases, history and physical examination are crucial for arriving at the diagnosis. **Table II** enlists the common conditions that may mimic childhood arthritis. For instance, skeletal dysplasias such as progressive pseudorheumatoid dysplasia (PPRD) may resemble juvenile idiopathic arthritis [24]. It is imperative to ascertain the diagnosis before commencing immunosuppressive drugs such as corticosteroids, which can mask sinister conditions like leukemia.

While laboratory tests and imaging studies such as plain radiographs, ultrasound scans, and magnetic resonance imaging (MRI) are valuable adjuncts, they usually complement the clinical assessment and play a supportive role in most cases [25]. Complete blood count, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) can indicate the presence of systemic inflammation. Liver and renal function tests, urine microscopy, muscle enzymes such as lactate dehydrogenase (LDH), creatinine phosphokinase (CPK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), aldolase and other markers of inflammation such as serum ferritin may be needed for specific organ inflammation and/or organ damage. Interpreting these results in the context of the child's symptomatology can provide further diagnostic leads. For instance, in a child with sJIA,serum ferritin levels of > 10,000 ng/mL are highly suggestive of MAS [26]. Specific autoimmune tests such as an antinuclear antibody (ANA) by immunofluorescence (IF), anti-neutrophil cytoplasmic antibodies (ANCA), complement levels, and human leucocyte antigen (HLA) typing may be required for further confirmation. A high pre-test suspicion of an autoimmune disease is required while ordering specific tests to decrease the probability of a false positive result [27].

SEQUELAE OF MISSED RHEUMATIC DISEASES

In addition to the damage to the involved joint/organ, chronic inflammation and immune dysregulation can predispose individuals to accelerated atherosclerosis, increasing the risk of coronary artery disease, myocardial infarction, and stroke. Coronary aneurysms can lead to thrombosis, myocardial infarction, and even sudden cardiac death, highlighting the critical importance of early recognition and intervention in KD [5]. Macropahge

Table I Key Clinical and Laboratory Features of Common Rheumatic Disorders

Rheumatic Disease	*Clinical Features*	*Evaluation*
Oligoarticular JIA	Arthritis affecting four or fewer joints during the first 6 months of disease Persistent oligoarthritis:Arthritis in four or fewer joints for the entire disease course Extended oligoarthritis: Arthritis in five or more joints after the initial 6 months of disease	• Elevated ESR and/or CRP • Positive ANA by IF • Associated with chronic anterior uveitis.
RF-negative polyarticular JIA	Arthritis affecting 5 or more joints during the first 6 months of disease	• Elevated ESR and/or CRP. • Elevated ESR and/or CRP. • RF negative.
RF-positive polyarticular JIA	Arthritis affecting 5 or more joints during the first 6 months of disease	• Elevated ESR and/or CRP. • 2 or more positive tests for RF at least 3 months apart during the first 6 months of disease
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least 2 of the following: 1. Dactylitis 2. Nail pitting or onycholysis 3. Psoriasis in a first-degree relative	• Elevated ESR and/or CRP. • RF and HLA- B27 are negative. • Associated with chronic anterior uveitis.
Enthesitis-related arthritis	Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following: 1. Presence or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain 2. Presence of HLA-B27 antigen 3. Onset of arthritis in a male over 6 years of age 4. Acute anterior uveitis 5. History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative	• Elevated ESR and/or CRP. • Positive for HLA- B27. • Associated with acute anterior uveitis.
Systemic Onset JIA	Arthritis in one or more joints with or preceded by fever of at least 2 weeks duration in which it is to documented to be daily for at least 3 days, AND Accompanied by one or more of the following: 1. Evanescent erythematous rash 2. Generalized lymph node enlargement 3. Hepatomegaly and/or splenomegaly 4. Serositis	• Elevated acute-phase reactants (ESR, CRP, Ferritin) • Leukocytosis with neutrophilia • Thrombocytosis • Elevated liver enzymes • ANA and RF are negative
Systemic Lupus Erythematosus (SLE)	• Butterfly rash (malar rash) • Photosensitivity •Arthritis or arthralgia involving multiple joints • Renal involvement (proteinuria, hematuria) • Oral ulcers and alopecia • Overwhelming fatigue	• Cytopenias • Elevated ESR and normal CRP • Positive ANA by IF (majority of cases) • Presence of anti-ds DNA antibodies, Sm antibodies, antiphospholipid antibodies • Low complement levels (C3, C4) • Proteinuria

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Rheumatic Disease	*Clinical Features*	*Evaluation*
Juvenile Dermatomyositis (JDM)	• Proximal muscle weakness • Gottron's papules • Heliotrope rash • Periungual erythema and telangiectasia • Anasarca	• Elevated muscle enzymes (CK, AST, ALT, LDH, aldolase) • Myositis specific or associated antibodies • MRI of proximal muscles confirming presence of muscle or fascial inflammation • Abnormal EMG findings • Muscle biopsy showing perifascicular atrophy and inflammatory infiltrates
Kawasaki Disease	• Prolonged fever (≥ 5 days) • Bilateral non suppurative conjunctival injection • Erythematous rash over the trunk with accentuation in the groin • Strawberry tongue, red lips • Unilateral cervical lymphadenopathy • Red indurated brawny edema of the extremities	• Elevated acute-phase reactants (ESR, CRP) • Leukocytosis with neutrophilia • Thrombocytopenia in the first week of illness followed by thrombocytosis • Elevated liver enzymes • Cardiac abnormalities on echocardiography usually seen after 7 days from onset of illness (coronary artery dilatation or aneurysms)
Small Vessel Vasculitis	• Purpura, petechiae, or ecchymoses • Arthralgia or arthritis • Colicky or spasmodic abdominal pain • Glomerulonephritis or renal involvement	• Elevated acute-phase reactants (ESR, CRP) • Positive ANCA • Microscopic hematuria and proteinuria • Renal biopsy showing pauci-immune glomerulonephritis
Large Vessel Vasculitis	• Fever, fatigue, weight loss • Claudication or limb pain • Arterial bruits or diminished pulses • Constitutional symptoms	• Elevated acute-phase reactants (ESR, CRP, Ferritin) • Elevated liver enzymes • Angiography demonstrating vessel inflammation or stenosis
Periodic Fever Syndromes	• Recurrent episodes of fever lasting several days to weeks • Rash, arthritis, abdominal pain, or serositis during febrile episodes	• Elevated acute-phase reactants (ESR, CRP, Ferritin) during fever episodes • Normal inflammatory markers between episodes • Genetic testing

JIA – Juvenile idiopathic arthritis, CRP- C-reactive protein, ESR- Erythrocyte sedimentation rate, ANA- Antinuclear antibody, IF- Immunofluorescence, RF- Rheumatoid factor, HLA- Human leucocyte antigen, CK- Creatinine kinase, AST- Aspartate aminotransferase, ALT- Alanine aminotransferase, LDH- lactate dehydrogenase, ANCA- antineutrophilic cytoplasmic antibody.

activation syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis (HLH) is a life threatening complication characterised by prolonged fever, multiorgan dysfunction, cytopenias, and elevated ferritin levels. It is most commonly reported with sJIA, but can also complicate other rheumatic conditions such as lupus and KD [23-26]. MAS can occur at the initial presentation of the underlying disease or may develop subsequently during the course of the illness. It requires prompt recognition and aggressive management, as delayed diagnosis can lead to rapid deterioration and high mortality rates ranging from 10-30% [23-26].

CONCLUSION

Delayed diagnosis of rheumatic diseases in children poses a substantial risk, often leading to the accrual of disease-related damage and complications. Early detection is paramount, as it significantly impacts outcomes, reduces the need for intensification of treatment strategies, and can prevent progression of organ damage. Early diagnosis impacts the psychological state of children and adolescents, as they experience symptom relief and

improved well-being, enhancing their overall quality of life. Sensing the subtle symptoms or signs of inflammation and conducting a focused clinical evaluation is essential to enable early diagnosis and subsequent early intervention, thereby improving outcomes in children.

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Web Fig. 21 (a-f): 2a: Gotton's papules 2b: Heliotrope and facial rash in a child with juvenile dermatomyositis; 2c:digital tip ulcers in a child with mixed connective tissue disorder; 2d:deforming arthritis in a child with juvenile idiopathic arthritis ; 2e: Reactivation of BCG scar in Kawasaki diease; 2f: Malar rash in systemic lupus erythematosus