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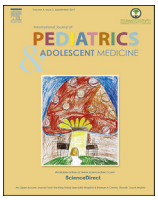

Invited review

Noninflammatory disorders mimic juvenile idiopathic arthritis

Sulaiman M. Al-Mayouf*

Pediatric Rheumatology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

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ABSTRACT

Juvenile idiopathic arthritis (JIA) is the most common chronic childhood arthritis; unfortunately, no diagnostic tool is available. Genetic disorders with musculoskeletal involvement that mimic chronic polyarthritis should be considered in the differential diagnostics of JIA. Normal inflammatory markers and characteristic radiological features are able to distinguish these disorders from JIA. Timely diagnosis of these disorders is crucial to offer the family proper genetic counseling and avoid inappropriate therapy. This review highlights selected noninflammatory disorders that often present with articular manifestations and that are often mislabeled as JIA. The focus is on the clinical, biochemical, and imaging features of these disorders.

1. Introduction

Juvenile idiopathic arthritis (JIA) is the most common childhood chronic inflammatory arthritis. The nomenclature and classification of JIA are based on the International League of Associations for Rheumatology (ILAR) criteria [1,2]. JIA is a diagnosis of exclusion and represents a phenotypically heterogeneous group of arthritides; however, they have similar inflammatory articular changes. It is crucial to recognize arthritis, which is a clinical finding manifested as stiffness, particularly in the morning, effusion/swelling, and limited range of motion of the affected joints [3]. Many children are referred to pediatric rheumatology clinics with musculoskeletal manifestations such as joint contracture, swelling, or deformity without signs of inflammation. A spectrum of systemic noninflammatory disorders may masquerade as JIA [4]. Patients with noninflammatory disorders have arthropathy rather than arthritis. Arthropathy can arise from bony dysplasia, thickened synovium, or noninflammatory effusion [5,6]. Unfortunately, it is not uncommon for the presence of noninflammatory arthropathy to mimic juvenile arthritis, which delays the correct diagnosis and the appropriate management [7,8].

We believe that a complete history, with emphasis on the family history, and thorough musculoskeletal examination supported by basic laboratory tests, including tests for acute-phase reactants, and proper imaging studies are sufficient to identify such disorders and eventually initiate the proper management and avoidance of unnecessary treatment [9]. This review highlights selected noninflammatory disorders that often present with articular manifestations; it is not uncommon to mislabel such disorders as JIA. The focus is on the clinical, biochemical, and imaging features of these disorders.

2. Idiopathic multicentric osteolysis

Idiopathic osteolysis is a rare inherited heterogeneous group of disorders. The exact cause and pathogenesis are not well identified. There are different forms with different names; the frequency of these disorders worldwide is unknown [10,11]. The affected patients are young children, usually presenting with restricted movements of the wrist and ankle joints simulating arthritis but with rapid progressive resorption of carpal and tarsal bones ending with severe deformities and functional disabilities [12,13]. Patients have pain due to severe osteoporosis rather than synovitis.

The initial presentation mimics arthritis; so it is not uncommon to mislabel such conditions as JIA [14,15]. However, careful clinical assessment demonstrated that these patients do not have morning stiffness or joint effusion. Plain radiography of the hands and feet revealed early destructive osteolytic changes of the carpal and tarsal bones, which are not consistent with inflammatory arthritis.

* College of Medicine, Alfaisal University, Pediatric Rheumatology, Department of Pediatrics, King Faisal Specialist Hospital and Research Center, Po Box 3354, Riyadh, 11211, Saudi Arabia.
E-mail address: mayouf@kfshrc.edu.sa.

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Furthermore, inflammatory markers, including erythrocyte sedimentation rate and C-reactive protein level, are typically within normal limits.

We described a large cohort of one of the idiopathic multicentric osteolysis disorders, named *nodulosis, arthropathy, and osteolysis (NAO) syndrome* [16]. NAO syndrome results from a mutation in the matrix metalloproteinase 2 gene (*MMP2*), at 16q12-21. Mutational inactivation of *MMP2* creates an imbalance between bone synthesis and resorption [17]. The main clinical findings are arthropathy in the form of limitation of motion with contractures and deformities affecting both hands and feet in addition to nodular lesions in both palmar and plantar surfaces (Fig. 1). A few patients have involvement of other joints, including elbows, knees, and hips. Radiography of the hands and feet shows advanced osteolytic changes (Fig. 2).

Unfortunately, no effective treatment is available for these disorders. Supportive treatment in the form of calcium and vitamin D supplementation in addition to bisphosphonate might increase the bone density but does not change the disease course [18,19].

3. Mucopolysaccharidosis

Mucopolysaccharidoses (MPS) are a heterogeneous group of inborn metabolic disorders of glycosaminoglycan. There are different phenotypes depending on the mutations of certain genes encoding glycosaminoglycan-degrading enzymes, resulting in the inability to metabolize certain glycosaminoglycans. Overall the frequency of MPS differs in each population but the most common form is MPS type I [20,21]. Patients usually look normal at birth. However, as they get older, they show progressive clinical features affecting multiple organ systems. Severe MPS phenotypes are typically under the care of medical genetic specialists. The diagnostic approach and management of MPS are beyond the scope of this review. However, a general pediatrician or another specialists may suspect or see mild cases initially. Accordingly, he or she can refer the patient to a medical genetic specialist for more confirmatory testing and management.

MPS type I has historically been delineated into three separate subtypes: Hurler syndrome (severe), Hurler-Scheie syndrome (intermediate), and Scheie syndrome (mild). Musculoskeletal manifestations such as stiffness and joint contractures are prominent in all forms of MPS; these manifestations include joint disorders that may mimic inflammatory arthritis and require consultation with a rheumatologist [7,22]. The milder phenotypes are more likely to be missed; unfortunately, diagnostic delays occur frequently in these patients. Rheumatologists and other specialists should be aware of the musculoskeletal manifestations of MPS. The proper history and physical examination should help in recognizing these cases. MPS

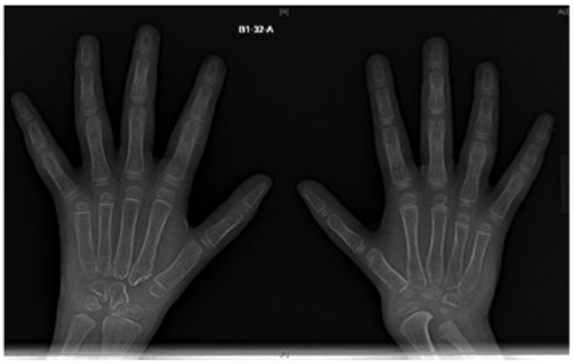

Fig. 2. Bilateral hand radiograph of both hands showing generalized osteopenia and advanced osteolytic changes in a patient with nodulosis, arthropathy, and osteolysis syndrome.

should be considered a differential diagnosis in children with joint contractures in the absence of signs of inflammation [23]. Furthermore, certain radiographic findings, such as characteristic dysplasia and dysostosis multiplex, should raise suspicion of MPS (Fig. 3) [24,25].

Early diagnosis and management are necessary to improve the outcome in affected patients. Enzyme activity assays based on cultured fibroblasts, leukocytes, plasma, or serum are considered the gold standard for diagnosis of MPS. Certain MPS disorders can be treated with hematopoietic stem cell transplantation or enzyme replacement therapy when this is available [25,26].

4. Camptodactyly-arthropathy–coxa vara–pericarditis syndrome

Camptodactyly-arthropathy–coxa vara–pericarditis (CACP) syndrome is a rare autosomal inherited disorder affecting mainly the joints. Usually, the affected individual does not report joint pain or morning stiffness. Typically, the manifestations start in the infancy period as camptodactyly of the fifth fingers. However, the hallmark features, such as swelling of interphalangeal joints, wrists, and knees, develop in early childhood. The swollen joints are due to synovial thickening and effusion, which are often associated with limited motion but without redness, tenderness, or hotness [8,27]. One of the important components of this disorder is femoral dysplasia; patients usually develop progressive coxa vara, some have other radiological findings such as acetabular cysts (Fig. 4). Ultrasonography is probably beneficial in differentiating CACP syndrome from inflammatory arthritis; CACP syndrome patients have prominent synovial proliferation with normal synovial

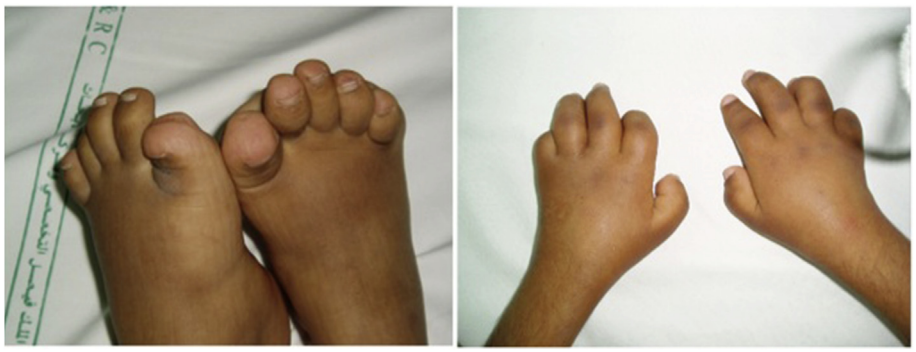

Fig. 1. Contractions of small joints of hands and feet in a patient with nodulosis, arthropathy, and osteolysis syndrome.

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