13 year old Female with Progressive Pseudorheumatoid Dysplasia misdiagnosed as Juvenile idiopathic arthritis

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Case Report

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Abstract

Background: Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood and is of unknown aetiology. Progressive pseudorheumatoid dysplasia is a rare, autosomal recessively inherited, non-inflammatory musculoskeletal disorder caused by mutations occurring in the WISP3 gene. Joint cartilage is the primary site of involvement, leading to arthralgia, joint stiffness, contractures, enlargement of the epiphyses and metaphysis of the hand joints, spinal abnormalities, short stature, early osteoarthritis, and osteoporosis. The clinical features resemble juvenile idiopathic arthritis (JIA), and patients with PPD are usually misdiagnosed as JIA.

Case Presentation: A 13 year old female presented to the rheumatology clinic with history of joint pains, bone pains and bone deformity for 5 years. Weight and Height were below the 3rd centiles. There was none tender swelling of metacarpophalangeal and interphalangeal joints and with scoliosis. Radiographs of the hands revealed widening of the epiphyses. With these findings Progressive Pseudorheumatoid Dysplasia was suspected and genetic testing for WISP1, WISP2 and WISP3 was requested. A homozygous, likely pathogenic, variant was identified in WISP3 gene which confirmed our diagnosis.

Conclusion: Progressive Pseudorheumatoid Dysplasia is a rare form of spondylo-epi-metaphyseal dysplasia and clinically misdiagnosed as Juvenile Idiopathic arthritis. It's important to consider PPD especially in patients with normal inflammatory markers who are being followed up for arthritis and not improving on anti-rheumatic intervention.

Background

Progressive pseudorheumatoid dysplasia (PPRD) is a joint disease that worsens over time. This condition is characterized by the degeneration of the articular cartilage which covers and protects the ends of bones (1).

PPRD has been estimated to occur in approximately 1 per million people in the United Kingdom. Though, this condition is thought to be more common in Turkey and the Middle East, its prevalence is unknown (2,3). The condition in all regions is likely underdiagnosed because it is often misdiagnosed as juvenile idiopathic arthritis (4).

PPRD usually begins in childhood, between ages 3 and 8 years (1,5). The first indications are usually an abnormal walking pattern, weakness and fatigue when active, and stiffness in the joints of the fingers and knees (6). Other signs and symptoms that develop over time include permanently bent fingers (camptodactyly), enlarged finger and knee joints (often mistaken as intraarticular swelling), and a reduced amount of space between the bones at the hip and knee joints. Hip pain is a common problem by adolescence. Affected individuals have flattened bones in the spine (platyspondyly) that are abnormally shaped (beaked), which leads to an abnormal front-to-back curvature of the spine (kyphosis) and a short torso (1). At birth, people with PPRD are of normal length, but by adulthood, they are usually shorter than their peers (6).

This disorder is caused by a loss of function of the WISP3 gene (Wnt-1 inducible signaling pathway protein 3; MIM603400) encoded on chromosome 6q21. WISP3 is essential in maintaining cartilage integrity by regulating the expression of type II collagen and aggrecan in chondrocytes. Therefore, it is crucial for bone formation and maintaining cartilage (5-7). The clinical features are similar to those of juvenile idiopathic arthritis (JIA), and patients with PPD are usually misdiagnosed as JIA (4).

We present this case report of a 13 year old girl misdiagnosed as JIA

Case Presentation

We report a case of a 13 year old female who was referred to the rheumatology clinic with history of joint pains, bone pains and bone deformity for 7 years. She was born via spontaneous vaginal delivery without complication to consanguineous parents of Yemeni origin. She is the third born in her family. There is no history of joint disorders in the family. Joint pains and bone pains started at 6 years of age. This was followed by easy fatigability and swelling of the proximal (PIP) and distal (DIP) interphalangeal joints followed by the elbow joints. This was accompanied by pain in the left hip causing her to limp and finally inability to walk.

Initially at the age of 9 years she presented to the general practitioners with joint and bone pains. She was diagnosed with arthritis and treated with NSAIDs. However, her condition kept on deteriorating despite the NSAIDs and therefore referred to pediatric rheumatologist for further management. Her weight and height on presentation was <3rd percentile and upper- to lower body segment ratio was 1. On examination patient was in fair general condition. She had marked prominence (swelling) of proximal (PIP) and distal (DIP) interphalangeal joints bilaterally which were non erythematous, and nontender (Figure 1). However there was limited mobility of the joints. Swelling of the knee and elbow joints bilaterally was also noted. She also had scoliosis on presentation. Laboratory tests done revealed a normal Erythrocyte sedimentation rate of 5mm after one hour (reference 0-20mm); HLA-B27 was not detected which the antinuclear factor (ANA) and rheumatoid factor (RF) were both negative.

She was prepubertal at 13 years of age. Neurological examination did not reveal any abnormal findings. Radiographs of the hands and spine was requested.

RADIOLOGICAL ASSESSMENT

Radiology of the hands and spine was taken and revealed the following findings: Reduced joint space in the 3rd and 4th proximal interphalangeal joints with increased soft tissue density around the proximal interphalangeal joints (Fig 2) Radiology of the hip revealed reduction in the left femoral epiphysis, with associated mild sclerosis. There was presence of left femoral epiphyseal subchondral lucency, consistent with avascular necrosis of the left femoral head (Fig 3). Radiograph of the thoracolumbar spine revealed

mild scoliosis with loss of height of the of the lower thoracic and upper lumbar vertebral bodies. Antero-superior endplate compression changes of multiple vertebrae were also noted (Fig 4)

DIAGNOSIS

In view of the clinical symptoms, laboratory and radiologic findings which were not in keeping with the diagnosis of Juvenile rheumatoid arthritis, Progressive Pseudorheumatoid Dysplasia was strongly suspected. Therefore, a genetic analysis of the WISP3 gene was carried out and a mutation in WISP3 gene was identified (Figure 5)

Discussion And Conclusion

Progressive pseudorheumatoid dysplasia (PPRD) is a skeletal dysplasia characterized by predominant involvement of articular cartilage with progressive joint stiffness and enlargement in the absence of inflammation. It starts between ages three and six years with the involvement of the interphalangeal joints as the initial clinical presentation (6). Over time, involvement of large joints and the spine causes significant joint contractures, gait abnormality, scoliosis or kyphosis which results in abnormal posture and significant morbidity (6). Likewise, our patient initially presented to the general practitioner with complaints of swelling of the proximal interphalangeal joints bilaterally. Like in our patient the condition in all regions is likely to be underdiagnosed because it is often misdiagnosed as juvenile idiopathic arthritis (JIA). PPRD is clearly differentiated from JRA by absence of inflammation, extra-skeletal manifestations and articular bone erosion. Moreover these patients do not respond to anti-rheumatic agents and therefore will not yield any clinical benefit. The radiological features are completely different from PPRD which include spondyloepiphyseal dysplasia with platyspondyly as an early finding, and the lack of destructive joint erosions (8,9).

Although radiologic examination has high accuracy in the diagnosis of PPRD, the definitive diagnosis is established in a proband with identification of the characteristic radiologic findings and biallelic pathogenic variants in the WISP3 gene on molecular genetic testing (6). As the case in our patient a novel compound heterozygous mutation in the WISP3 variant c.746delT p. (Val249Glyfs*10) creating a premature stop codon 9 positions downstream was identified.

In conclusion patients presenting with musculoskeletal symptoms should be evaluated appropriately so that inappropriate therapy can be prevented and appropriate therapy started on time. Genetic testing and counseling should be offered to these families to plan for next generation.

List Of Abbreviations

ANA: Antinuclear antibody

JIA: Juvenile idiopathic arthritis

PIP: Proximal interphalangeal

DIP: distal interphalangeal

PPRD: Progressive pseudorheumatoid dysplasia

RF: Rheumatic factor

HLA-B27: Human Leucocyte Antigen

WISP3: WNT1-inducible signaling pathway protein 3

NSAIDs: Non steroid anti-inflammatory drugs

Declarations

Ethics approval and consent to participate: Written, informed consent was obtained from the affected individual and her legal guardians for both genetic analysis and publication of patients' photographs and imaging studies.

Consent for publication: Written, informed consent was obtained from the affected individual or their legal guardians for genetic analysis, publication of the case report and publication of patients' photographs and imaging studies.

Availability of data and materials: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study

Competing Interest: Authors declare that they have no competing interest

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Authors' contributions: Anjumanara Omar and Lawrence Owino were major contributor in reviewing the literature and writing the manuscript and management of the patient. Salman Ahmed and John Chris Rodrigues had major roles in the radiological assessment of the patient. Centogene did the molecular analysis including the gene sequencing. All authors read and approved the final manuscript.

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Figures

Figure 1

Swelling of the proximal and distal interphalangeal joints.

Figure 2

Reduced joint space 3rd and 4th interphalangeal joints

Figure 3

Fig 3: Reduction in left femoral epiphysis, with sclerosis

Figure 4

Antero-Superior endplate compression of the vertebra

GENE	VARIANT COORDINATES	AMINO ACID CHANGE	SNP IDENTIFIER	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES**	TYPE AND CLASSIFICATION***
WISP3	NM_198239.1:c.746delT	p.Val249fs	N/A	homozygous	PolyPhen: N/A Align-GVGD: N/A SIFT: N/A MutationTaster: N/A Conservation_nt: Conservation_aa:	GnomAD: - 1K Genome:- ESP: - CenoMD: -	Frameshift Likely Pathogenic (class 2)

Variant description based on OTFA (using VEP v83). * AlignGVGD: C0: least likely to interfere with function, C65: most likely to interfere with function; splicing predictions: Ada and RF scores. ** Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G) and CentoMD® (latest database available). *** based on ACMG recommendations.

Figure 5

Mutation in the WISP3 gene