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REVIEW

Progressive pseudorheumatoid dysplasia: a rare childhood disease

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Abstract

Progressive pseudorheumatoid dysplasia (PPRD) is a genetic bone disorder characterised by the progressive degeneration of articular cartilage that leads to pain, stiffness and joint enlargement. As PPRD is a rare disease, available literature is mainly represented by single case reports and only a few larger case series. Our aim is to review the literature concerning clinical, laboratory and radiological features of PPRD. PPRD is due to a mutation in Wnt1-inducible signalling protein 3 (*WISP3*) gene, which encodes a signalling factor involved in cartilage homeostasis. The disease onset in childhood and skeletal changes progresses over time leading to significant disability. PPRD is a rare condition that should be suspected if a child develops symmetrical polyarticular involvement without systemic inflammation, knobbly interphalangeal joints of the hands, and gait abnormalities. A full skeletal survey, or at least a lateral radiograph of the spine, can direct towards a correct diagnosis that can be confirmed molecularly. More than 70 *WISP3* mutations have so far been reported. Genetic testing should start with the study of genomic DNA extracted from blood leucocytes, but intronic mutations in *WISP3* causing splicing aberrations can only be detected by analysing *WISP3* mRNA, which can be extracted from cultured skin fibroblasts. A skin biopsy is, therefore, indicated in patients with typical PPRD findings and negative mutation screening of genomic DNA.

Keywords Progressive pseudorheumatoid dysplasia · Progressive pseudorheumatoid arthropathy of childhood · Spondyloepiphyseal dysplasia tarda with progressive arthropathy · Juvenile idiopathic arthritis

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Introduction

First described in 1982 [1], progressive pseudorheumatoid dysplasia (PPRD, also known as spondyloepiphyseal dysplasia tarda with progressive arthropathy) is a genetic skeletal disorder with autosomal recessive inheritance that was listed in groups 13 and 31 of the 2011 Classification of Genetic Skeletal Disorders [2]. It is a rare disease whose estimated incidence is 1/1,000,000 in the UK [1], but apparently higher in the Middle East and Gulf States, Turkey, India and other endogamic communities [3–7]. Only a few cases have been described in Latin America [8, 9]. PPRD is caused by bi-allelic loss-of-function mutations in the Wnt1-inducible signalling protein 3 (*WISP3*) gene, which maps to chromosome 6q22 [10]. WISP3 is a growth factor involved in cartilage homeostasis and bone growth by promoting type II collagen and aggrecan expression and regulating chondrocyte proliferation and differentiation; more than 70 *WISP3* mutations have so far been reported.

PPRD usually presents between the ages of 3 and 6 years, and is characterised by polyarticular involvement, gait

abnormalities and fatigability. The skeletal changes progress with age and are responsible for short adult stature, kyphoscoliosis, joint contractures, hip disease and camptodactyly [11].

Search strategy

A systematic search of publications in the electronic databases PubMed and Scopus was conducted from inception to January 2018, according to published guidance on narrative reviews [12], using the search terms "progressive pseudorheumatoid dysplasia" OR "SEDT-PA" OR "progressive pseudorheumatoid arthropathy of childhood" OR "spondyloepiphyseal dysplasia tarda with progressive arthropathy". Seventy-nine articles were identified using PubMed and 88 using Scopus. Duplicates, articles with no full text available, not in the English language, or not pertinent were excluded. The reference lists of the identified articles were manually reviewed for additional citations. Seventy-eight publications in total were included in the review. Fourteen articles focused on WISP3 function without describing patients affected by PPRD; of the 64 publications describing clinical, laboratory and radiographic features of PPRD patients, 28 were single case reports and 27 were case series with no more than ten patients. Six case series included 11–30 patients. Only three articles included more than 30 patients, with the largest series counting 63 patients [11].

Pathogenesis

WISP3 belongs to the CYR61/CTGF/NOV (CCN) gene family of growth factors that regulate cell proliferation, differentiation and migration in connective tissue [10, 13–17], and *WISP3* mutations frequently affect cysteine residues and alter protein structure and function [5, 18, 19]. *WISP3* encodes a 354 amino acid protein that includes an insulin-like growth factor-binding protein (IGFBP) domain, a von Willebrand factor type C repeat domain, a thrombospondin (THBS) type I-like domain, and a cysteine knot domain [10]. It is thought that the IGFBP domain is responsible for insulin-like growth factor 1 (IGF-1) signalling modulation in the growth plate [18, 20, 21]. It has been shown that WISP3 can interact with IGF-1 and cause chondrocyte hypertrophy which, even though the exact mechanism is unknown, may also explain the short stature of patients with *WISP3* mutations, especially in the IGFBP domain [22].

Ex vivo studies have shown that *WISP3* regulates the expression of collagen type II, aggrecan and transcription factor SOX9 in chondrocytes, promotes superoxide dismutase activity [18, 23, 24], inhibits cell proliferation and viability, and promotes the precursor cell differentiation of human chondrocytes, thus affecting cartilage homeostasis [25]. A biopsy of the iliac crest of one affected patient showed abnormal nests of chondrocytes and the loss of normal columnar organisation in the growth plate [26]. Nest-like clustering of chondrocytes in cartilage has also been observed also in the femoral head of a patient who underwent total hip arthroplasty [27]. Human chondrocytes from another PPRD patient have shown increased cell proliferation and altered processing of matrix metalloproteinase-1, -3 and -13 [28].

Hyperproliferative chondrocytes associated with low levels of *WISP3* may explain the enlarged metaphyses of PPRD patients, whereas delayed collagen synthesis and reduced extracellular collagen secretion may be responsible for decreased cartilage flexibility [28, 29].

Homozygous or compound heterozygous *WISP3* mutations finally cause the loss of articular cartilage, which leads to the progressive narrowing of all articular spaces and reduced joint mobility.

WISP3 mutations

Mutations may be located in all of the protein domains, and include base pair substitutions, deletions, duplications, and substitution/deletions. The mutations often cause premature protein termination, but may also lead to amino acid substitutions or the removal/insertion of amino acids [10, 11]. The disease in two Moroccan siblings was due to a homozygous large deletion of the 5′UTR and the first coding exon of *WISP3* [30]. In a study of 63 patients with molecularly confirmed PPRD, 24 were homozygotes for the most common pathogenic mutation (c.156 C > A; p.Cys52*), 25 were homozygotes for other mutations, 12 were compound heterozygotes, and 2 had heterozygous c.156 C > A mutations plus an intronic mutation causing a splicing aberration that was found by analysing cDNA [11].

The frequency of the different mutations varies geographically; c.156C > A mutations are frequently found in areas such as Turkey, Lebanon, Syria, Italy, France and India, but the most frequent mutations in India are c.1010G > A and c.233G > A [4–6, 10, 11, 31, 32].

Table 1 summarises all of the mutations and polymorphisms (in italics) observed in the *WISP3* gene.

No genotype–phenotype correlations have been observed. Heterozygotes, including parents and siblings, do not present any articular sign or symptom [10, 11, 32]. Only one report has described the mother of a patient as showing "minimal features of the disease" [33]. Inter- and intra-familial clinical heterogeneity has been described even in siblings carrying the same mutations [4–6, 10, 34, 35].

Table 1 Mutations and polymorphisms (in italics) observed in the WISP3 gene

Location	Coding sequence	Protein	Reported by
Exon 1	c.43_44delGC	p.Ala15Thrfs*17	Hurvitz [10]
Intron 1	c.48 + dupT	Splicing	Hurvitz [10], Garcia Segarra et al. [11], Chouery [78]
	c.49-1G > A	Splicing	Bhavani [6]
	c.49-763G > T	p.Phe17Asnfs*42	Garcia Segarra et al. [11]
Exon 2	c.105dupT	p.Gly36fs*10	Liu et al. [74]
	c.136C > T	p.Gln46*	Yue [66], Ye et al. [46], Yu et al. [51]
	c.156C > A	p.Cys52*	Hurvitz et al. [10], Delague et al. [4], Temiz et al. [31], Dalal et al. [5], Garcia Segarra et al. [11], Bhavani [6], Rai et al. [7], Madhuri et al. [32], Sailani et al. [53]
	c.168G > T	*p.Gln56His*	Hurvitz et al. [10], Delague et al. [4], Garcia Segarra et al. [11]
	c.182G > T	p.Cys61Phe	Garcia Segarra et al. [11]
	c.185delC	p.Pro62Leufs*4	Garcia Segarra et al. [11]
	c.190G > A	p.Gly64Arg	Montané et al. [8]
	c.197G > A	p.Ser66Asn	Garcia Segarra et al. [11], Montané et al. [8]
	c.232T > C	p.Cys78Arg	Hurvitz et al. [10]
	c.233G > A	p.Cys78Tyr	Dalal et al. [5], Ekbote et al. [34], Bhavani [6], Madhuri et al. [32]
	c.236-237CC > AA	p.Ala79Glu	Garcia Segarra et al. [11]
	c.246delA	p.Glu84Lysfs*21	Hurvitz et al. [10]
	c.248G > A	*p.Gly83Glu*	Delague et al. [4], Temiz et al. [31], Garcia Segarra et al. [11], Dalal et al. [5], Ekbote et al. [34], Bhavani [6], Rai et al. [7]
	c.296A > T	p.Tyr99Phe	Bhavani [6]
	c.298T > A	p.Cys100Ser	Bhavani [6]
	c.327C > A	p.Tyr109	Garcia Segarra et al. [11]
	c.334G > C	p.Gly112Arg	Unpublished data
	c.340T > C	p.Cys114Arg	Dalal et al. [5]
	c.341G > A	p.Cys114Tyr	Yue et al. [66]
	c.342T > G	p.Cys114Trp	Ye et al. [46], Sun et al. [35], Yu et al. [51]
	c.342_343delTG	p.Ala115Ilefs*16	Garcia Segarra et al. [11]
Intron 2	c.346 + 1G > T	p.Tyr109Met195delins9	Garcia Segarra et al. [11]
	c.347-2A > G	Splicing	Bhavani [6]
	c. 347-1 347-3delCAG	Splicing	Bhavani [6]
Exon 3	c.348C > A	p.Tyr116*	Dalal et al. [5], Bhavani [6], Madhuri et al. [32]
	c. 396T > G	p.Cys132Trp	Yan et al. [64]
	c.433T > C	p.Cys145Arg	Dalal et al. [5], Bhavani [6]
	c.434G > A	p.Cys145Tyr	Hurvitz et al. [10]
	c.530C > A	p.Ser177*	Bhavani [6]
	c.536_537delGT	p.Cys179*	Delague et al. [4]
	c.589G > C	p.Ala197Glyfs*5	Delague et al. [4]
	c.589G > A	p.Ala197Glyfs*5	Garcia Segarra et al. [11]
Intron 3	c.589 + 27C > G	p.Ala197Glyfs*5	Garcia Segarra et al. [11]
	c.589 + 2T > C	splicing	Sun et al. [35]

Table 1 (continued)

Location	Coding sequence	Protein	Reported by
Exon 4	c. 593_597delATAGA	p.Tyr198*	Madhuri et al. [32]
	c.621_622delAAinsT	p.Lys207Asnfs*25	Garcia Segarra et al. [11]
	c.624dupA	p.Cys209Metfs*21	Ye et al. [46], Garcia Segarra et al. [11], Bhavani [6], Chouery et al. [78]
	c.624delA	p. Lys208fs*24	Liu et al. [74]
	c.643 + 1G > A	Not known*	Rai et al. [7]
	c.667T > G	p.Cys223Gly	Ye et al. [46], Yu et al. [51], Luo et al. [50], Al Kaissi et al. [52]
	c.670G > A	p.Gly224Arg	Garcia Segarra et al. [11]
	c. 670dupA	–	Hu et al. [60]
	c.677G > T	p.Gly226Val	Garcia Segarra et al. [11], Bhavani [6], Madhuri et al. [32]
	c.679dup	p.Cys227Leufs*21	Ye et al. [46], Yan et al. [64]
	c.682T > C	p.Ser228Pro	Dalal et al. [5], Ekbote et al. [34]
	c.683_684insT	p.Asn229*	Bhavani [6]
	c.685_686insATCTA	p.Arg230Leufs*4	Bhavani [6]
	c.708dupC	p.Asn237Glnfs*3	Garcia Segarra et al. [11]
	c.716_722del	p.Glu239fs*16	Sun et al. [35]
	c.721T > G	p.Cys241Gly	Yan et al. [64]
	c.725_726delAA	p.Lys242Argfs*36	Garcia Segarra et al. [11]
	c.727_731delGAGAA	p.Glu243Lysfs*34	Garcia Segarra et al. [11]
	c.729-735delGAGAAAA	p.Glu243Aspfs*13	Ye et al. [46]
	c.739_740delTG	p.Cys247Leufs*31	Ehl et al. [67], Dalal et al. [5], Bhavani [6]
	c.740_741delGT	p.Cys247Leufs*31	Bhavani [6]
	c.756C > A	p.Cys252*	Luo et al. [50], Hu et al. [60]
	c.779_783 + 1delTAAAGG	p.Ile260Asnfs*17	Bhavani [6]
Exon 5	c.794_795delGT	p.Cys265LeufsX31	Cassa et al. [49]
	c.802T > G	p.Cys268Gly	Dalal et al. [5]
	c.804delC	p.Gln269Asnfs*44	Bhavani [6]
	c.807A > G	*p.Gln269Gln*	Hurvitz et al. [10], Garcia Segarra et al. [11]
	c.840delT	p.Phe280Leufs*33	Sun et al. [35], Yang et al. [47]
	c.850G > T	p.Gly284*	Garcia Segarra et al. [11]
	c.857C > G	p.Ser286*	Garcia Segarra et al. [11], Yu et al. [51]
	c.862_863dupAC	p.Gln289Leufs*25	Hurvitz et al. [10], Garcia Segarra et al. [11]
	c.866dupA	p.Ser290Glufs*13	Ye et al. [46], Garcia Segarra et al. [11], Yu et al. [51]
	c.868-869delAG	p.Ser290Leufs*12	Hurvitz et al. [10], Garcia Segarra et al. [11]
	c.947_951delAATTT	p.Gln316Argfs*5	Dalal et al. [5]
	c.993G > A	p.Trp331*	Hurvitz et al. [10]
	c.1000T > C	p.Ser334Pro	Sun et al. [35]
	c.1004G > A	p.Cys335Tyr	Garcia Segarra et al. [11]
	c.1010G > A	p.Cys337Tyr	Dalal et al. [5], Garcia Segarra et al. [11], Ekbote et al. [34], Bhavani [6], Madhuri et al. [32]

*The mutation may cause exon skipping, alternative splicing, or premature protein termination and needs further experimental validation [7]

Clinical findings

Affected children are typically healthy at birth, and develop normally during the first years of life. PPRD usually onsets between the ages of 3 and 8 years, but some patients may be asymptomatic until the age of 16 or develop clinical manifestations as early as in the first year of life [3–5, 7–10, 27, 30, 31, 36–57]. It has also been reported that the disease presented at birth with the involvement of interphalangeal joints in two patients [34, 46]. Diagnosis is often delayed, sometimes for decades [58–60], although the time between symptom onset and diagnosis is shorter in Turkish patients, probably because of a better knowledge of the disease in the country, and the fact that the high rate of consanguinity increases the suspicion of genetic disease [11].

The most frequent presenting clinical features include gait abnormalities, fatigability, stiffness in multiple joints (particularly the hip), and enlarged interphalangeal joints of the hands. Figure 1 displays the typical enlargement of interphalangeal joints of the hand in a 6-year-old patient; to be noted, as in every joint involved, the swelling has a bony consistence, being due to metaphyseal enlargement and not to synovial inflammation. Pain is less frequently reported as an initial symptom (possibly also because of the lack of recognition of pain in children, which may actually be responsible for the fatigability and gait abnormalities), but develops over time in most patients [5, 11, 32, 34, 50, 51, 61–63]. However, the pain is usually disproportionately mild in comparison with the severity of the arthropathy [29].

Stiffness usually appears symmetrically, first at the interphalangeal joints, knees and hips, and only rarely at the cervical spine, elbows, wrists and shoulders; however, the movement of almost all of the joints becomes limited over time [11]. The involvement of the temporomandibular joints has not been reported. Walking difficulties worsen until the patients lose autonomous mobility, usually in the second decade of life [4, 27, 28, 32, 35, 36, 46, 50, 57, 64–67]. At the beginning, mild proximal and distal muscle weakness may be prominent as a result of the joint stiffness causing fatigability and an abnormal gait [52]. Morning stiffness has also been described in some patients [68].

Skeletal changes become more evident over time and are responsible for kyphoscoliosis, short adult stature (below the third centile) with a short trunk, joint contractures, progressive hip disease and camptodactyly [1, 3, 11, 26, 37, 69, 70]. One patient with a c.804delC mutation and his brother (not genetically analysed) showed considerable humerus involvement with rhizomelic upper limb shortening [6].

Stature is normal in infancy, but the growth curve subsequently declines [11, 51, 71] and some patients may be referred to an endocrinologist because of their short stature [10, 72], although a short trunk may be noted before the decrease in height [51]. Flexus of the hips and knees, and vertebral anomalies also contribute to the reduction in height. The stature of most a series of 63 patients with PPRD was reported to be below the third centile at the time of diagnosis [11], probably because of a delay in recognising the disease. However, it has been reported that some patients reach normal adult stature, although these did not have a molecular diagnosis and presented atypical features such as bilateral talipes equinovarus at birth, brachycephaly with mid-facial hypoplasia, bifid uvula and a nasal voice [73]. In adult patients, the acute worsening of articular symptoms with signs of systemic inflammation may be due to pseudogout [65]. Table 2 summarises the clinical features of PPRD by skeletal segment.

Intelligence and appearance are normal and no extra-skeletal manifestations have been reported [7, 53, 61, 64], although one patient with a genetically unconfirmed clinical diagnosis of PPRD is reported to have had a subcapsular cataract; however, this association has not been described in any other cases [48]. Neurological manifestations may appear during the course of the disease as a consequence of spinal canal stenosis and spinal cord compression [47, 50].

Although the clinical manifestations gradually worsen over time, two Chinese siblings experienced a transient phase of clinical improvement during the disease course [50].

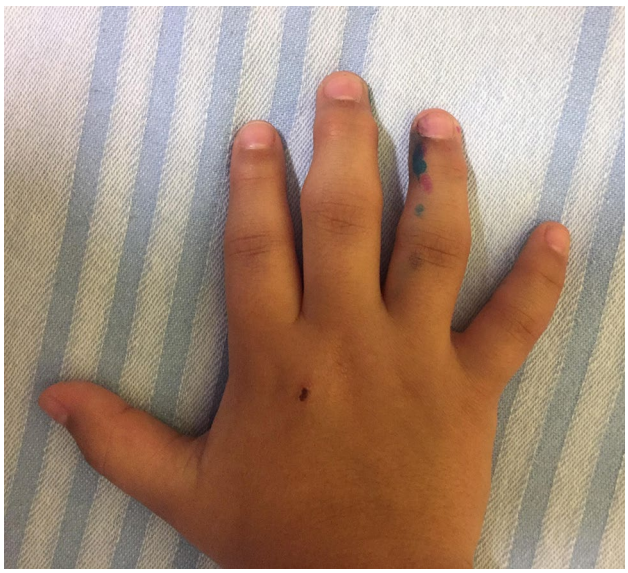

Fig. 1 Stubby appearance of the fingers and enlargement of interphalangeal joints in a 6-year-old affected by PPRD

Radiological findings

Radiological features include spondyloepiphyseal dysplasia with platyspondyly, a short and wide femoral neck, large femoral and tibial epiphyses, narrow joint spaces at the hips and knees, enlarged epi-metaphyseal portions of the metacarpals and phalanges, and osteopenia [4, 5, 11, 35, 36, 41, 44, 46, 53, 57, 60, 66, 67, 71, 74]. Metaphyseal enlargement of the interphalangeal joints is an early radiological finding [11].

Skeletal radiographs recorded at 3 years of age did not show any sign of skeletal dysplasia in two children with PPRD [37, 69], but radiological evaluations of two affected sisters showed that the 9-year-old girl revealed enlarged epiphyses and metaphyses of the metacarpals and phalanges, enlarged femoral necks with reduced articular space in the hip, and reduced articular space in the knees and feet, and her 26-year-old sister had additional abnormalities, including enlarged carpal bones with reduced

Table 2 Clinical features of PPRD by skeletal segment

Segment	Clinical features
Hands	Bony enlargement of the interphalangeal joints is a frequent presenting feature of PPRD The metacarpophalangeal and distal interphalangeal joints become involved after the proximal interphalangeal joints Camptodactyly is almost always present in adulthood [7, 9, 36, 42, 64, 72]
Spine	Spine involvement with platyspondyly develops in late childhood and adolescence Spine involvement leads to a short trunk and thoracolumbar kyphosis Lordosis may also be seen Scoliosis is sometimes observed, mainly in adult cases, and may be severe enough to require corrective surgery [4, 5, 9, 10, 27, 42, 47, 74] The neck is sometimes affected, but usually less severely than the thoracolumbar spine [5, 27, 29, 34, 38, 47] Involvement of the odontoid process has been described, associated with suboccipital pain [44, 45] A tilted pelvis is responsible for gait abnormalities Back pain is common [7, 52]
Hip and femur	Progressive hip stiffness and pain develop over time Hip involvement becomes a major problem in adolescence, often finally requiring hip replacement surgery [9, 64, 71]
Knee	Knee deformity was the presenting sign in 20% of a large cohort of PPRD patients [9] Enlargement of knees has been often reported as an initial disease manifestation [7, 57], but this may also occur later [64] Genu varum may contribute to gait disturbance [4, 7, 50] Genu valgum may also develop [5, 30, 61, 66, 75] Knee flexus is typical of young adults [7, 9]
Ankle	Enlarged ankles have been reported as a presenting feature of PPRD [7, 72]
Feet	Camptodactyly also develops in toes [10]
Shoulder	Shoulder involvement has been reported during the course of the disease, but it is not usually severe [5, 7, 10, 71]
Elbow	Enlarged elbows have been reported as an initial symptom of the disease, but may also appear later [7, 64, 71] Elbow flexus develops in young adults [7, 9, 10, 49]
Wrist	Wrist involvement has been described, with a limited range of motion and radial deviation [49, 64, 68]
Other	Rib involvement has been described A mild S-shaped deformity of the tibiae and tibia vara has also been described [7, 32, 64]

interosseous space and camptodactyly, enlarged and flat femoral heads with the complete loss of articular space in the hip joints, osteopenia, a pelvic tilt due to the abnormal curvature of the spine, the complete loss of articular space in the knees, fused cervical vertebrae, kyphoscoliosis, platyspondyly, end plate erosions, and narrowing intervertebral disc spaces [7]. Figure 2 displays initial flattening of some thoracolumbar vertebral bodies in the spine X-rays of a 6-year-old PPRD patient.

Progressive cartilage loss is seen with age, but usually not the destructive bone erosions typical of juvenile idiopathic arthritis (JIA) [11, 64]. Patients with longer lasting disease show irregular epiphyses and metaphyses [34].

Osteophytic formations and periarticular calcifications may be seen in the hands, shoulders, knees, feet and elbows of adults and also adolescents [11, 49, 74, 75] as osteophytic calcifications appear earlier in patients with PPRD than in those with non-genetic osteoarthritis. Radiological findings become non-specific in adulthood and secondary changes due to ageing make diagnosis more difficult [11, 64].

Table 3 summarises the radiological features of PPRD by skeletal segment.

Laboratory findings

Inflammatory parameters, including the ESR and CRP levels are normal; RF and autoantibodies such as antinuclear antibodies and anti-citrullinated protein antibodies are negative; complement is within the normal range; synovial biopsy findings are normal [4, 7, 11, 34, 35, 37, 44, 47, 49, 50, 61, 64, 66, 68, 71]. Calcium, alkaline phosphatase, haemoglobin and blood sugar levels have also been reported to be normal [7]. When tested, basal fasting concentrations of growth hormone, insulin-like growth factor-1, IGFBP-3 and insulin levels have been within normal limits [31].

Diagnosis

In some affected families, the diagnosis has been made on the basis of whole-exome sequencing [7, 64] but when clinical and radiological findings suggest PPRD, *WISP3* gene sequence analysis can be sufficient to confirm the

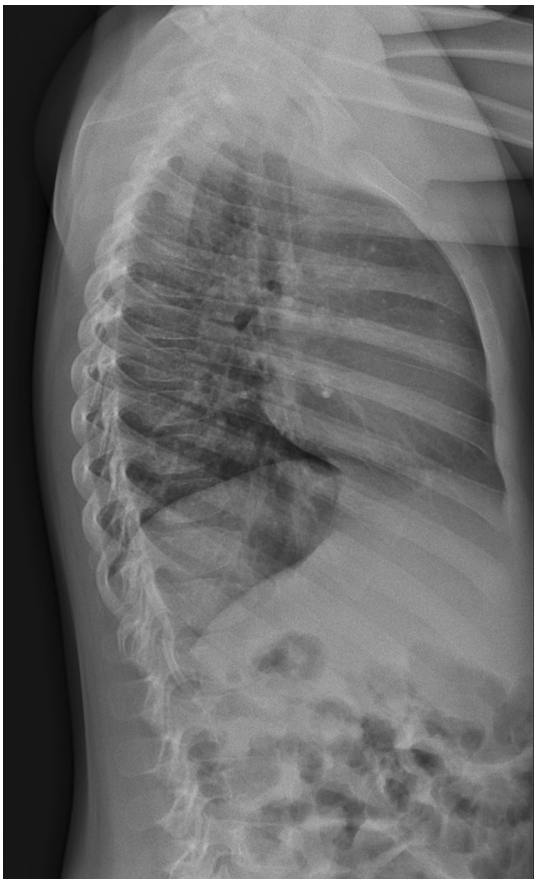

Fig. 2 Spine X-rays of a PPRD patient at the age of 6, showing initial flattening of some thoracolumbar vertebral bodies

diagnosis [11]. A multi-gene panel that includes *WISP3* and other genes of interest is another option that is particularly useful in the differential diagnosis of similar conditions [29].

There are still no formal diagnostic criteria but, in a study of 81 patients with suspected PPRD, Segarra et al. defined "typical PPRD" as the concomitant presence of onset in early childhood, stiffness and pain in multiple joints, enlarged interphalangeal joints, normal inflammatory parameters, and the absence of extra-skeletal manifestations. The radiological criteria defining typical PPRD included metaphyseal enlargement of the interphalangeal joints, reduced articular space with large dysplastic epyphyses at the hips and knees, platyspondyly with the anterior breakage of vertebral bodies, the absence of articular bone erosions, and generalised osteopenia starting in adolescence. Patients with a clinical picture suggesting PPRD, but with disease onset before 3 or after 8 years of age, or the absence of interphalangeal and/or spine involvement, or painless joint stiffness/contractures, or the presence of extra-skeletal manifestations were considered atypical. In 63 out of 64 typical forms, mutation analysis of *WISP3* confirmed the diagnosis of PPRD, whereas mutation screening was negative in all of the 17 patients with suspected atypical PPRD [11].

The above-mentioned atypical features should, therefore, encourage clinicians to consider other diagnoses, although PPRD should not be excluded only because of an atypical age at onset, as bi-allelic *WISP3* mutations have been found and the diagnosis of PPRD confirmed in two affected siblings with a late disease onset (9 and 11 years old) and in one patient with an early disease onset (1.5 years) [10, 32].

Genetic testing should start with the study of genomic DNA extracted from blood leucocytes, but intronic mutations in *WISP3* causing splicing aberrations can only be detected by analysing *WISP3* mRNA, which can be extracted from cultured skin fibroblasts and subsequently studied by generating and amplifying double-stranded cDNA. A skin biopsy is, therefore, indicated in patients with typical PPRD findings and negative mutation screening of genomic DNA [11].

Prenatal diagnosis for pregnancies at increased risk is possible if *WISP3* pathogenic variants have been identified in an affected family member [29].

Differential diagnoses

The clinical findings in PPRD patients may initially resemble those of patients with JIA, but negative inflammatory markers, typical radiological findings, a poor response to immunosuppressive therapy, and the marked decrease in growth rate can suggest the correct diagnosis. A lateral radiograph of the spine may help in diagnosing PPRD in a child with chronic arthropathy and no clear signs of inflammation [11, 34, 39, 40, 61, 72].

Myopathy may be suspected in some patients in whom motor weakness (usually starting from the age of three) is the dominating sign, but joint stiffness and enlargement, together with normal serum creatine kinase and plasma lactate levels are distinctive features of PPRD. However, it is worth noting that electromyography and muscle magnetic resonance imaging may show minimal non-specific myopathic changes in patients with PPRD [37, 52, 77, 78].

The early and progressive involvement of multiple joints differentiates PPRD from other bone dysplasias [37].

In three patients with suspected atypical PPRD and negative mutation screening, the final diagnoses were, respectively, CACP syndrome (coxa vara, arthropathy, camptodactyly, pericarditis), Winchester syndrome, and COL2A1-related disorder [11]. In Winchester syndrome, a short stature and early-onset severe joint contractures are associated with peripheral corneal opacities, coarsened facies, the dissolution of carpal and tarsal bones, and generalised osteoporosis [79]. COL2A1-related dysplasias, which may resemble PPRD, include Czech dysplasia and

Table 3 Radiological features of PPRD by skeletal segment

Segment part	Radiological features
Hands	Hand X-rays initially show minimal metaphyseal enlargement at the interphalangeal joints Interphalangeal joints enlargement progresses with age Metacarpophalangeal and interphalangeal joint spaces, particularly in the proximal interphalangeal joints, become progressively smaller and finally disappear The interosseus space between the carpal bones, which may be normal at disease onset, decreases over time [5, 9, 64]
Spine	Vertebral bodies may be minimally involved in the early stages of the disease Defective ossification of the anterior portions of the upper and lower end plates appears over time [37, 64] Platyspondyly, end plate irregularities, anterior breaking of vertebral bodies and wedging leading to kyphoscoliosis appear with age Osteopenia develops over time Intervertebral spaces progressively decrease [9, 34, 36, 37, 40, 64, 72, 74]
Hip and femur	At disease onset, pelvis X-rays may be normal Changes that develop with age include the following: Femoral heads become larger and flatter Femoral necks become shorter and wider The ilia broaden The acetabulum forms a distinct lip overriding the femoral head There is a reduction in articular space [5, 9, 10, 29, 37, 47] Affected patients may develop coxa vara or valga [42, 61] Osteopenia may be seen in adults [9, 52, 64] Irregular densities and cyst-like structures in the femoral head and neck have been described [64] Femoral head fracture and necrosis have been reported [66] Ischiopubic synchondrosis has been observed in an affected boy [44]
Knee	Articular surfaces of the knee appear flattened and irregular Articular space is reduced [64] Osteophytic formations and periarticular calcifications may be present [29]
Feet	Enlarged and irregular os trigonum has been detected in foot X-rays [41, 67, 71, 75, 76]
Shoulder	Osteophytic formations and periarticular calcifications may be present [29] Osteochondromatosis of both glenohumeral joints has been described [43]

Strudwick-type spondyloepimetaphyseal dysplasia. Czech dysplasia (also known as progressive pseudorheumatoid dysplasia with hypoplastic toes) is characterised by early-onset osteoarthritis and hypoplastic third, fourth and fifth toes. Radiological findings in patients with Czech dysplasia, which consist of platyspondyly with irregular endplates and elongated vertebral bodies, coxa vara, a short femoral neck, and narrow joint spaces, may mimic PPRD, but their normal stature and short post-axial toes are distinctive features [80, 81]. Strudwick-type spondyloepimetaphyseal dysplasia shares the disproportionately short stature and spinal abnormalities (mainly scoliosis in spondyloepimetaphyseal dysplasia) of PPRD, but pectus carinatum and dappled metaphyses are useful distinguishing features [82–84].

Stickler's syndrome, a clinically and genetically heterogeneous disorder sometimes due to mutations in the *COL2A1* gene, is a spondyloepiphyseal dysplasia characterised by multiple joint arthropathy, but it can be differentiated from PPRD on the basis of the presence of ophthalmic abnormalities, particularly progressive myopia [85]. As the spectrum of type II collagenopathies is broadening, if a patient shows PPRD features but has no pathogenic *WISP3* mutation, it is advisable to consider and screen for a possible COL2A1-related disorder [86].

Patients with corner fracture-type (Sutcliffe-type) spondylometaphyseal dysplasia present with a short stature and developmental coxa vara, and may resemble some phenotypic variants of PPRD [29].

X-linked spondyloepiphyseal dysplasia tarda, which develops in adolescence or adulthood, is characterised by a short stature, platyspondyly with posterior humps of the vertebral bodies, and osteoarthritis without the involvement of peripheral joints, and some forms of polyepiphyseal dysplasia can mimic PPRD [87].

Other disorders with platyspondyly, such as mucopolysaccharidosis, have relatively characteristic features and can be differentiated from PPRD because of the presence of extra-skeletal manifestations such as coarse facies, corneal abnormalities, hepatomegaly and intellectual disability. Furthermore, the small joints of the hand and larger joints such as the knee appear to be normal in patients with mucopolysaccharidosis [46].

Spinal involvement in PPRD may mimic Scheuermann's disease which, however, presents at puberty [29, 43].

A careful anamnesis and clinical examination, together with a complete skeletal survey, blood tests (ESR, CRP, RF, ANA) and an ophthalmological evaluation are important diagnostic tools.

Treatment and management

The current treatment for PPRD is only supportive and based on pain medication, physical therapy, and surgical interventions.

Some patients have been treated with steroids and immunosuppressants such as methotrexate and cyclosporine, but these have not been beneficial [11, 34, 67]. Intra-articular steroid injections have transiently relieved pain in a few patients, but were otherwise not useful [11]. A lack of response to anti-rheumatic drugs is typical of PPRD, and anti-inflammatory treatment does not usually lead to any clinical improvement [34, 42, 46, 64]; however, anti-inflammatory drugs may be of some help in adult patients who experience phases during which there is an increase in the levels of markers of inflammation probably because of secondary inflammation following cartilage destruction [11].

Treatment with intravenous pamidronate did not lead to any improvement in bone density or height in three affected siblings [31].

Physical therapy may help preserve joint mobility [62]. Immobilisation (e.g. plaster casts) should be avoided. Scoliosis and mild kyphosis can be managed with bracing.

Surgical interventions include hip and knee joint replacement (which may be necessary by the third decade of life), realignment of the lower limbs, and spinal surgery to treat spinal stenosis and/or scoliosis [10, 11, 29, 30, 37, 47, 49]. Given the considerable disability caused by the disease, hip joint replacement may be a reasonable therapeutic option to relieve pain and re-establish the ability to walk [11, 27, 47, 88]. The best timing for joint replacement depends on the patient's conditions, but it should not be used before lower limb epiphyseal closure to avoid secondary length discrepancy [27].

A complete skeletal survey is indicated after a diagnosis of PPRD. The patient should be referred to an orthopaedic surgeon specialised in treating bone dysplasias and a medical geneticist.

Conclusion

PPRD is a rare condition with a considerable impact on the patients' quality of life, therefore, needs to be recognised by paediatricians, rheumatologists and endocrinologists, not only to avoid unnecessary anti-inflammatory or immunosuppressive treatment, but also to be able to offer patients and their families access to genetic counselling. PPRD should be highly suspected if a child develops symmetrical polyarticular involvement in the absence of systemic inflammation, knobbly interphalangeal joints of the hands, an abnormal gait and fatigability. A full skeletal survey or, at least, a lateral radiograph of the spine, can direct clinicians towards a correct diagnosis that can then be confirmed molecularly. No etiological treatment is currently available, but a better understanding of the pathogenesis of PPRD may allow the development of new and effective therapies.

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