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Case report

Progressive Pseudorheumatoid Dysplasia – A Rare Arthropathy of Childhood

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Abstract

Background

Progressive pseudorheumatoid dysplasia (PPRD; MIM#208230), also known as Progressive pseudorheumatoid arthropathy of childhood or Spondyloepiphyseal dysplasia tarda with progressive arthropathy, is a rare progressive degenerating arthropathy that usually presents between ages 3 to 6 years. It is caused by mutations in the WNT1-inducible signaling pathway protein 3 gene (CCN6 gene) on chromosome 6. The real incidence is unkown, with an estimated incidence of 1:1,000,000 in the United Kingdom, thought to be higher in the Middle East and Gulf States, Turkey and India.It presents with interphalangeal joints involvement, with arthralgia and stiffness. As the disease progresses, epiphyseal and metaphyseal enlargement appear, often mistaken as swelling, leading to erroneous juvenile idiopathic arthritis (JIA) diagnosis.

Case Presentation

Twelve-year-old Iraqi girl, only-child born from consanguineous healthy parents, referred due to a suspected JIA/Farber disease. She reported onset around 2 to 3 years of age with enlarged interphalangeal (IP) joints of hands and nodules, progressive restricted mobility, severe scoliosis and gait abnormalities. Previous medical care had been sparse, without specific treatments. Examination revealed short stature, severe thoracolumbar kyphoscoliosis, genu varum and lower limb dysmetria. Fixed finger contractures with IP nodules, without effusion, and painless restricted mobility of all peripheral joints and cervical limitation were also present.

Bone radiographies showed periarticular osteopenia, platyspondyly with narrowed intervertebral disc spaces, enlarged epiphyses and widened metaphysis. Laboratorial workup revealed normal inflammatory markers, negative rheumatoid factor, negative anti-citrullinated protein antibodies and positive antinuclear antibodies. Abdominal ultrasound and DXA scan were normal. PPRD was suspected and a skeletal dysplasia NGS panel was performed, identifying an apparently homozygous likely pathogenic variant NM_003880.3:c.850G>T,p.(Gly284*) in the CCN6 gene. Mixed array confirmed a probable homozygosity, establishing the diagnosis of PPRD. She initiated intensive physical rehabilitation with improvement.

Conclusion

The diagnosis of PPRD allows adequate management and avoids unnecessary and potentially harmful treatments. The absence of inflammation and the radiological findings (platyspondyly, enlargement of the epiphyses and metaphysis, osteopenia and absence of joint erosions) can help to distinguish PPRD from JIA. The definitive diagnosis is made by molecular genetic testing, identifying mutations in CCN6 gene.

Keywords: Bone Dysplasias; CCN6 gene; Juvenile idiopathic arthritis; Progressive pseudorheumatoid dysplasia; Spondyloepiphyseal dysplasia tarda with progressive arthropathy

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Abbreviations

ACPA: Anti-citrullinated protein antibodies

ANA: Antinuclear antibodies

IP: Interphalangeal

JIA: Juvenile idiopathic arthritis

FD: Farber disease

PPRD: Progressive pseudorheumatoid dysplasia

Background

Progressive pseudorheumatoid dysplasia (PPRD; MIM#208230), also known as Progressive pseudorheumatoid arthropathy of childhood or Spondyloepiphyseal dysplasia tarda with progressive arthropathy, is a rare autosomal-recessive noninflammatory arthropathy of childhood, that can be misdiagnosed as juvenile idiopathic

arthritis (JIA). It usually presents between ages 3 to 6 years and affects multiple joints with progressive stiffness and enlargement, in the absence of joint inflammation, affecting other locations as the disease progresses, causing epiphyseal and metaphyseal enlargement, osteoporosis, spinal abnormalities as platyspondyly and kyphosis [1,2]. It is caused by mutations in the WNT1-inducible signaling pathway protein 3 gene (*CCN6* gene) on chromosome 6, leading to articular cartilage degeneration [1,3]. The estimated incidence is 1:1,000,000 in the United Kingdom, thought to be higher in the Middle East and Gulf States, Turkey and India [1].

Case Presentation

Twelve-year-old Iraqi girl referred due to suspected JIA/Farber disease (FD). She was the only-child born from consanguineous healthy parents. Three paternal second cousins have similar phenotype. She reported onset around 2 to 3 years of age with enlarged interphalangeal (IP) joints of hands and nodules, progressive restricted mobility, severe scoliosis and gait abnormalities. She had normal intelligence. Previous medical care had been sparse and had not received any specific treatments. Physical examination revealed short stature, no dysmorphic facial features, a normal voice, severe thoracolumbar kyphoscoliosis, genu varum and lower limb dysmetria. Fixed finger contractures with IP nodules, without effusion, were also present, as well as painless restricted mobility of all peripheral joints and cervical limitation. She required a wheelchair to move. Bone radiographies were performed (Figure1), showing periarticular osteopenia, platyspondyly with narrowed intervertebral disc spaces, enlarged epiphyses and widened metaphysis. Laboratorial workup revealed normal inflammatory markers, negative rheumatoid factor, negative anti-citrullinated protein antibodies (ACPA) and positive antinuclear antibodies (ANA). Abdominal ultrasound was normal. DXA scan showed normal Z-scores. PPRD was suspected and a skeletal dysplasia NGS panel was performed, identifying an apparently homozygous likely pathogenic variant NM_003880.3:c.850G>T, p.(Gly284*), in the *CCN6* gene. Mixed array confirmed a probable homozygosity and helped establishing a molecular diagnosis of PPRD. The patient received genetic counselling and was managed with intensive physical rehabilitation and occupational therapy and was referred to Orthopedics who prescribed bracing for scoliosis. Two years later, she presents improvement of stiffness and joint mobility, attends school fulltime and is able to use crutches as a walking aid.

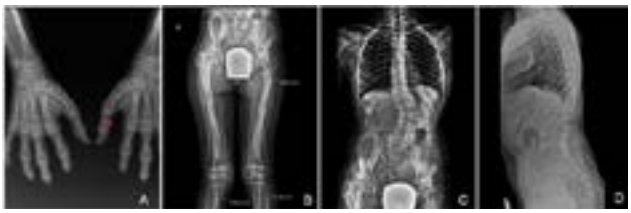

Figure 1: A - Hand radiography showing periarticular osteopenia, epiphyseal enlargement, particularly on the radius, and widened metaphysis of metacarpals and phalanges, with surface irregularities; **B** - Lower limb radiography showing flattening of the femoral head and dysmetria, as well as periarticular osteopenia and valgus knee; **C, D** - Spine radiograph showing platyspondyly (flattening of some vertebral bodies) and severe scolioses with right lumbar curvature.

Discussion

The previous suspicion of FD was due to the IP nodules and osteopenia. FD is a rare lysosomal storage disorder caused by variants in the ASAH1 gene, decreasing acid ceramidase activity and leading to ceramide accumulation. It manifests with subcutaneous nodules, joint contractures and hoarse voice. In PPRD, the enlarged epiphyses and metaphysis are often mistaken as swelling, leading to JIA misdiagnosis, as happened in this case.

Conclusion

Despite its rarity, the diagnosis of PPRD is crucial as it allows adequate management and avoids unnecessary and potentially harmful treatments. The absence of inflammation as well as the radiological findings (platyspondyly, epiphyseal and metaphyseal enlargement, osteopenia and absence of joint erosions) can help to distinguish from JIA [1,4,5]. The definitive diagnosis is made by genetic testing, identifying pathogenic variants in the *CCN6* gene [1,5].

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Author's contribution

ALC was the main author. MGB and MR participated in acquisition of data. TC, PL, MR and IB participated in the analysis or interpretation of data. All authors approved the final manuscript and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Verbal and written informed assent and consent were obtained.

Competing interests

The authors declare that they have no competing interests.

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