Skeletal Radiol (2004) 33:157–164
DOI 10.1007/s00256-003-0708-z

ARTICLE

Ivo Marik
Olga Marikova
Dana Zemkova
Miroslav Kuklik
Kazimierz Kozlowski

Dominantly inherited progressive pseudorheumatoid dysplasia with hypoplastic toes

Received: 3 April 2003
Revised: 2 June 2003
Accepted: 23 September 2003
Published online: 17 January 2004

I. Marik · O. Marikova · D. Zemkova · M. Kuklik
Ambulant Centre for Defects of the Locomotor Apparatus, Prague, Czech Republic

O. Marikova
Department of Anthropology and Human Genetics, The Faculty of Science, Charles University, Prague, Czech Republic

D. Zemkova
Second Paediatric Clinic, Motol Teaching Hospital, Prague, Czech Republic

K. Kozlowski (✉)
Department of Medical Imaging, The Children's Hospital at Westmead, Locked Bag 4001, NSW 2145 Sydney, Australia
e-mail: Kaz.Kozlowski @ bigpond.com
Tel.: +61-2-94382562
Fax: +61-2-94382562

Abstract *Objective:* To present four related patients with progressive pseudorheumatoid dysplasia (PPsRD) each with distinctive history, unique phenotype and some peculiar radiographic findings. *Results and conclusions:* The history was characterised by weather-dependent articular pain. The unique phenotypic features were hypoplasia/dysplasia of one or two toes. Peculiar radiographic findings were hypoplasia of the 3rd and 4th metatarsals, platyspondyly with rectangular shape of the lumbar spinal canal, progressive narrowing of the joint spaces and early synovial chondromatosis. Finally, the condition was inherited as a dominant trait. This constellation of abnormalities constitutes a distinct form of PPsRD. PPsRD must be differentiated from other bone dysplasias, specifically spondyloepiphyseal dysplasias, autosomal dominant spondylarthropathy, juvenile rheumatoid arthritis and osteoarthritis.

Keywords Bone dysplasia · Pseudorheumatoid arthritis · Chondromatosis · Toes · Dominant inheritance

Introduction

Progressive pseudorheumatoid dysplasia (PPsRD) is a hereditary condition characterised by polyarthralgia, multiple joint contractures, prominent interphalangeal joints and short stature. Radiographic examination documents moderate platyspondyly, narrowing of the intervertebral discs and joint spaces, widening of the metaphyses, minor epiphyseal changes and early osteoarthritis. The disorder is inherited as a recessive trait. Tests for rheumatoid arthritis are negative.

Following the original report by Spranger et al. in 1980 [1] about 50 cases of PPsRD were reported up to 1995 [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13]. The frequency is about 1:1,000,000 with the highest incidence in the Arab countries [12].

We report four related patients, aged 5 to 30 years (1 male, 3 females) who presented with most of the major features of PPsRD. The characteristic history, unique phenotype and distinctive radiographic findings allow us to distinguish our family from other patients with PPsRD (Fig. 1).

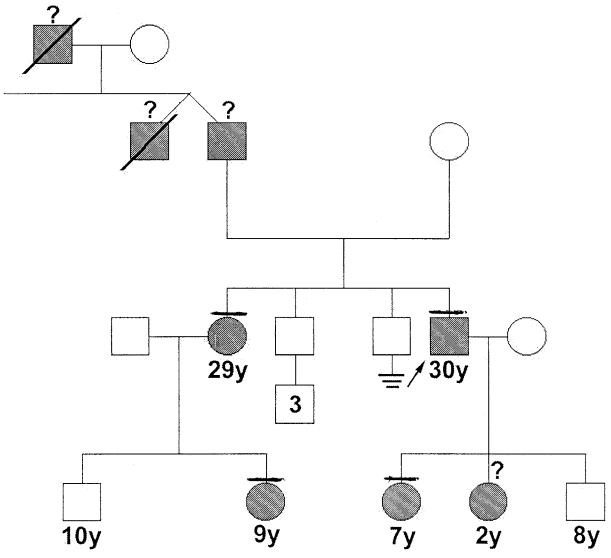


Fig. 1 Family pedigree of the patients with dominant-type progressive pseudorheumatoid dysplasia. Standard nomenclature is used for the symbols

Case reports

Case 1

This 29-year-old man was seen at the Centre for Defects of the Locomotor Apparatus for orthopaedic evaluation. His sister, daughter and niece are similarly affected. His mother and two brothers are healthy. The father, father's twin brother and the grandfather had been affected by a "crippling joint disease". The patient's 2-year-old daughter is probably also affected as she shows some deformity of the toes. Since early childhood the patient has had joint pains that are dependent on the weather. He experienced increased walking difficulties from early school age and at the age of 12 years developed a progressive limp, following an episode of acute left hip joint pain after sporting activities. At the age of 15 years his height was 170 cm, weight 52.5 kg, with shortening of the trunk (–1.2 SD) and decreased transverse and increased anteroposterior diameter of the chest (Fig. 2A). There was shortening of the 4th and 5th toes bilaterally (Fig. 2B). The range of movement in all the joints, particularly the spine, hip and knee joints was decreased. His IQ was 86. The ophthalmological, neurological, otorhinolaryngological and cardiological examinations were all normal. Skeletal survey documented platyspondyly with a rectangular lumbar spinal canal, narrowing of the joints spaces and hypoplasia of the 4th and 5th metatarsals (Fig. 2C–G). Diagnosis was considered to be multiple epiphyseal dysplasia or X-linked spondyloepiphyseal dysplasia tarda. In the following years his health deteriorated in spite of physiotherapy and anti-rheumatoid medication (ibuprofen, nimesulid, diclofenac). At the age of 27 years, the diagnosis of osteochondromatosis of the knee was made because of increasing flexion of the knee joints complicated by instability and presence of loose bodies. This was confirmed by radiographs. The histological diagnosis was synovial osteochondromatosis.

At 29 years of age his face was normal apart from slight hypertelorism, and the interphalangeal joints of his hands were swollen and hard. There was shortening of the trunk, kyphosis of the thoracic spine, hyperlordosis of the lumbo-sacral spine with limitation of spinal movements. The chest was narrow. The range of movement in all joints was limited, with the hip and knee joints most severely affected. There were flexion contractures of the hip and knee joints, and he was confined to a wheelchair. The radiographs demonstrated osteopenia, most marked in the spine and around joints, with moderate platyspondyly and minimal narrowing of the intervertebral discs. The lumbar spinal canal was rectangular in the anteroposterior projection. There was narrowing of the joint spaces, most marked in the hip and knee joints, with secondary degenerative changes. There was some overgrowth of the articular ends of the tubular bones. The femoral and humeral heads were prominent (Fig. 2E).

Case 2

The daughter of case 1, aged 5 years 8 months, had complained of pain in the lower limbs, which was dependent on the weather conditions, since the age of 3 years. Her height was 115 cm (50th percentile) and weight 21 kg. There was striking facial similarity with the father. The 4th toes were shortened (Fig. 3A). There was some prominence of the thoracic kyphosis and lumbo-sacral hyperlordosis. There was some limitation of the hip movements, but the mobility of the remaining joints was normal. The knees were prominent and the mobility of the patellae was increased. In the hands the interphalangeal joints were prominent. Her mental development was normal.

Radiographs demonstrated platyspondyly with oval-shaped vertebral bodies, marked flattening of the distal tibial epiphyses, large greater trochanters, slight overgrowth of the articular ends of the short tubular bones and advanced bone age. There was hypoplasia of the 4th metatarsals (Fig. 3B–D).

Case 3

The sister of case 1, aged 28 years, has a similar clinical history to her brother with weather-dependent joint pain and stiffness since early childhood. She underwent knee surgery for instability secondary to synovial osteochondromatosis at 16 years of age.

On examination her height was 163 cm (50th percentile), weight 69 kg. The 3rd and 4th toes were shortened (Fig. 4A). In the hands, the interphalangeal joints were swollen and hard. There was some shortening of the trunk with a mild thoracic kyphosis.

There was marked movement limitation in all the joints, the hip and knee joints and the cervical spine being most severely affected. She was confined to a wheelchair.

Radiographic examination documented changes resembling those of her brother (Fig. 4B–F). Her mental development was normal.

Case 4

The daughter of case 3, aged 6 years and 5 months, has been complaining of weather-dependent pains in the joints of the fingers for 2 years. She showed striking facial similarities to her uncle (case 1).

Her height was 119 cm (25th–50th percentile), weight 24 kg. The interphalangeal, wrist, elbow and knee joints were prominent. There was limitation of movement in all the joints, with the hand and elbow joints most severely affected. The movements in the finger joints were slightly painful. There was shortening of the 3rd and 4th toes of the left foot and of the 4th toe on the right foot (Fig. 5A).

Radiographs documented significant platyspondyly with oval-shaped vertebral bodies, flattening of the knee epiphyses, large greater trochanters, broad femoral necks and hypoplasia of the 3rd and 4th metatarsals. In the hands there was minimal narrowing

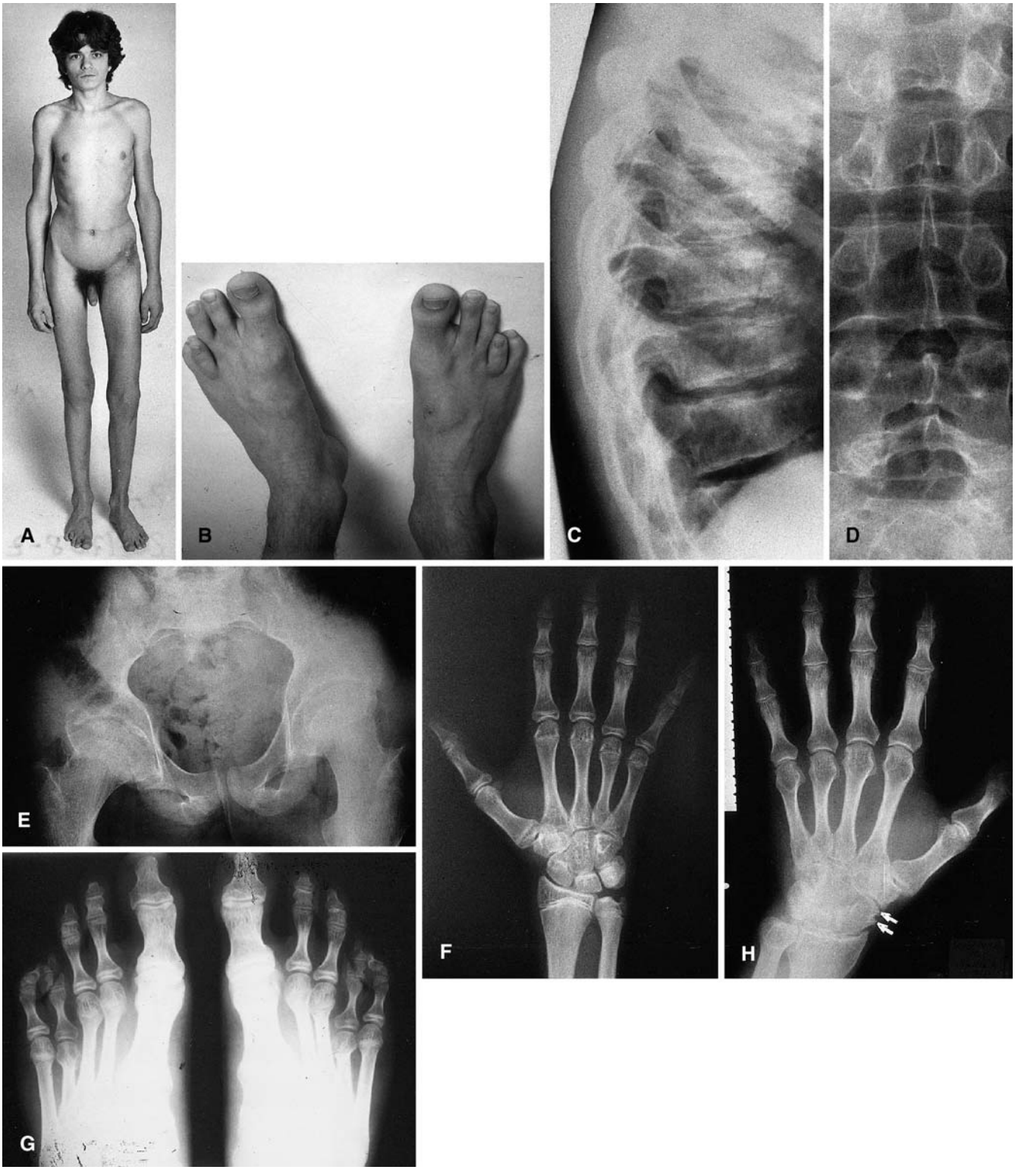


Fig. 2A–H Case 1. **A–G** At 15 years old. **A, B** Note the shortening of the trunk and hypoplastic/dysplastic 4th and 5th toes. **C** Flattened thoracic vertebral bodies with irregular vertebral plates. **D** Rectangular lumbar spinal canal. **E** The lower portions of the ilia are broad. Marked narrowing of the hip joint space. Slightly flattened, irregular femoral heads. Coxa valga. **F** Narrowing of all the hand joint spaces. Slight carpal osteo-arthritic changes. **G** Hypoplastic/dysplastic 5th and 4th toes. **H** At 29 years old. Narrowing of all hand joint spaces most marked in the wrist. Osteoarthritic changes (*arrowed*)

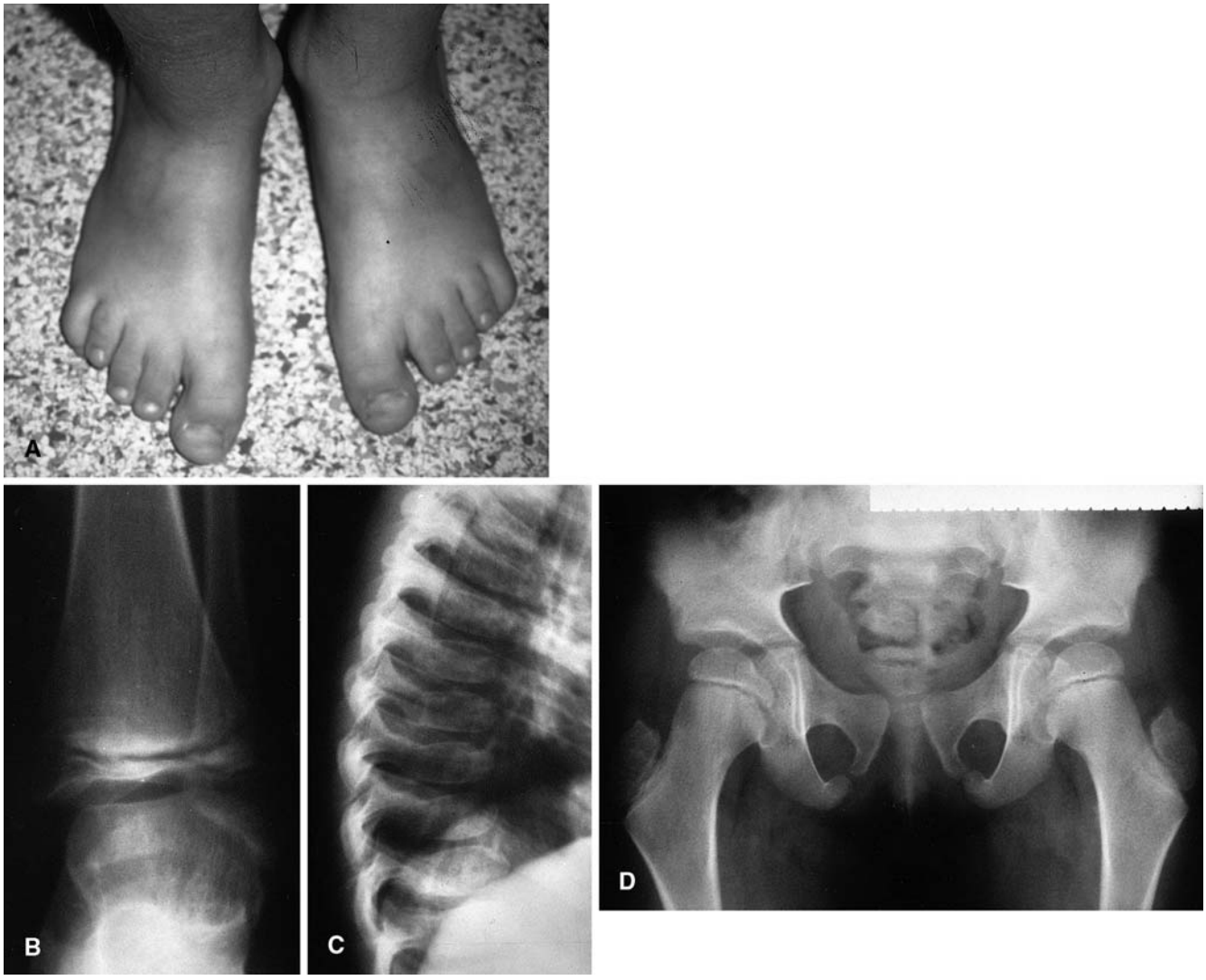


Fig. 3A–D Case 2, 6 years old. **A** Hypoplastic/dysplastic 4th toes. **B** Significantly flattened, oval thoracic vertebral bodies. **C** The lower portion of the ilia are broad. Coxa valga. Slightly flattened right capital femoral epiphyses. Broad proximal femoral metaphyses. **D** Flattened distal tibial epiphyses and trochlea tali

of the joint spaces and slight advancement of the bone age (Fig. 5B–F).

Her mental development was normal.

Biochemical results

The routine blood and urine tests, serum electrolytes and rheumatoid tests (C-reactive protein, ESR, antibodies against beta-haemolytic streptococci, rheumatoid factor) were negative in all the patients. In case 1, serum and urinary amino acids, urinary oligosaccharides and mucopolysaccharides and renal function tests yielded normal results. Markers of bone metabolism (S-osteocalcin, bone isoenzyme of alkaline phosphatase, U-pyridinoline/creatinine, U-deoxypyridinoline) showed increased chondro- and osteo-resorption in all the patients. Osteosynthesis was normal in cases 1, 3 and 4, and slightly elevated in case 2. Densitometry in case 3 showed normal bone density of the spine but decreased bone density of the femoral necks.

Discussion

The clinical history and course, negative rheumatoid tests and the radiographic examinations are consistent with PPsRD.

There are, however, some particular features in the clinical history, some unique phenotypic features and unusual radiographic findings which distinguish our family from other patients with PPsRD. In the clinical history, all our patients stress the weather-dependent articular pain. Moreover, PPsRD is inherited as a

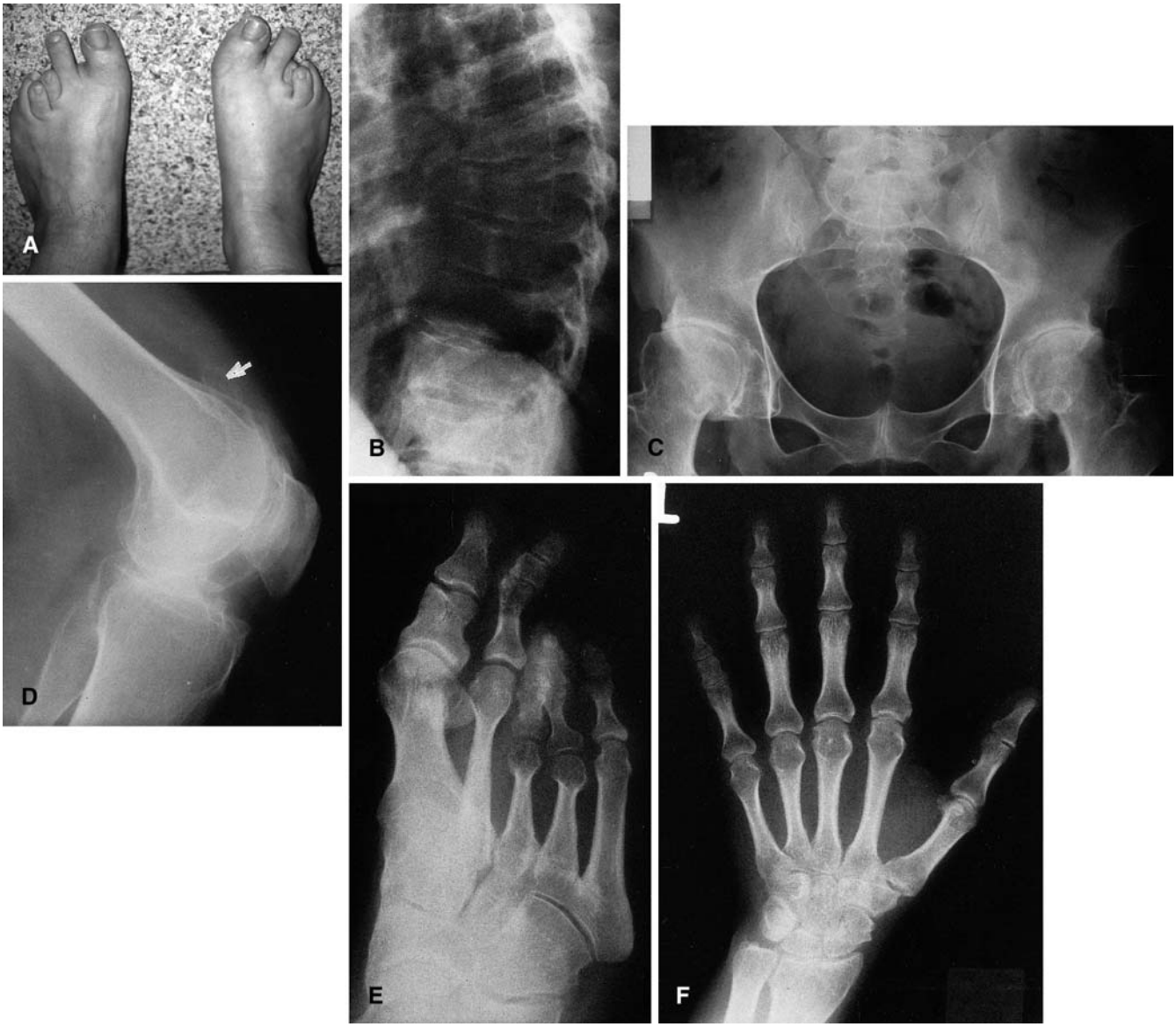
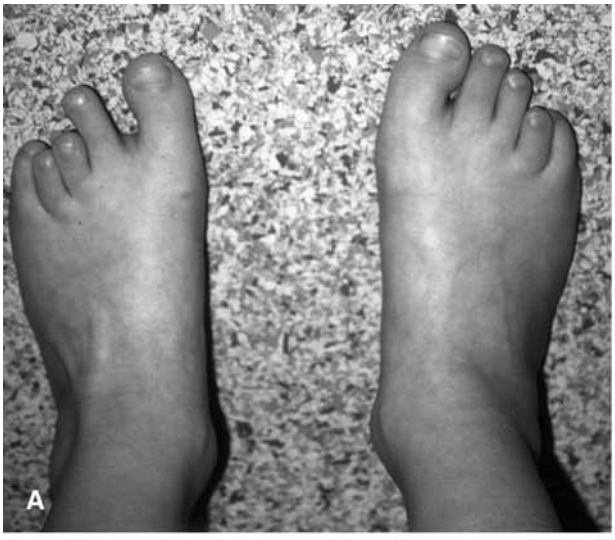
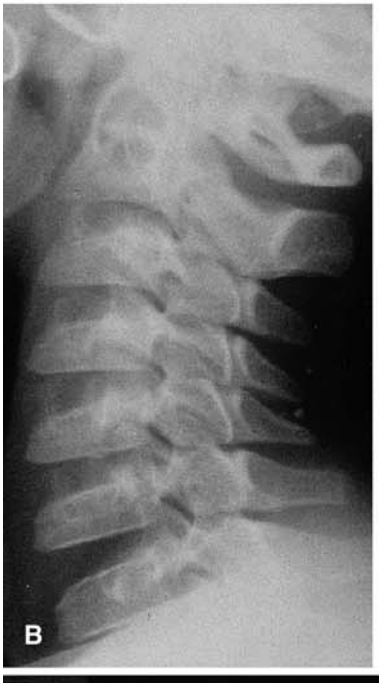
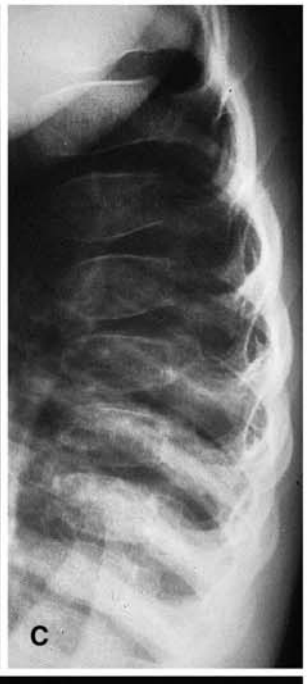


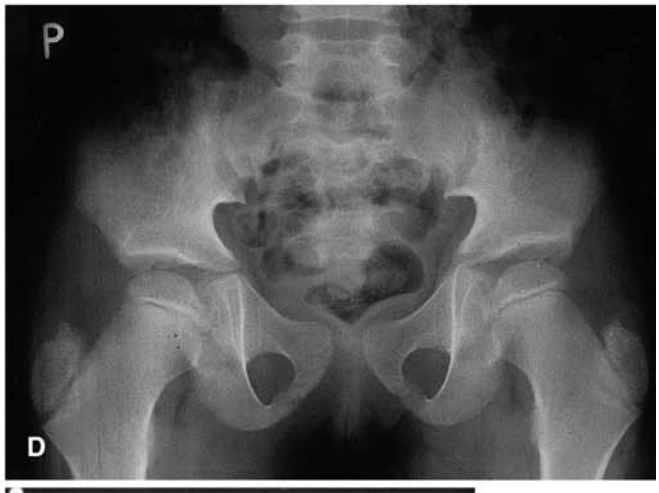
Fig. 4A–F Case 3, 28 years old. **A** Hypoplastic/dysplastic 3rd and 4th toes. **B** Platyspondyly. Slightly irregular vertebral plates. **C** The lower portions of the ilia are short and broad. Marked narrowing of all joints spaces. Flattened, slightly irregular femoral heads. **D** Irregular tibial plateau. Narrow knee joint space. Osteoarthritic changes. Loose body at the anterior aspect of the femur (*arrowed*) **E** Shortening of the 3rd and 4th metatarsals. **F** Narrowed articular spaces of all the hand joints. Osteoarthritic changes in the wrists

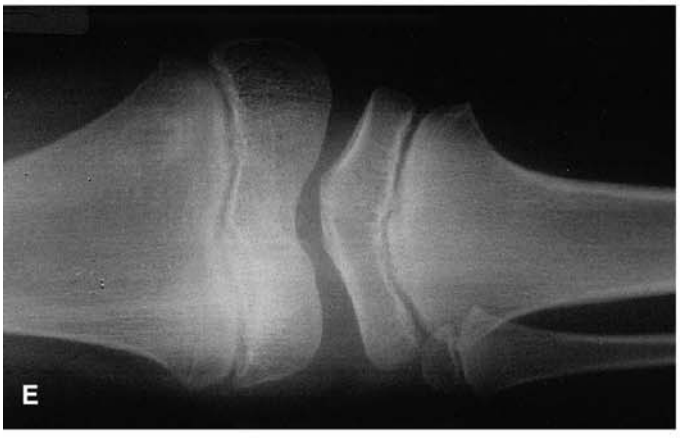
recessive trait, whereas in our family the genetic transmission is dominant. Distinctive phenotypic features not reported in PPsRD were hypoplasia/dysplasia of one or two toes in the feet, present in all our patients. Similar, slightly peculiar faces with hypertelorism in cases 1, 2 and 4 are probably a family trait not related to PPsRD. Early, severe synovial chondromatosis is an unusual finding in PPsRD. All our patients were of normal height. Peculiar radiographic findings are hypoplasia of the 3rd and/or 4th metatarsals presenting clinically as hypoplasia/dysplasia of the toes (Fig. 4E). In the spine there was an increase in the anteroposterior diameter of the vertebral bodies, and in the children, in addition, there was a biconvex shape of the vertebral bodies. The shape of the lumbar spinal canal in the anteroposterior projection was rectangular (constant interpediculate distances L1–L5). Early synovial chondromatosis(cases 1 and 3) has not been documented in PPsRD. Finally radiographs of the hands do not show the striking changes found in the autosomal recessive type of PPsRD: expansion of the metaphyses adjacent to the proximal interphalangeal


A


B


C


P
D


E

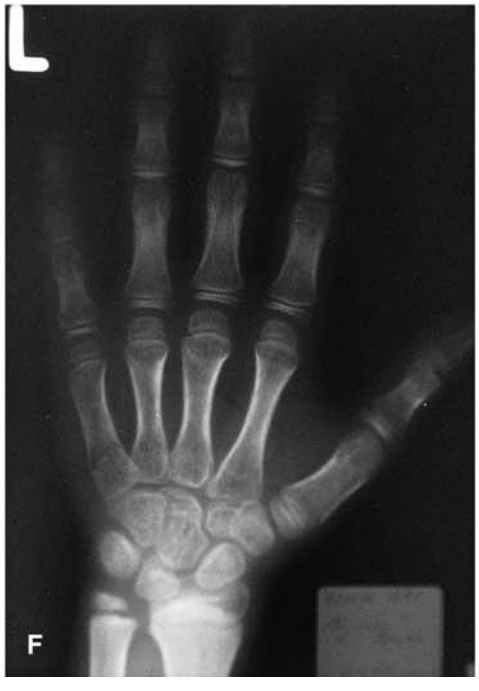

L
F

Fig. 5A–F Case 4, 5 years 8 months old. **A** Hypoplastic/dysplastic right 4th and left 3rd and 4th toes. **B** Flattened, anteriorly wedged cervical vertebral bodies. **C** Flattened, ovoid thoracic vertebral bodies. **D** The lower portions of ilia are short and broad. Flattened capital femoral epiphyses. Broad femoral necks. **E** Slightly flattened knee epiphyses. Narrowing of the knee joint space. Widened knee metaphyses. **F** Narrowing of all the hand joint spaces. Advanced bone age

joints, that is at the ends of the proximal phalanges and the proximal ends of the middle phalanges.

The differential diagnosis is juvenile rheumatoid arthritis (JRA). This term describes a heterogeneous group of chronic inflammatory arthritides that begin in childhood [16]. Confusion with the disorder as presented in our patients is unlikely as JRA is associated with systemic symptoms such as fever, skin rash, lymphadenopathy, hepatosplenomegaly and positive rheumatoid tests. The radiographic changes are characterised by osteoporosis. Some of the JRA forms—systemic arthritis and polyarthritis—may give rise to crippling disabilities but not to the radiographic appearances documented in our family.

Confusion with other bone dysplasias, specifically spondyloepiphyseal dysplasias (SED), autosomal dominant spondylarthropathy (ADS) and spondyloepiphyseal dysplasia tarda, X-linked (SEDT), is unlikely if the observer is familiar with PPsRD. Patients with "pure" SED (without significant metaphyseal involvement) do not have severe joint pain in the first decade of life and shortening of the stature is often the first and major clinical finding. In SED the most severely affected joints are also the hip and knee joints, but the clinical course is less debilitating than in PPsRD. ADS presents in the second decade of life or later and progresses slowly [14]. SEDT, X-linked is usually asymptomatic in early childhood [15]. Toe hypoplasia secondary to shortened metatarsals is a distinctive finding in our family. Synovial chondromatosis was reported in one family with PPsRD—a 36-year-old man and his older sister [7]. These patients were, like ours, of normal adult height. The mother of Rasore-Quartino et al.'s patient [9] showed minimal features of the disease. Her spine was normal. As variable expressivity is typical of an autosomal dominant trait and mild manifestations of autosomal recessive disorder may be present in a heterozygote, the mode of inheritance in this Italian family is uncertain. The possibility of osteoarthritis not related to PPsRD cannot be excluded with certainty. The clinical history, clinical examination, biochemical tests and radiographic documentation of our patients are consistent with PPsRD. In spite of overlaps with the previously reported families, additional distinctive manifestations of our family—dominant type of inheritance, weather-dependent arthralgia, unique phenotypic and radiographic features characterised by hypoplasia of the metatarsals, rectangular lumbar spinal canal in adults, and osteoarthritis complicated by early severe synovial chondromatosis—have, to the best of our knowledge, not previously been described in PPsRD.

The gene responsible for the recessive type of PPsRD is localised on the long arm of chromosome 6–6q22 [4].

We believe that our patients have a previously unreported dominant form of PPsRD.

References

1. Spranger J, Albert C, Schilling F. A progressive connective tissue disease with features of juvenile rheumatoid arthritis and osteochondrodysplasia. Eur J Pediatr 1980; 133:187.
2. Al-Awadi SA, Farag TI, Naguib K, El-Khalifa MY, Cuschieri A, Hosny G, Zahran M, Al-Ansari AG. Spondyloepiphyseal dysplasia tarda with progressive arthropathy. J Med Genet 1984; 21:193–196.
3. El-Shanti HE, Omari HZ, Qubain HI. Progressive pseudorheumatoid dysplasia: report of a family and review. J Med Genet 1997; 34:559–563.
4. Hurvitz JR, Suwairi WM, Van Hul W, El-Shanti H, Superti-Furga A, Roudier J, Holderbaum D, Pauli RM, Herd JK, Van Hul E, Rezai-Delui H, Legius E, Le Merrer M, Al-Alami J, Bahabri SA, Warman ML. Mutations in the CCN gene family member WISP3 cause progressive pseudorheumatoid dysplasia. Nat Genet 1999; 23:94–98.
5. Kaibara N, Takagishi K, Katsuki I, Eguchi M, Masumi S, Nishio A. Spondyloepiphyseal dysplasia tarda with progressive arthropathy. Skeletal Radiol 1983; 10:13–16.
6. Kozlowski K, Kennedy J, Lewis IC. Radiographic features of progressive pseudorheumatoid arthritis. Australas Radiol 1986; 30:244–250.
7. Legius E, Mulier M, Van Damme B, Fryns JP. Progressive pseudorheumatoid arthritis of childhood (PPAC) and normal adult height. Clin Genet 1993; 44:152–155.
8. Perri G, Vichi G, Pacibi M, Jenusco R, Bartolozzi G, Calzolari C. Unusual cone shaped epiphyses in spondyloepiphyseal dysplasia. Case report. Pediatr Radiol 1987; 17:223–225.
9. Rasore-Quartino A, Camera A, Camera G. Spondyloepiphyseal dysplasia tarda with progressive arthropathy: description of a patient whose mother showed minimal features of the disease. Pathologia 1993; 85:225–231.
10. Rezai-Delui H, Mamoori G, Sadri-Mahvelati E, Noori NM. Progressive pseudorheumatoid chondrodysplasia: a report of nine cases in three families. Skeletal Radiol 1994; 23:411–419.
11. Spranger J, Albert C, Schilling F, Bartsokas C, Stoss H. Progressive pseudorheumatoid arthritis of childhood (PPAC). A hereditary disorder simulating rheumatoid arthritis. Eur J Pediatr 1983; 140:34–40.

12. Teebi AS, Al Awadi SA. Spondyloepiphyseal dysplasia tarda with progressive arthropathy: a rare disorder frequently diagnosed among Arabs. J Med Genet 1986; 23:189–191.
13. Wynne-Davies R, Hall C, Ansell BM. Spondylo-epiphyseal dysplasia tarda with progressive arthropathy. A "new" disorder of autosomal recessive inheritance. J Bone Joint Surg Br 1982; 64:442–445.
14. Spranger JW, Brill PW, Poznanski AK. Bone dysplasia, 2nd[nd] edn. New York: Oxford University Press, 2002:168–169.
15. Maroteaux P, Le Merrer M. Maladies osseuses de l'enfant, 4th edn. Paris: Flammarion, 2002:146–148.
16. Schneider R, Passo MH. Juvenile rheumatoid arthritis. Rheum Dis Clin North Am 2002; 28:503–530.