Open Access

OBM Genetics

LIDSEN Publishing Inc.

Case Report

Progressive Pseudo-Rheumatoid Dysplasia a Rare Genetic Musculoskeletal Condition Causing Crippling Disability in a Young Boy- a Case Report

Sumant Chavda *, Subhranshu Sekhar Kar, Alyaa Kamal Al Ramah

RAK College of Medical Sciences, RAK Medical and Health Sciences University, Ras al Khaimah, UAE;
E-Mails: drsumant.chavda@gmail.com; subhranshu.kar@rakmhsu.ac.ae; alyaaramah@gmail.com

* **Correspondence:** Sumant Chavda; E-Mail: drsumant.chavda@gmail.com

Academic Editor: François Rousseau

OBM Genetics
2023, volume 7, issue 4
doi:10.21926/obm.genet.2304202

Received: July 05, 2023
Accepted: October 23, 2023
Published: October 30, 2023

Abstract

Progressive pseudo-rheumatoid dysplasia (PPRD) is an uncommon genetic condition inherited in an autosomal recessive mode caused by a mutation in the WNT1-inducible signaling pathway protein 3 (WISP3) located on chromosome 6q21. In this condition, the articular cartilage gradually deteriorates, causing severe discomfort, stiffness, and joint deformities with a relatively high prevalence in Middle Eastern countries. Camptodactyly and platyspondyly are the standard features found in this condition. We present a very young boy diagnosed with bilateral hip dysplasia during early childhood and developing increasing pain, stiffness and deformities in the hands, elbow, hips, knee, and ankle. The diagnosis was suspected based on characteristic clinical and radiological features. The diagnosis was confirmed by genetic testing and the absence of elevated serum inflammatory markers. He was born out of a consanguineous marriage, and his parents were unaffected. They are three siblings; his elder sister has a milder condition, while his elder brother is unaffected. There were no adverse events during pregnancy. Birth weight was within normal limits, met all developmental milestones on time, and had no significant past medical history. Compounded by hip dysplasia, he developed a severe disability and had to undergo joint replacement surgery at a very young age. PPRD should be suspected in children from Middle Eastern countries of 3-8 years of age who present with multiple joint pain and stiffness and are born

out of inbred family marriages. Diagnosis can be suspected by the characteristic clinical and radiological features coupled with the absence of raised serum inflammatory markers and confirmed by genetic testing. Genetic counseling and pre-marriage testing are of valuable help in prevention.

Keywords
Progressive pseudo-rheumatoid dysplasia; rare genetic musculoskeletal disorder

1. Introduction

Progressive pseudo-rheumatoid dysplasia (PPRD) and juvenile idiopathic arthritis (JIA) typically affect youngsters between 3 and 8 years and may be confusing. PPRD is an uncommon genetic condition inherited in an autosomal recessive mode. It is caused by a mutation in the WNT1-inducible signaling pathway protein 3 (WISP3) located on chromosome 6q21. The WISP3 gene is essential for cartilage maintenance and bone formation as it regulates the expression of type 2 collagen and aggrecan in chondrocytes [1]. In a patient with PPRD, the articular cartilage gradually deteriorates, causing severe discomfort, stiffness, and joint deformities [2]. Although its incidence is unknown, it is believed to be more prevalent in Turkey and Middle East [3]. The Centre of Arab Genome Studies has reported more than 20 cases from Arab world, though from the United Arab Emirates, no case has yet been reported. The condition is most likely underdiagnosed as it is often misdiagnosed as juvenile idiopathic arthritis. The prevalence of PPRD in the UK has been estimated to be 1 per million [3]. The primary clinical manifestations are polyarticular involvement, fatigability, and gait abnormalities [2]. Over time, they develop permanently bent fingers (camptodactyly) with enlarged interphalangeal joints and arthritic changes in the hip and knee joints with enlargement. A prevalent issue among adolescents is hip pain. They also have flattened, abnormally formed, beaked vertebral bodies (platyspondyly), which causes an abnormal curvature in the spine (kyphosis/scoliosis) and a short torso [4]. At birth, PPRD patients are of average length. However, they are typically shorter than their contemporaries (<3rd centile) [1].

Herein, we present a case of a 14-year-old boy who was earlier diagnosed with hip dysplasia at the age of 4 years and subsequently diagnosed with PPRD with characteristic signs and symptoms development.

2. Case Presentation

The patient is one of the three siblings born to a Yemeni couple (first cousins) whose mothers were sisters. He was diagnosed with bilateral hip dysplasia in early childhood and had a waddling gait. At the age of around four, his father noticed that he had started developing increasing pain and stiffness in small joints, the proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints of both hands and in the hips, causing difficulty while walking that worsened over subsequent years. Within the following year, parents also noticed a decrease in growth velocity. It was detected from the age of 6 from the 50th to the 5th percentile of height. Subsequently, the condition involved his ankle-foot, knees, shoulder and elbow. At eight years of age, he developed increased pain, stiffness, and genu valgum deformity on his left knee, for which he had to undergo corrective proximal tibial

epiphysiodesis surgery. Over the next few years, his pain and stiffness in the hips worsened for which he received non-steroidal anti-inflammatory drugs (NSAIDs- Naproxen 250 mg twice daily), intra-articular injections (Injection Triamcinolone hexanoate-1 mg/kg) and immunosuppressive medication (Injection Methotrexate-15 mg/0.3 ml subcutaneous) without any benefit. His pretreatment and post-treatment laboratory results were nonremarkable. He also could not tolerate these medications and developed gastrointestinal side effects and joint effusion, for which treatment was discontinued. The hip pain became so bad in the following years that it started interfering with his daily activities and sleep. He started avoiding walking and preferred to be in wheelchairs. He had to undergo joint replacement surgery on his right hip at 14. He also developed pain, increasing stiffness, and deformity in the back. The spine showed marked restriction of movements, especially extension. He developed scoliosis and a barrel chest.

There were no problems during pregnancy. However, he was delivered by caesarian section due to breech presentation. Birth weight was within normal limits, and no extended nursing stay was required. He met all developmental milestones on time and had no significant past medical history. One of the elder sister has a similar condition but with less severe manifestations. Both parents are normal and healthy, and there is no family history of known hereditary diseases. The laboratory results like Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Rheumatoid factor (RF), and antinuclear antibodies (ANA) are all negative and are not suggestive of inflammatory arthritis. Genetic diagnosis was established by Whole Exome Sequencing (WES) and homozygosity mapping. The patient is found to be homozygous for c.707delG in the WISP3 gene and heterozygous for c.2230 G>T in the MEFV gene. Both parents are heterozygous for c.707delG and c.2230 G>T. The affected sister is homozygous for both c.707delG and c.2230 G>T, and the healthy brother doesn't harbor the variant in the WISP3 gene and MEFV gene.

The clinical profile (Figure 1) at age 14 shows a height of 147 cm. and weight of 56 kg. BMI is 25.9, and arm span 147 cm. His size falls to the 3rd percentile at his 14 years of age. Hand examination shows a thickened wrist, PIPs, and DIPS with flexion contractures and limited flexions of the fingers; however, there is no marked tenderness over small joints and wrists. Both elbows have mild flexion contracture with little extension. Shoulders have limited abduction up to 100 degrees. After hip replacement surgery, the movements of the right hip have improved. His knees have mild genu varum and flexion contracture with limited flexion terminally. Ankles are thickened on the dorsal aspect with mild limitation of plantar flexion. Spline flexion is limited by pain.

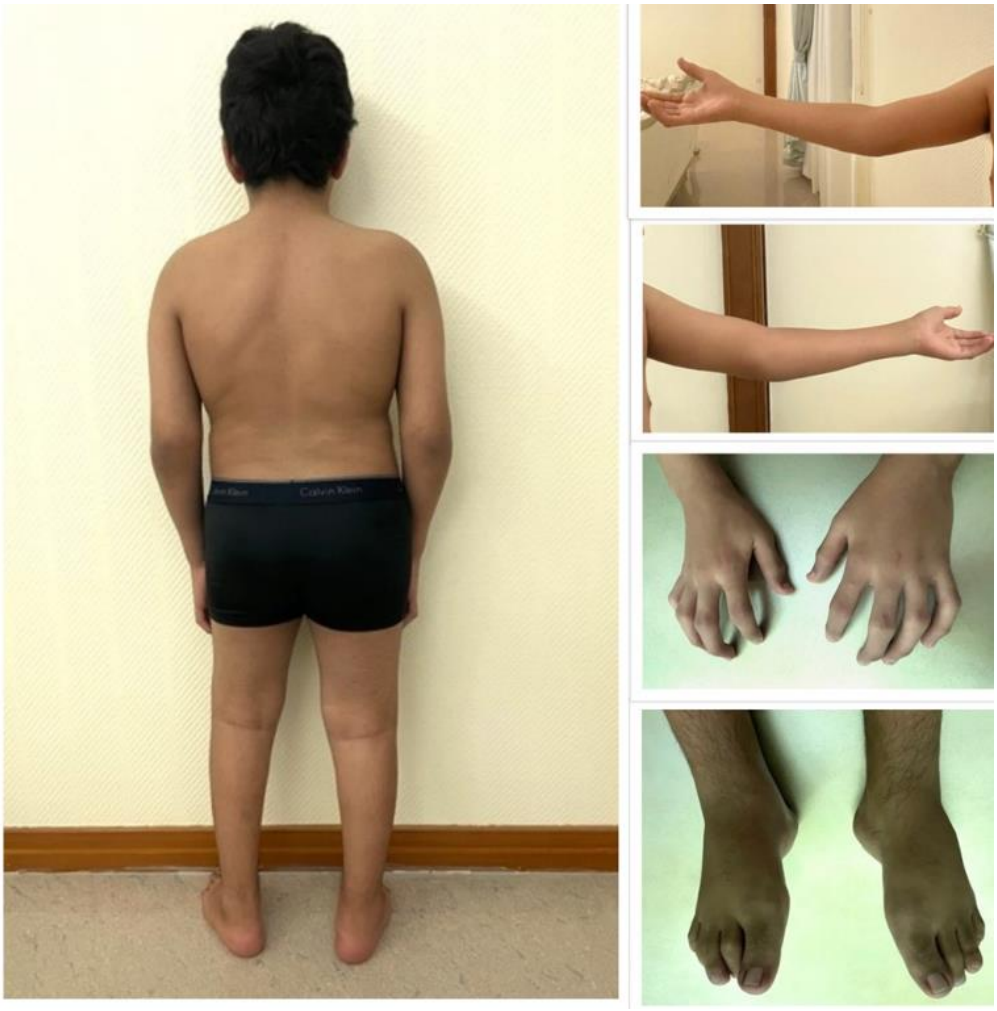

Figure 1 Clinical profile of patient.

Plain radiographic evaluation of both hips at seven showed dysplastic changes with bilateral coxa valga, widened epiphyses, and irregular acetabular roof (Figure 2).

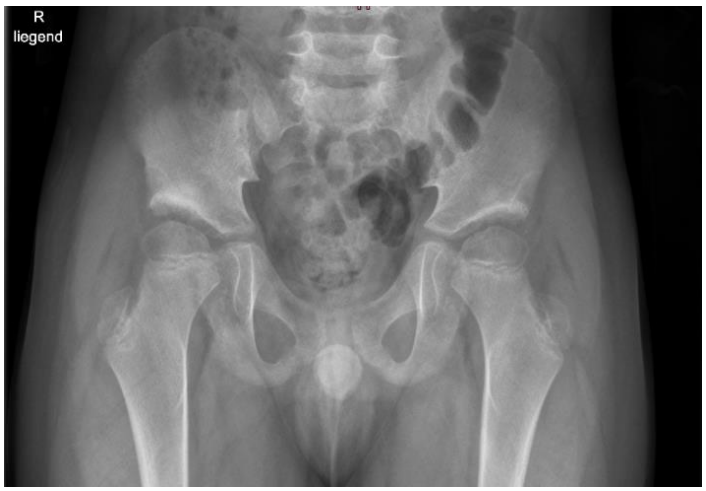

Figure 2 Plain x-ray of both hips AP view at the age of seven.

At 13, both hips showed a wide neck, enlarged and flat epiphyses, loss of joint space, irregular acetabular roofs, and osteopenic bones. He had to undergo total hip arthroplasty of the right hip due to severe arthritis (Figure 3).

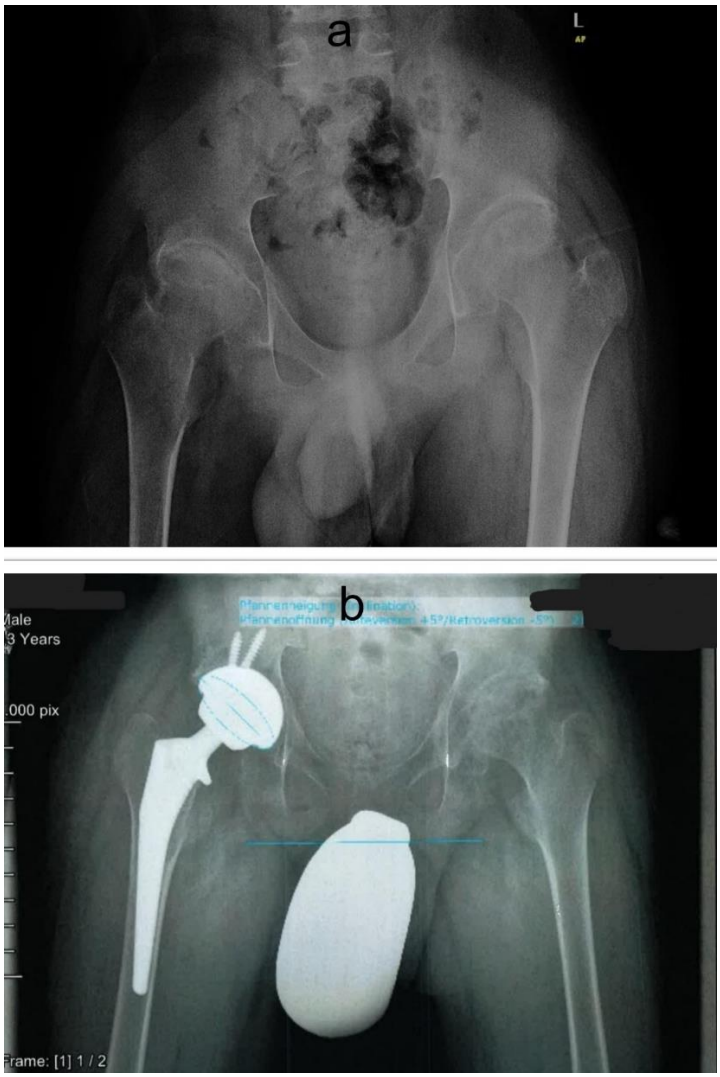

Figure 3 Plain x-ray of both hips AP, preoperative and postoperative at thirteen.

The x-rays of both hands show typical changes of PPRD, enlarged epiphyses, widened metaphyses, and narrow joint spaces in the metacarpophalangeal and interphalangeal joints with flexion deformity (Figure 4).

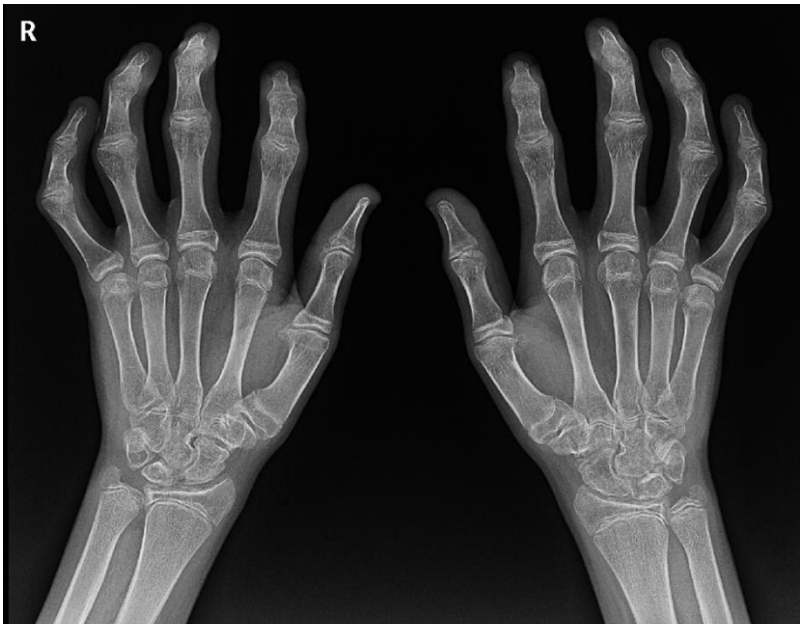

Figure 4 Plain x-ray of both hands PA view at the age of fourteen.

The x-rays of the lumbar spine AP and lateral show scoliosis and platyspondyly. There is an anterior wedging in vertebral bodies; some appear bullet-shaped (Figure 5).

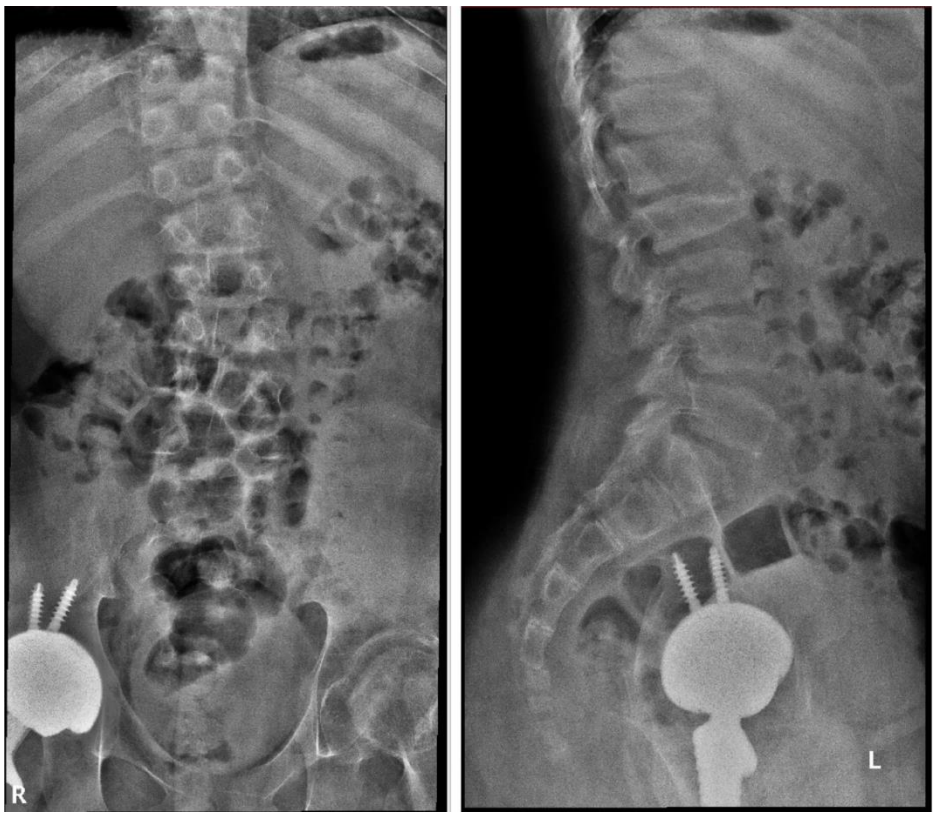

Figure 5 Plain x-ray of lumbosacral spine AP and lateral view.

The x-ray of ankles shows narrowed joint space, enlarged metaphyses, and diffuse osteopenia(Figure 6).

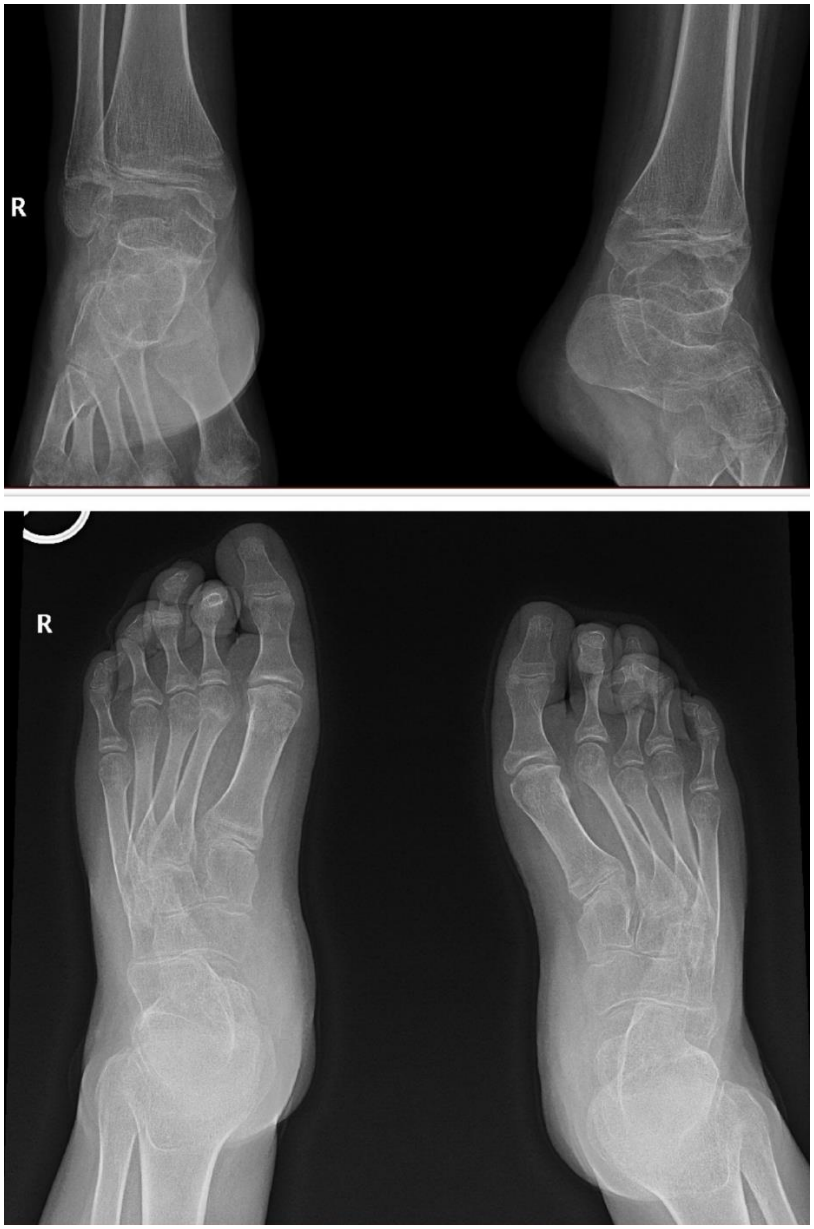

Figure 6 Plain x-ray of both ankle AP and foot PA view.

3. Discussion

A rare genetic disorder known as progressive pseudo-rheumatoid dysplasia, also described as spondyloepiphyseal dysplasia tarda with progressive arthropathy or progressive pseudo-rheumatoid arthropathy of childhood, is acquired via the autosomal recessive mode of inheritance [5]. It results from mutations in the WISP3 gene, crucial for type II collagen and aggrecan production in chondrocytes and preserving cartilage integrity [1]. Due to joint pain and stiffness, the condition can be mistaken for juvenile rheumatoid arthritis and does not show symptoms in early childhood.

This condition is thought to have increased prevalence among Middle Eastern countries such as Kuwait, Bahrain, Oman, Iran, Iraq, Turkey, Yemen, and Saudi Arabia. The parents of the patient are from Yemen. In populations with a high percentage of consanguinity, the time between the start of symptoms and diagnosis is shorter, raising the possibility of hereditary illnesses [4]. This patient was born from a consanguineous marriage. His parents are cousins. None of his parents suffers from the

disease. However, two out of three children have exhibited symptoms. His elder sister is suffering from a similar illness but in a milder form.

As it is described in the published literature, the condition usually manifests between the ages of 3 and 8 years. This boy developed symptoms of increasing pain and stiffness in both hands and hips at age 4 that gradually worsened. Some initial clinical signs are progressive joint stiffness and enlarged interphalangeal joints in the hands. Still, in contrast to JIA, the discomfort is modest given the severity of the arthropathy, and the swelling has a bony consistency. Another differentiating feature is the absence of elevated inflammatory markers, negative rheumatoid factor, and antinuclear antibody that was observed in this patient. Although NSAIDs may help ease pain, swelling, and stiffness of the involved joints, it does not stop the deterioration of articular cartilage [2]. This was witnessed in this patient as he gradually deteriorated his joints. Over time, progressive bony alterations result in more severe deterioration of joint function, development of permanent deformities, and gait abnormalities. This patient's hip functions, especially on the right side, deteriorated rapidly within seven years, and underwent joint replacement surgery at 14. He has developed flexion contractures in the knees, elbow, and hands. Camptodactyly and platyspondyly are characteristic findings that become evident later in the disease [6]. Camptodactyly results from the severe stiffness of the interphalangeal joints and enlargement of epiphysis. At the same time, platyspondyly is caused by irregular ossification in vertebral endplates, leading to reduced distance between the vertebral end plates that can cause spine deformity such as kyphoscoliosis. This patient has developed Camptodactyly and kyphoscoliosis. PPRD does not show involvement of systems other than musculoskeletal and does not affect cognitive function [1]. This patient's cognitive function is normal, and he has good intellectual capacity.

The plain x-ray is the first line of radiological imaging tool in PPRD [7]. Generalized arthropathy, unique deformity of the hands, flattened vertebral bodies, and diffuse osteoporosis at a later stage are the characteristic radiological features seen in PPRD [4, 8]. The typical findings in hands are loss or narrow joint space, wide metaphysis, and enlarged epiphyses in the interphalangeal joints, especially proximal interphalangeal and metacarpophalangeal joints [4, 9]. The characteristic findings in the hips are a short and wide femoral neck, flattened and expanded capital femoral epiphyses, irregular acetabular roofs, and broadened iliac blades [4, 9]. Plain x-rays of the spine show flattened vertebral bodies (platyspondyly) and anterior beaking due to progressive abnormalities in the vertebral endplates' ossification. There is also a loss or narrowing of disc spaces [4, 9]. These changes were observed in this patient. Generalized osteopenia is also a notable feature of this condition that was noticed in this patient. Magnetic resonance imaging (MRI) can be an essential radiological tool to differentiate PPRD from inflammatory joint diseases such as JIA. In patients with PPRD, signs of inflammatory processes such as articular erosions, synovitis, joint effusions, and edema of the surrounding soft tissue will be absent.

The diagnosis of PPRD should be suspected in children aged 3-8 with characteristic clinical and radiographic features from the geographical area that has reportedly had high prevalence, such as in Middle Eastern countries. Identification of biallelic pathogenic mutations in cellular communication network factor 6 (CCN6), formerly called WISP3, by molecular genetic testing will be necessary for the final diagnosis [1]. Depending on the phenotype, molecular genetic testing methods can include gene-targeted testing (single-gene testing, multigene panel) and complete genomic testing (exome sequencing, genome sequencing) [1]. The crucial differentiating feature from JIA is the absence of serum elevation of inflammatory markers.

There is no curative treatment available for PPRD at the moment. The treatment is directed to control pain and to preserve joint function. The pain is mainly due to secondary osteoarthritis that can respond to NSAIDs. However, severe joint pain due to advanced osteoarthritis and deformities will require surgical intervention in joint debridement, corrective osteotomy, or joint replacement. Physical and occupational therapy have an essential role in the treatment. Physiotherapy will help maintain joint mobility and muscle strength. Patients may be advised for activity modification and use of walking aids. Mild kyphosis or scoliosis may be treated with spine bracing.

PPRD is an inherited autosomal recessive genetic disorder. Genetic counseling and pre-marriage testing help prevent such conditions in inbred family marriages. Young adults who are affected, carriers, or at risk of being carriers can be provided with appropriate counseling on potential threats to the offspring and reproductive options [1]. Each sib of an afflicted person has a 25% probability of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier at conception if both parents are known to be heterozygous for a CCN6 pathogenic variation. If both CCN6 pathogenic mutations have been found in an affected family member, carrier testing for at-risk relatives and prenatal testing for pregnancies at greater risk are also options [1].

4. Conclusions

PPRD is a rare genetic disorder. All clinicians, pediatricians, and rheumatologists should suspect all children in the age group between 3 to 8 presenting with multiple joint pain and stiffness, especially of the hands, and who are born out of inbred family marriages and are from countries located in relatively highly prevalent geographical area such as Middle-East. Diagnosis can be established by the characteristic clinical and radiological features coupled with the absence of raised serum inflammatory markers. Genetic counseling and pre-marriage testing are of valuable help in prevention.

Acknowledgments

We sincerely acknowledge the cooperation and consent of parents.

Author Contributions

All authors contribute to the preparation of the manuscript. All authors approved the final version of the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Bhavani GS, Shah H, Shukla A, Dalal A, Girisha KM. Progressive Pseudorheumatoid Dysplasia. GeneReviews. Seattle, WA, US: University of Washington; 1993.
2. Maatallah K, Boussaa H, Lassoued Ferjani H, Kaffel D, Hamdi W. Progressive pseudorheumatoid dysplasia: A rare entity mimicking juvenile idiopathic arthritis. Clin Case Rep. 2021; 9: e04670.

3. Giray E, Yağcı İ, Elçioğlu HN. Progressive pseudorheumotoid dysplasia: A presentation of four cases with slow and rapid progression and effects of early rehabilitation program. Turk J Phys Med Rehabil. 2019; 65: 290-297.
4. Garcia Segarra N, Mittaz L, Campos Xavier AB, Bartels CF, Tuysuz B, Alanay Y, et al. The diagnostic challenge of progressive pseudorheumatoid dysplasia (PPRD): A review of clinical features, radiographic features, and WISP3 mutations in 63 affected individuals. Am J Med Genet Part C Semin Med Genet. 2012; 160: 217-229.
5. Wynne Davies R, Hall C, Ansell BM. Spondylo-epiphysial dysplasia tarda with progressive arthropathy - A "new" disorder of autosomal recessive inheritance. J Bone Joint Surg Br. 1982; 64: 442-445.
6. Torreggiani S, Torcoletti M, Campos Xavier B, Baldo F, Agostoni C, Superti Furga A, et al. Progressive pseudorheumatoid dysplasia: A rare childhood disease. Rheumatol Int. 2019; 39: 441-452.
7. Pomeranz CB, Reid JR. Progressive pseudorheumatoid dysplasia: A report of three cases and a review of radiographic and magnetic resonance imaging findings. Skeletal Radiol. 2019; 48: 1323-1328.
8. Ehl S, Uhl M, Berner R, Bonafé L, Superti Furga A, Kirchhoff A. Clinical, radiographic, and genetic diagnosis of progressive pseudorheumatoid dysplasia in a patient with severe polyarthropathy. Rheumatol Int. 2004; 24: 53-56.
9. Dalal A, Bhavani G SL, Togarrati PP, Bierhals T, Nandineni MR, Danda S, et al. Analysis of the *WISP3* gene in Indian families with progressive pseudorheumatoid dysplasia. Am J Med Genet Part A. 2012; 158: 2820-2828.