PROGRESSIVE PSEUDORHEUMATOID SKELETAL DYSPLASIA PRESENTING WITH PROPORTIONATE SHORT STATURE AND POSITIVE WISP3 MUTATION: A CASE REPORT

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ABSTRACT

Progressive pseudorheumatoid dysplasia (PPD) is a genetic non-inflammatory arthropathy, known to transmit in a recessive pattern is caused by a mutation in WISP3 (Wnt1-inducible signal pathway) gene. It is a highly debilitating multi-joint disease that presents with a disproportionate short stature, usually affecting the children between 3 to 8 years of age. PPD is diagnosed clinically along with imaging, but confirmed with the help of a precise genetic analysis. It is a rare disease with an approximate incidence of 1/1,000,000 in the UK but a bit higher in Middle East and Asian region. The case reports regarding PPD in Pakistan are very scarce. It is usually very rare for PPD to present with a proportionate short stature which we have reported. It is the first case from Pakistan to be confirmed through a genetic analysis and will further pave the way for clinicians to use this tool for confirming the diagnosis.

Keywords: short stature, skeletal dysplasia, non-inflammatory arthropathy.

Introduction

Pseudorheumatoid skeletal dysplasia (PPD) is a rare genetic non-inflammatory arthropathy of childhood involving axial skeleton and small joints.[1] It is a rare disease with an approximate incidence of 1/1,000,000 in the UK but a bit higher in Middle East and Asian region.[2] It typically occurs in children between 3 to 8 years of age and presents with the involvement of interphalangeal joints at the beginning further involving the large joints and spine causing contractures, gait disturbances, postural instability and asymmetric short stature.[3] The basic pathophysiological mechanism behind its consequences is the degeneration of articular cartilage in multiple joints.[4] It is usually diagnosed through combination of methods including examination and radiological findings such as complete skeletal survey but the definitive diagnosis still relies on genetic analysis that confirms the genetic mutation. The case reports regarding PPD in Pakistan is very scarce and this is the inaugural case report on this subject from Pakistan to be confirmed through a genetic analysis.

Case Report

We present the case of a 9-year-old non-vaccinated child presented to us with short stature since 4 years of age. The patient was growing well until the age of 4 years till his parents noticed difference in his growth in comparison to other siblings. He was not gaining

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height and weight and his feet and knees both turn towards each other. His height was 105cm (below 3rd centile) (-4.96 SDS) and weight was 17kg (below 3rd centile) (-4.51 SDS). The upper segment to lower segment ratio was 1.05 which suggests proportionate stature. His father also complained of difficulty in walking (gelling) after the rest of one to two hours. His other siblings and parents are healthy and normal in height. Haematological investigations including serum calcium/phosphate, thyroid hormones, full blood count, C reactive protein, erythrocyte sedimentation rate, rheumatoid factor, and antinuclear antibody levels were all negative. He was brought to the clinic where he was examined and swelling on interphalangeal joints of both hands was identified and a complete skeletal survey was done.

Skeletal Survey Findings:

Generalized bone density is reduced. Skull showed widely patent fontanelles with intra-sutural wormian bones. Vertical height reduction with beaking of the anterior vertebral bodies and platyspondyly with narrowing on the intervertebral disc space were observed in x-ray of spine. Early premature osteoarthritic changes in bilateral hip joints, angular deformity of neck of femur (coxa vera) and bilateral irregular iliac crests found in pelvis. Extremities showed large epiphyses and widened metaphyses of the metacarpals and phalanges without erosion.

Genetic Analysis:

Two Pathogenic variants, c.156C>A (p. Cys52*) (homozygous), were identified. WISP3, Exon 3, c.156C>A (p. Cys52*), homozygous is pathogenic. This sequence change creates a premature translational stop signal (p. Cys52*) in the WISP3 gene. It is expected to result in an absent or disrupted protein product. Loss-of-function variants in WISP3 are known to be pathogenic.This variant is present in population databases (rs121908901, ExAC 0.006%). This variant has been observed in individual(s) with progressive pseudorheumatoid dysplasia. ClinVar contains an entry for this variant. For these reasons, this variant has been classified as Pathogenic.

Gene Variant Zygosity Variant Classification:

WISP3 c.156C>A (p. Cys52*) homozygous PATHOGENIC.
C2CD3 c.2843G>A (p. Arg948Gln) heterozygous Uncertain Significance.
OBSL1 c.3295G>A (p. Val1099Met) heterozygous Uncertain Significance.
ORC4 c.412T>C (p. Phe138Leu) heterozygous Uncertain Significance.
SETBP1 c.4599_4607del (p. Pro1535_Pro1537del) heterozygous Uncertain Significance.
TNFRSF11A c.1766C>G (p. Pro589Arg) heterozygous Uncertain Significance.
VAC14 c.1308G>A (p. Met436Ile) heterozygous Uncertain Significance.

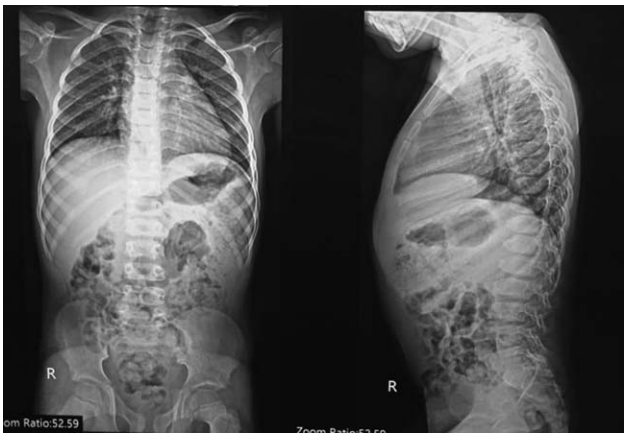

Figure 1: Reduced vertical height of the thoracolumbar vertebral bodies without evidence of gross platyspondyly. Superior and inferior heaping up and hyperostosis involving posterior 2/3rd of end plates giving rise-humped shaped appearance. Beaking of anterior vertebral bodies with narrowing of intervertebral disc space are also observed.

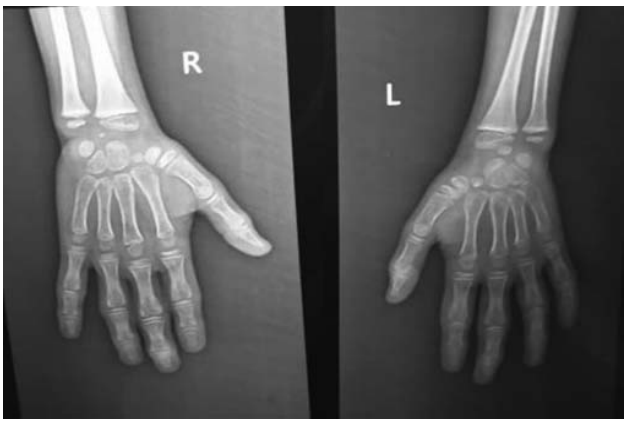

Figure 2: Periarticular soft tissue swelling involving proximal interphalangeal and distal interphalangeal joints of both hands. The metacarpal and phalanges show enlarged epiphysis and metaphysis without erosive changes/periosteal reaction.

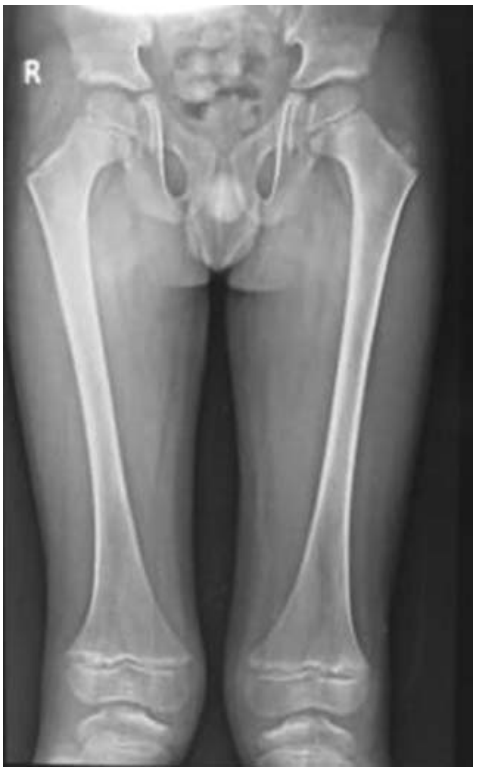

Figure 3: Early osteoarthritic changes are seen in both hip joint showing asymmetrical joint space reduction and mildly flattened epiphysis.

Discussion

The initial case of PPD was diagnosed some four decades ago, but it took almost two decades to figure out that mutation in a member of CCN gene family WISP3 is the cause of this autosomal recessive disorder.[5] There are multiple different mutations identified in WISP3 gene which is essential for normal post-natal skeletal growth and cartilage homeostasis. It can be misdiagnosed as JIA initially and the patient may be asymptomatic but the symptoms start to appear gradually as cartilage destruction ensues. The WISP3 c.156C>A (p. Cys52*) mutation is rare and results in premature termination of the WISP3 protein.[6]

The integrity of the cartilage is dependent on its regulation through collage type II and aggrecan which is supported by WISP3.[7] Dysregulation in this physiology due to the mutation in WISP3 leads to cartilage destruction in PPD. WISP3 is also implicated in cartilage differentiation and inhibiting its enlargement and its mutation results in joint destruction through lack of stability and degeneration of the cartilage. Mutations in WISP3 can be located in a single or in every protein domain and include base pair substitutions, deletions, duplications, and substitution / deletions.[8]

Clinically, PPD is characterized by multiple joint destruction and swelling which increases as the child increases in age. It is a debilitating joint condition that presents with disproportionate short stature. It involves multiple joints and cartilaginous areas of the skeleton. The onset of the disease usually occurs between 4 to 6 years of age.[9] During adolescence, platyspondyly with posterior humps of the vertebral bodies, osteoarthritis and other spinal or vertebral abnormalities such as lordosis, kyphosis, scoliosis and spinal nerve abnormalities starts to occur which starts to get worsen with increasing age.[10] It is not a life-threatening condition but affects the quality of life to a very large extent making the patient physically challenged.

The treatment of PPD is always challenging as there is no standard disease specific treatment available. Due to the genetic nature of the disease the treatment depends on the features of the disease and varies through different individuals.[2] The treatment is aimed at reducing maximum amount of physical disability and pain through intense sessions of physical therapy and pain medications respectively. Surgical intervention is usually needed in later parts of life and some major affected joints such as hip and knee are partially or totally replaced via surgery. Immune modulators and other anti-inflammatory drugs do not provide significant beneficial effects and are usually avoided in this condition.[2] Counselling should be done properly in order to decrease the psychological burden of the patient and his family. As it is a recessive genetic condition pre-marital counselling should be done as well in order to prevent this condition from prevailing further in the family.

Conclusion

Pseudorheumatoid skeletal dysplasia is a rare genetic non-inflammatory arthropathy that leads to a wide array of skeletal deformities. It is usually misdiagnosed

by the clinicians as juvenile idiopathic arthritis which changes the dimension of the treatment causing severe inconvenience to the patient and the family. A good clinical assessment along with a complete skeletal survey and genetic analysis would help in diagnosing this condition earlier and without any error. Due to the physical deformities associated with this condition, early rehabilitation and counselling of the patient and the family will yield some fruitful results.

Conflict of Interest: None

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