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CASE REPORT

Progressive pseudorheumatoid dysplasia in an Omani family: a case report

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ABSTRACT

Background: Progressive pseudorheumatoid dysplasia (PPRD) is an inherited autosomal recessive musculoskeletal condition caused by mutations in the Cellular Communication Network Factor 6 (*CCN6*) gene. This causes a variety of clinical features such as short stature, genu varum, etc.

Case Presentation: This study reported cases of three patients from the same family who exhibited the clinical features of PPRD, and the condition was diagnosed through confirmatory genetic testing. The whole exome sequencing test results for the 15-year-old and 3-year-old males revealed a class-5 pathogenic homozygous mutation in the *CCN6* gene, resulting in both individuals being diagnosed with autosomal recessive PPRD. The results for the third patient had not come out yet.

Conclusion: For patients with PPRD, it is necessary to take the full family history and genetic testing that might help in the diagnosis and treatment of the condition.

Keywords: Case report, progressive pseudorheumatoid dysplasia, CCN6, PPRD, Oman.

Introduction

Progressive pseudorheumatoid dysplasia (PPRD) [Online Mendelian Inheritance in Man (OMIM) 208230] is a rare autosomal recessive genetic disorder that affects the articular cartilage, which protects both ends of bones. It involves progressive and non-inflammatory destruction of these cartilages, leading to symptoms such as pain and joint stiffness. PPRD usually starts during childhood after the age of 3 years and before the age of 8 years. Abnormal walking, weakness, fatigue, and joint stiffness are the first signs that can be detected in children. Additionally, camptodactyly, enlargement of finger joints, as well as reduced space between bones at the knee or hip joints, might develop over time due to this condition (1).

It has been estimated that PPRD occurs in about 1 per million people in UK but it appears to be more common in the Middle Eastern countries with no recorded data available on its exact prevalence rate. To diagnose PPRD, physicians use a combination of clinical examinations and investigations such as X-ray imaging along with laboratory tests. The condition could be underdiagnosed since it shares similar features to juvenile rheumatoid arthritis (1).

A mutation in Cellular Communication Network Factor 6 (*CCN6*) gene is responsible for causing PPRD. *CCN6* is a protein-coding gene located in 6q21 (OMIM 603400) (Gene ID 8838) which is produced from chondrocytes, and it is involved in the processes of bone growth and connective tissue maintenance (2). To explain the function of this gene furthermore, it encodes a member of the *WNT1* inducible signaling pathway (WISP) protein subfamily (3), Wnt1-inducible signaling protein 3 (WISP3), which encodes cysteine-rich secreted proteins that have important roles in cell growth and differentiation (4).

This study reported cases of three patients from the same family who exhibited the clinical features of the condition, and the condition was diagnosed through confirmatory genetic testing.

Case Presentation

In this report, we present the cases of three members from an Omani family with specific symptoms of PPRD .

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First case was of a 4-year-old female child (III. 4), who was referred from Khoula Hospital (a well-known orthopedic hospital in Oman) to the genetic clinic in the National Genetic Centre of the Sultanate of Oman for evaluation of genu varum. The child was a term baby with a birth weight of 3 kg. She was born by spontaneous vaginal delivery with a good Appearance, Pulse, Grimace, Activity and Respiration score. The family history was significant as it was consanguineous marriage of the parents and a positive family history with the same presentation in her older brother and one cousin (III.3 and III.5) was noted. The child started to walk when she was 13 months old. At that time, the mother noticed that the child had bowing in both of her legs. She was found to have vitamin D deficiency and was discharged on supplements. The child was further referred to the orthopedics in Khoula hospital for the bowing of her legs. They started the treatment with special shoes that she should wear for a certain period. In September 2022, she underwent surgical correction of her legs. When the child was seen in November 2022, the patient was examined, and the features displayed PPRD (Figure 1).

Second case was of the eldest brother, who was 15 years old (III. 3), and was first presented at the age of 5 years with complaint of flat foot and interphalangeal joint swelling along with bowing of both of his legs. Correction surgery for his legs was done at Khoula Hospital at that time. He was taken to India for treatment and whole exome sequencing (WES) was done for him. The two other siblings were healthy with no symptoms.

The third case was of the 3-year-old male cousin (III. 5) who started to have similar symptoms like the previous family members such as interphalangeal joint swelling and bowing of the legs at the age of 2 years. His family history is significant for consanguineous marriage, and he has only one older sister, who was healthy without any symptoms (Figure 2).

The WES test results for the 15-year-old and 3-year-old males revealed a class 5 pathogenic homozygous

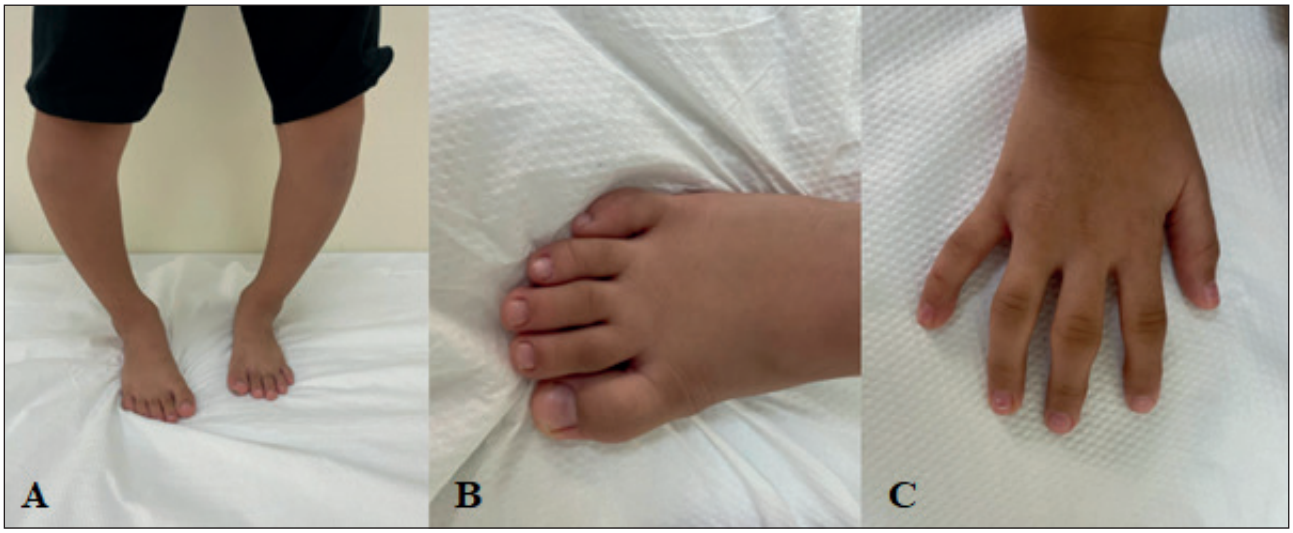

Figure 1. *This figure displays the features of PPRD. A: genu varum; B and C: interphalangeal swelling in the toes and fingers.*

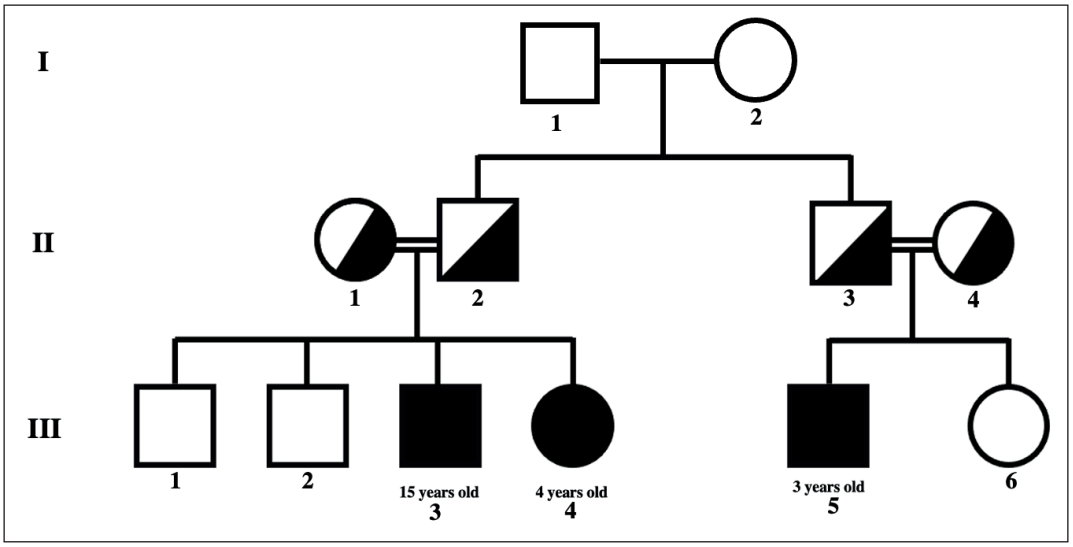

Figure 2. *This family pedigree chart of the whole family showing the affected patients.*

mutation in the *CCN6* gene, resulting in both individuals being diagnosed with autosomal recessive PPRD. In a molecular study, investigations of the patient's brother and first cousin showed similar mutation variants c.922_923del, p.(Ser308Leufs*12) which causes a shift in the reading frame starting at codon 308. The new reading frame ends in a stop codon 11 positions downstream, known to cause PPRD.

In addition, it was mentioned that PPRD presents as spondyloepiphyseal dysplasia tarda with progressive arthropathy and is described as a specific autosomal recessive subtype of spondyloepiphyseal dysplasia (SED). In addition, most patients would start showing symptoms before the age of 8 years and the symptoms would not appear in infancy. Bowing of the legs, muscle weakness, symmetric swelling of the proximal interphalangeal joints, motion range limitation, deformities, and progressive pain are the most common symptoms of PPRD. Some patients could develop some spinal manifestations like exaggerated lumbar lordosis, thoracic kyphosis, and scoliosis. However, extra-skeletal manifestations are usually not present in those patients, and they exhibit completely normal facial appearance and normal intelligence.

The 4-year-old female child presented in this case report is not diagnosed yet, the target mutation test for the CCN6 gene was sent and the results have not been out yet.

Discussion

PPRD is a rare genetic and skeletal disease affecting children. It was first described by Spranger et al. (5) as a progressive chondropathy, which mostly affects the articular cartilages and results in specific skeletal abnormalities.

In 2000, Mampaey et al. (6) reported a case of PPRD that involved spinal and articular features which were initially interpreted as juvenile rheumatoid arthritis and Scheuermann's disease but later excluded. In 2007, three cases of PPRD were reported in Morocco from the same family by Bennani et al. (7). The three reported cases (a 4-year-old girl, a 15-year-old boy and an uncle who was examined at the age of 4 years) had similar articular features. A Chinese study published in 2011 reported seven cases of PPRD from six different unrelated families all presenting with symptoms of PPRD and were diagnosed with the condition according to the clinical signs and symptoms, as well as radiographic imaging (8). In 2017, Sailani et al. (9) reported PPRD due to WISP3 mutation of in four patients from the same family. Alawbathani et al. (10) reported a case in 2017 of a 24-year-old Yemeni gentleman born to consanguineous parents and had features of PPRD (Table 1).

Comparing between the published variants in the previous studies and this study, the patients in this study had c.992_923delAG (p.Ser308Leufs*12) variant which causes a shift in the reading frame starting at codon 308 and was therefore found to cause PPRD. The case of the Yemeni patient reported by Alawbathani et al. (10), had homozygous frame shift mutation in WISP3 in exon 5; c.868_869delAG, p.Ser290Leufs*12, this protein change is a bit like the current study. Sailani et al. (9) found that there are around 71 pathogenic mutations

Table 1. *Comparison of clinical features between this case report and the previously published case reports.*

Study	Joint swelling	Genu varum	Flat foot	Arthritis/ arthralgia	Spinal manifestations (e.g., thoracic kyphosis, increased lumbar lordosis, scoliosis)	Stiffness / flexion contracture	Coxa valga	Short stature	Muscle weakness/ atrophy	Waddling gait or other gait abnormalities
Current study, 2023	X	X	X							X
Mampaey et al., 2000 (6)	X			X		X			X	X
Bennani et al., 2007 (7)	X			X	X	X	X			
Ye et al., 2011 (8)	X	X		X	X	X		X	X	X
Sailani et al., 2017 (9)	X				X	X				X
Alawbathani et al., 2017 (10)	X			X	X	X				X

of WISP3 distributed worldwide. The most common reported variant is c.156C>A (p.Cys52*) variant with 33 reported case distributed in Italy, France, Lebanon, Turkey, Germany, and India. The second most common variant is c.1010G>A (p.Cys337Tyr) with 18 reported cases located in India only (9). Therefore, the specific variant found in this study was not previously reported. This is the first reported case of PPRD in Oman, and this is the first case reported of this specific variant on an international level.

Although there is no standard treatment for PPRD, rehabilitation at an early age is a good approach to prevent disabling consequences. Previous studies showed that early rehabilitation could lead to pain-free walking and mobility in PPRD patients. In addition, surgical interventions such as arthroplasty and osteotomy are necessary in such cases to adjust bowing of the bones. Genetic testing and counseling are essential steps for families with PPRD to raise awareness about the disease and its implications on their lives (7).

Conclusion

PPRD is a life-altering medical condition, which could cause permanent deformity if left untreated, therefore, early diagnosis should always be sought by those who are suffering from any related symptoms associated with it, so they can get a proper treatment plan tailored for them accordingly.

Acknowledgments

National Genetic Centre of the Sultanate of Oman.

List of Abbreviations

CCN6	Cellular Communication Network Factor 6
PPRD	Progressive pseudorheumatoid dysplasia
WES	Whole exome sequencing
WISP3	Wnt1-inducible signaling protein 3

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None.

Declaration of conflicting interests

The authors declare that there is no conflict of interest regarding the publication of this article.

Consent for publication

Informed consent was obtained from the parents of the patient to publish the case and the accompanying images.

Ethical approval

Ethical approval is not required at our institute for an anonymous case report.

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