



Case Report

Progressive pseudorheumatoid dysplasia: A presentation of four cases with slow and rapid progression and effects of early rehabilitation program

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ABSTRACT

Progressive pseudorheumatoid dysplasia (PPD) is a rare hereditary musculoskeletal disorder which is usually misdiagnosed due to its clinical resemblance to juvenile idiopathic arthritis. It has a high incidence in the Middle East, Gulf States, and countries of Mediterranean basin. Herein, we present four cases of PPD from Turkey (two siblings pair from the same kindred who are far paternal cousins) showing different disease courses. The progression of disease was particularly aggressive in the male sibling who suffered from severe scoliosis with more crippling joint disease. These four cases of PPD support the clinical heterogeneity and variable expressivity of PPD. In this article, we draw attention to the effects of patient education and early rehabilitation which helped to slow progression of range of motion loss.

Keywords: Juvenile idiopathic arthritis; progressive arthropathy; progressive pseudorheumatoid dysplasia.

Progressive pseudorheumatoid dysplasia (PPD, MIM 208230) is a rare, autosomal recessively inherited, non-inflammatory musculoskeletal disorder caused by mutations occurring in the WISP3 (Wnt1-inducible signaling pathway protein 3; MIM603400) on chromosome 6q21.^[1,2] The WISP3 encodes the WNT1-inducible signaling pathway protein 3 which plays a major role in cartilage homeostasis by regulating proliferation and differentiation of chondrocytes. Therefore, it is crucial for bone formation and maintaining cartilage.^[1,3,4] Joint cartilage is the primary site of involvement, leading to main clinical features of the disease arthralgia, joint stiffness, contractures, enlargement of the epiphyses and metaphysis of the hand joints, spinal abnormalities, short stature, early osteoarthritis, and osteoporosis.^[3,5-7] The clinical features are reminiscent of juvenile idiopathic arthritis (JIA), and patients with PPD are usually misdiagnosed as JIA. In addition, different types of WISP3 mutations may have an impact on clinical features. Different types

of WISP3 mutations may lead to atypical presentations, such as different disease progression rates and severity.

The prevalence of PPD is 1/1,000,000 in the United Kingdom (UK).^[8] Despite the low prevalence in the UK, it is more common in the Middle East, Gulf States, Arabic countries, and countries of the Mediterranean basin.^[3,9,10] To date, to the best of our knowledge, 15 case reports from Turkey have been published.^[2-6,10-18] Herein, we present four cases of PPD (two sisters and their two second cousins) in two related families from Turkey, one of them showing more progressive and severe disease course to draw attention to the different types of disease course and effects of early rehabilitation program on disease course.

CASE REPORT

Case 1- A 23-year-old female patient was referred to our rheumatology outpatient clinic with complaints of arthralgia, knobby fingers, joint stiffness, and

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limitations and hobbling gait, when she was 12 years old. The patients' complaints started when she was six years old. The initial signs were joint pain, waddling gait, and difficulty in walking. She was previously misdiagnosed as JIA at different health centers and started on antirheumatic therapy with prednisolone 5 mg a day and methotrexate 10 mg weekly. However, she was unresponsive to these drugs and initiated treatment with subcutaneous etanercept injections, 50 mg once a week. However, her health status

worsened and previous medications were discontinued. Meanwhile, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor, and antinuclear antibody were within normal ranges. She had no signs or symptoms of inflammatory arthritis such as redness, heat, effusion, or soft tissue swelling. She had short stature which was also erroneously thought to be due to growth retardation seen in JIA (Table 1). Upon examination, we found decreased range of motion (ROM) of the hip, ankle, knee, and

Table 1. Comparison of juvenile idiopathic arthritis and progressive pseudorheumatoid dysplasia in terms of main clinical, laboratory and radiologic features^[10,18]

Clinical, laboratory and radiologic features	JIA	PPD
Limitation in ROM	+	+
Arthralgia	+	+
Painful joints	+	+
Joint swelling	+	+
Red joints	+	-
Symmetric joint involvement	+/-	+
Joint contractures	+	+
Growth retardation in childhood	+	-
Growth retardation in adolescence	+	+
Age of onset (year)	1-3 and 8-10 *	3-8
Iridocyclitis	+	-
Hepatosplenomegaly	+	-
Lymphadenopathy	+	-
Anemia	+	-
Leukocytosis	+	-
Thrombocytosis	+	-
Erythrocyte sedimentation rate elevation	+	- **
ANA, CRP, RF	+	- **
Being product of a consanguineous marriage	Uncommon	+
Similar symptoms emerging in relatives	Uncommon	+
Low body mineral density	+	+
Bone X-ray findings		
Soft tissue swelling	+	-
Bony erosions	+	-
Narrow articular space	+	+
Ankylosis	+	+
Abnormal acetabulum***	-	+
Platyspondyly	-	+
Scoliosis	+/-	+
Kyphosis	+/-	+
Anterior ossification defects in vertebrae	-	+
Spondyloepiphyseal dysplasia	-	+

JIA: Juvenile idiopathic arthritis; PPD: Progressive pseudorheumatoid dysplasia; ROM: Range of motion; ANA: Anti-nuclear antibody; CRP: C-reactive protein; RF: Rheumatoid factor; * The peak incidence of JIA occurred at one to three years. A second, less prominent peak was noted between ages 8 and 10 years; this peak included more boys with oligoarticular JIA.^[30] ** Mild increase may occur due to inflammation due to secondary osteoporosis but usually erythrocyte sedimentation rate is in normal limits with negative CRP.^[13] *** Narrowed joint space, epiphyseal dysplasia, wide and flattened epiphysis and irregular acetabulum.^[10]

Table 2. Comparison of features of the cases

Clinical, laboratory and radiologic features	Case 1	Case 2	Case 3	Case 4
Arthralgia	+	+	+	+
Painful joints	+	+	+	+
Joint swelling	+	+	+	+
Scoliosis	+	-	+	-
Growth retardation in childhood	-	-	-	-
Growth retardation in adolescence	+		+	
Age of onset (years)	6	3	1	6
Low body mineral density	+	+	+	+
Joint contractures	++	+	++++	++
ROM (Right/left)				
Shoulder				
Flexion	160/150	180/180	150/150	170/170
Extension	45/45	80/80	50/45	70/70
External rotation	45/70	90/70	80/60	80/80
Internal rotation	45/70	90/70	20/70	80/60
Abduction	160/100	180/180	90/150	180/180
Adduction	40/40	45/45	45/45	45/45
Elbow				
Flexion	110/120	170/170	90/90	160/160
Extension	-30/-40	+10/+10	-30/-45	0/0
Pronation	-20/90	90/90	10/10	90/90
Supination	-30/-30	90/90	90/30	90/90
Wrist				
Flexion	65/65	90/90	70/70	80/80
Dorsiflexion	0/0	30/30	-5/-30	60/80
Radial deviation	3/3	40/40	0/0	10/5
Ulnar deviation	3/3	30/30	0/0	30/30
Thumb				
CMC				
Flexion	10/5	15/15	30/10	15/15
Extension	-5/0	15/15	0/30	15/15
MCP				
Flexion	45/60	40/40	90/70	40/40
Extension	0/0	0/0	0/0	0/0
DIP				
Flexion	10/10	60/60	40/40	60/60
Extension	0/0	0/0	0/0	0/0
2nd finger				
MCP				
Flexion	80/80	60/60	80/70	60/60
Extension	20/30	0/0	0/20	0/0
PIP				
Flexion	100/90	60/60	120/100	60/60
Extension	-30/-10	0/0	-30/-30	0/0
DIP				
Flexion	60/40	60/60	50/50	60/60
Extension	-30/-10	-10/-10	-40/-40	0/0
3rd finger				
MCP				
Flexion	90/90	60/60	120/90	60/60
Extension	30/30	0/0	0/10	0/0
PIP				
Flexion	120/90	60/60	120/90	60/60
Extension	-30/-30	-5/0	-30/-30	0/0

ROM: Range of motion; CMC: Carpometacarpal; MCP: Metacarpophalangeal; DIP: Distal interphalangeal; PIP: Proximal interphalangeal.

Table 2. Continue

Clinical, laboratory and radiologic features	Case 1	Case 2	Case 3	Case 4
DIP				
Flexion	50/60	60/60	80/60	60/60
Extension	-20/-10	-10/-10	-10/-30	0/0
4th finger				
MCP				
Flexion	100/100	60/60	120/100	60/60
Extension	30/35	0/0	0/20	0/0
PIP				
Flexion	100/100	60/60	120/100	60/60
Extension	-20/-40	-5/0	-45/-40	0/0
DIP				
Flexion	20/-10	60/60	50/60	60/60
Extension	45/-20	-10/-10	-40/-40	0/0
5th finger				
MCP				
Flexion	110/110	60/60	130/110	60/60
Extension	40/45	0/0	0/20	0/0
PIP				
Flexion	90/110	60/60	110/120	60/60
Extension	-10/-20	0/-10	-30/-10	0/0
DIP				
Flexion	30/80	60/60	50/70	60/60
Extension	-10/-20	0/0	-40/-10	0/0
Hip				
Flexion	90/90	160/160	150/150	160/160
Extension	30/30	30/30	-45/-45	20/20
External rotation	0/0	60/60	30/30	60/60
Internal rotation	30/30	60/60	10/10	45/45
Knee				
Flexion	160/160	160/160	160/160	160/160
Extension	-45/-45	0/0	-60/45	0/0
Ankle				
Plantar flexion	10/10	20/10	10/10	30/30
Dorsiflexion	5/5	70/45	20/30	50/50

ROM: Range of motion; CMC: Carpometacarpal; MCP: Metacarpophalangeal; DIP: Distal interphalangeal; PIP: Proximal interphalangeal.

shoulder. Flexion contractures and widening of the interphalangeal joints were also noticed. She was diagnosed with PPD based on genetic testing, and treatment with non-steroidal anti-inflammatory drugs (NSAIDs) was initiated. The patient was admitted to our inpatient rehabilitation clinic for pain relief and improvement of mobility and daily functions with physical therapy and rehabilitation. Transcutaneous electric stimulation and hot pack were applied for pain control and the ease of performing exercises. The ROM stretching and strengthening exercises were also instructed. She was discharged from the hospital after a prescription of home-based exercise and education program. She underwent physical therapy and rehabilitation program several times during follow-up. During inpatient rehabilitation,

improvements in the ROM of the hip, knee, and elbow with variable degrees were achieved. During follow-up with NSAIDs and home-based exercise program, low bone mineral density (BMD) was detected, when she was 18 years old. Her little sister showed waddling gate and swollen interphalangeal joints and limitation of the right ankle at the age of three. They were products of a consanguineous marriage; their parents were healthy and first cousins. Homozygous mutation c[727-731delGAGAA] was identified on the WISP3 gene through molecular genetic analysis which was compatible with PPD in both sisters.^[19] After she fell in the bathroom and had a distal fibula fracture, BMD was measured using dual X-ray absorptiometry (DXA). Lumbar vertebrae showed a Z-score of -3. She had a long bone fracture with a BMD Z-score of <-2,



Figure 1. Typical hand appearance of Case 2.



Figure 2. Vertebral deformity of Case 3.

fulfilling the criteria for a diagnosis of osteoporosis in the pediatric age range and started bisphosphonate.^[20]

Case 2- A three-year-old girl, younger sister of Case 1 was admitted to our rheumatology outpatient clinic with difficulty in climbing up and down the stair. Physical examination findings were completely normal. Her mother was suspicious of occurrence of the same illness which her elder sister was suffering from due to similar initial symptoms. The patient was referred to the genetics and the same mutation as her older sister was detected. After one year, the patients' ROM started to decrease and typical finger appearance of PPD started (Figure 1). She had mild limitation of ROM of the left ankle and 2nd, 3rd, and 4th distal interphalangeal joints. She was initiated treatment with NSAIDs, physical therapy, and rehabilitation program. She was admitted to the Pediatric Rehabilitation Treatment Unit and superficial heat (hot pack), electrotherapy (transcutaneous electrical nerve stimulation) and ROM stretching and strength exercises were applied to maintain and to increase the muscle strength and ROM.

The third and fourth cases are two brothers who are paternal cousins of Case 1 and 2.

Case 3- A 17-year-old male (elder brother of Case 4) was examined as part of the family study of

Case 1, and the same mutation on the WISP3 gene was detected through molecular genetic analysis. He was the second cousin of Case 1. On his medical history, knobbles on the finger joints were noticed, when he was 10 months old. He became able to walk at the age of 18 months, although he had a waddling gait pattern. He had more crippling joint disease, he was only able to be ambulated with bilateral crutches, since he was 12 years old. He had a history of severe progressive deterioration of spinal deformity and ROM of shoulder, elbow, wrist, hip, knee, and ankle joints over time. He was also previously diagnosed with JIA at different outpatient clinics; however, he refused to use antirheumatic drugs, as he believed that these drugs did not help Case 1.

He was a slender man of short stature. Anteroposterior and lateral spine radiographs revealed a scoliosis deformity with a Cobb angle of 17 degrees and kyphosis of 46 degrees (Figure 2). He complained about dyspnea. Also, severe contractures in the hip joints were found. The patient needed several surgical interventions, including vertebral deformity correction and hip arthroplasty. The patient was referred to orthopedic surgeons for surgical management.

Case 4- A six-year-old boy who had a normal growth rate was admitted to the rheumatology outpatient clinic, due to similar symptoms as in his elder brother,

Case 3. He complained about difficulty in standing up from a sitting or squatting position. He was also previously diagnosed with JIA. However, he was not given any medication, except NSAIDs. Since Case 4 showed identical symptoms with his brother, Case 3, he was evaluated as a part of family study to determine any hereditary condition. Molecular analysis revealed the same homozygous mutation c[727-731delGAGAA] on the WISP3 gene.

DISCUSSION

Progressive pseudoreumotoid dysplasia usually begins with the involvement of interphalangeal joints or gait disturbances. Involvement of the large joints and spine may, in turn, cause severe joint contractures, gait impairment, and spinal deformities. Over time, patients with PPD experience continued cartilage loss and destructive bony changes, as assessed both clinically and radiographically. Although the initial growth rate is normal, short torso becomes evident during adolescence which is a period of rapid skeletal growth.^[1-5,9-18,21]

These four cases had common and separate aspects. In the literature, age of onset of the disease ranges between 3 and 8 years.^[2,5] In previously reported cases from Turkey, age of onset was 3 to 8 years.^[2-6,10-18] In our cases, age of onset of symptoms also varied. Disease manifestations started earlier than the others in Case 3. Before deformities were noticed, complaints about difficulty in particularly standing up from the seated position was the first emerging symptom of the disease. In addition, the time of diagnosis is often second decade. However, Cefle et al.^[5] reported a case of PPD who was diagnosed in the fifth decade.

In the present cases, the hand appearance at the time of presentation to physicians was the main reason for the misdiagnosis. The loss of ROM was progressing over time. However, the rate of progression varied among the cases. Case 1 and Case 3 were at similar ages, although deterioration of the joints and spine was more evident in Case 3. Also, Case 1 received education regarding joint protection and rehabilitation managements earlier and regular than that of Case 3. Case 1 had more hospital access than Case 3 and Case 4 who were living in the rural part of Turkey, and they were more likely to have to travel long distances to access healthcare services. During follow-up, limitations of the ROM of joints did not progress in Case 1 as much as in Case 3, who was her younger cousin. Among the four cousins, Case 3 had the worst clinical picture (Figure 1); he had a more

crippling joint disease with severe scoliosis which progressively worsened.

Spinal involvement is widely demonstrated in patients with PPD. Irregularity of vertebral endplates, narrowing of the intervertebral space, short pedicles leading to short torso and short trunk usually starting in late childhood and adolescence are common.^[5,22] Although there are a few reports on scoliosis in patients with PPD, severe scoliosis was seen less common, particularly at younger ages.^[9,10,13,21-26] Recently, Montané et al.^[22] reported a case of PPD with early severe scoliosis. The progression of disease was particularly aggressive in a male patient who was suffering from severe scoliosis which was unusual as in Case 3 we reported. A novel compound heterozygous mutation in the WISP3 exon 2 (p.[(Gly64Arg)];[(Ser66Asn)]) was identified in mutation screening which was undertaken in the two siblings. In the present cases, a known homozygous mutation (c[727-731delGAGAA]) was identified on the WISP3 gene through molecular genetic analysis.

Those different types of disease courses in our cases can be presumably explained by variable expressivity. The range of phenotypic expression is called expressivity which measures the extent to which a given genotype is expressed at the phenotypic level.^[24] Although some genetic disorders exhibit little variations, most have signs and symptoms that differ among affected individuals. Variable expressivity can be described as the range of signs and symptoms which can occur in each individual with the same genetic condition. Although the features differ among affected individuals, most patients with this disorder share a common mutation in the same gene. Variable expressivity is probably caused by a combination of genetic, epigenetic, environmental, and lifestyle factors, most of which have not been identified, yet.^[4]

Radiological criteria for PPD include metaphyseal enlargement of the interphalangeal joints, reduced articular space with large dysplastic epiphyses of the hip and knee, platyspondyly with anterior beaking of vertebral bodies, absence of articular bone erosion, and generalized osteopenia starting during adolescence.^[19] Osteoporosis was also less mentioned in the previous reports of PPD cases. There are few reports of localized or diffuse osteoporosis.^[1,3,9,11,12,14-16,23,26-28] Reported osteopenia or osteoporosis are commonly periarticular and noticed on radiographs in all four present cases. The Wnt pathway is found to be associated with BMD variation.^[29] Low BMD was detected in all four present cases. Osteoporosis may be direct result of disease

itself, and also it is caused by immobilization due to joint contractures.^[5]

As mentioned previously, PPD is an autosomal recessively inherited disorder. Parents of the both siblings in our cases were consanguineous, which increases the chance of having autosomal recessive diseases. Previously reported patients from Turkey were all also offspring of a consanguineous marriage. Usually, most of the previously reported patients with PPD both from Turkey and other countries are formerly misdiagnosed with JIA as in our cases.^[3,11-14,16-18,25,27] Except Case 2, all cases were also misdiagnosed as JIA. Nonetheless, PPD and JIA exhibit common and different features. For instance, age of onset is similar for both PPD and JIA. Arthralgia, painful joints, joint swelling, symmetrical involvement and limitation in ROM are both can be seen in PPD and JIA. However, patients with PPD do not show red joints, elevated ESR or CRP. Despite this difference, short torso and growth retardation in adolescence are common in both. However, patients with PPD usually do not show growth retardation and short torso in childhood. Therefore, we strongly recommend reconsideration of diagnosis of JIA, if (i) the signs of inflammatory arthritis are not noticed by physicians; (ii) a patient is a product of a consanguineous marriage and occurrence of same symptoms in another relative; (iii) laboratory studies reveal normal values; and (iv) the condition of the patient worsens, despite antirheumatic therapy.^[6,13] Other rare diagnosis which may erroneously be made are Blount disease, Scheuermann's disease, Stickler syndrome, and mucopolysaccharidosis.^[3,15,16,18] Batmaz et al.^[7] reported a case of PPD mimicking spondyloarthropathy due to back and buttock pain, morning stiffness, osteopenia, and suspected sacroiliitis (sclerosis and narrowed joint space) on anteroposterior radiography of the pelvis.

These disorders should be kept in mind in the differential diagnosis to avoid using unnecessary therapies. Therefore, rehabilitation can be started earlier, before the deformities progress leading to less disability as in Case 1. Pain-free walking distance and mobility has been reported to increase with early rehabilitation.^[2,10] There is no standard treatment for PPD.^[16] Pain relief, rehabilitation, and surgical interventions such as osteotomy and arthroplasty, when necessary, are the mainstay of treatment.^[16,30] The strength of these case presentations is showing clinical heterogeneity of PPD and utility of early patient education and rehabilitative management, although the lack of screening for novel mutations can

be viewed as a limitation. If novel mutations related to disease progression rate can be detected in the WISP3 gene, it may help to aid clinical care and to provide genetic counselling to families.^[22]

In conclusion, these four cases of PPD support the clinical heterogeneity and variable expressivity of PPD. Early rehabilitation program may help to slow the progression rate of the ROM loss.

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