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ORIGINAL PAPER

Pachydermoperiostosis–critical analysis with report of five unusual cases

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Abstract Pachydermoperiostosis (idiopathic hypertrophic arthropathy) {MIM 167100} is an uncommon disease characterized by unique phenotype (digital clubbing and pachydermia) and distinctive radiographic appearances (periostosis). Two families are reported that, in additional to the typical phenotype and radiographic characteristics of pachydermoperiostosis, show some rare and/or unusual, not yet reported, clinical findings. In the first family, distinctive features were severe progressive arthritis with villonodular involvement of the knees. The clinical course of the disease was much more severe than usually reported. The older brother was disabled at the age of 29 years. In the second family, the clinical history was exceptional, with unique early appearance of clinical signs. Pachydermoperiostosis is usually inherited as a dominant trait, but probable autosomal recessive inheritance has been reported. Also in the present families, autosomal recessive inheritance is likely, possibly explaining the severe clinical course of the disease. Differential diagnosis and the confusing nomenclature of pachydermoperiostosis are discussed.

Keywords Pachydermoperiostosis · Pachydermia · Digital clubbing · Periostosis · Villonodular synovitis

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Introduction

Pachydermoperiostosis (PP) is characterized by digital clubbing, pachydermia and periostosis [1, 2, 5, 7, 8, 11, 13–17, 19–31]. The disease is easy to diagnose when all three major characteristics are present. Symptoms usually appear in the second decade of life, progress slowly and became stationary or even regress after approximately 10 years. Diagnostic difficulties and nomenclature confusion do appear in the early stages of the disease, in single, nonfamilial cases presenting with two ("incomplete form") or especially one characteristic ("form fruste") [4, 12, 22]. We report on two families of PP with noteworthy symptoms and signs and discuss the differential diagnosis and the confusing nomenclature of PP.

Case reports

Family I

Patient I

This 20-year-old man presented to the Ambulant Centre for Defects of Locomotor Apparatus for evaluation of abnormal gait, back pain and swollen knees and ankles. He was

born to a 19-year-old C1P1AO mother and 23-year-old father after a pregnancy of 40-weeks gestation and normal delivery. Birth weight, length and OFC were all around 50th percentile. The parents were healthy and not related but from the same geographical area. The family history was noncontributory. His physical development was normal in the first decade of life.

Bilateral, progressive, intermittent pain and restriction of knee joint motion were noted early in the second decade of life. This was followed by joint swelling. At that time, clubbing of his digits was noted. His mental development was normal. PP was diagnosed in the Paediatric Department in Klatovy at the age of 16.5 years. At the age of 18 years, a partial synovectomy of the left knee was performed. Villonodular synovitis was diagnosed. On examination at the age of 20 years, his height was 180 cm, weight 64 kg. Pertinent physical findings were painful waddling gait, relatively long extremities and short trunk. All the big joints were prominent. Effusion was noted in the knee and ankle joints. There was generalized restriction in joint movements with the knees being most severely affected.

The skin of the head was thick and greasy. The nasolabial folds and transverse furrowing of the forehead were prominent. There was eyelid ptosis more marked on the left. The hands and feet were large with marked clubbing of the digits. There was thickened skin of the palms and soles, which sweated profusely (Fig. 1a,b). Radiographic examination documented narrowing of the hip joint space. There was expansion of the tubular bones and periosteal thickening most marked at the distal end of the long bones of the forearms, shanks and proximal end of the femora. In the hands, there were osteoarthritic changes in the carpal bones, with narrowing of the joint space. The proximal ends of the middle phalanges were widened, and there was periosteal thickening of the second through fourth metacarpals. There was sclerosis of the base of the skull (Fig. 1c–f).

Biochemical tests revealed slightly low levels of hemoglobin, elevated ESR and low total cholesterol (2.76 mmol/l; norm 3.20–5.20 mmol/l). Remaining routine blood and urine examinations were normal. There was marked increase in C-reactive protein (CRP) (106.7 mg/l; norm 0–10 mg/l) and bone-modelling markers (serum osteocalcine, urine pyridinoline and deoxypridinoline).

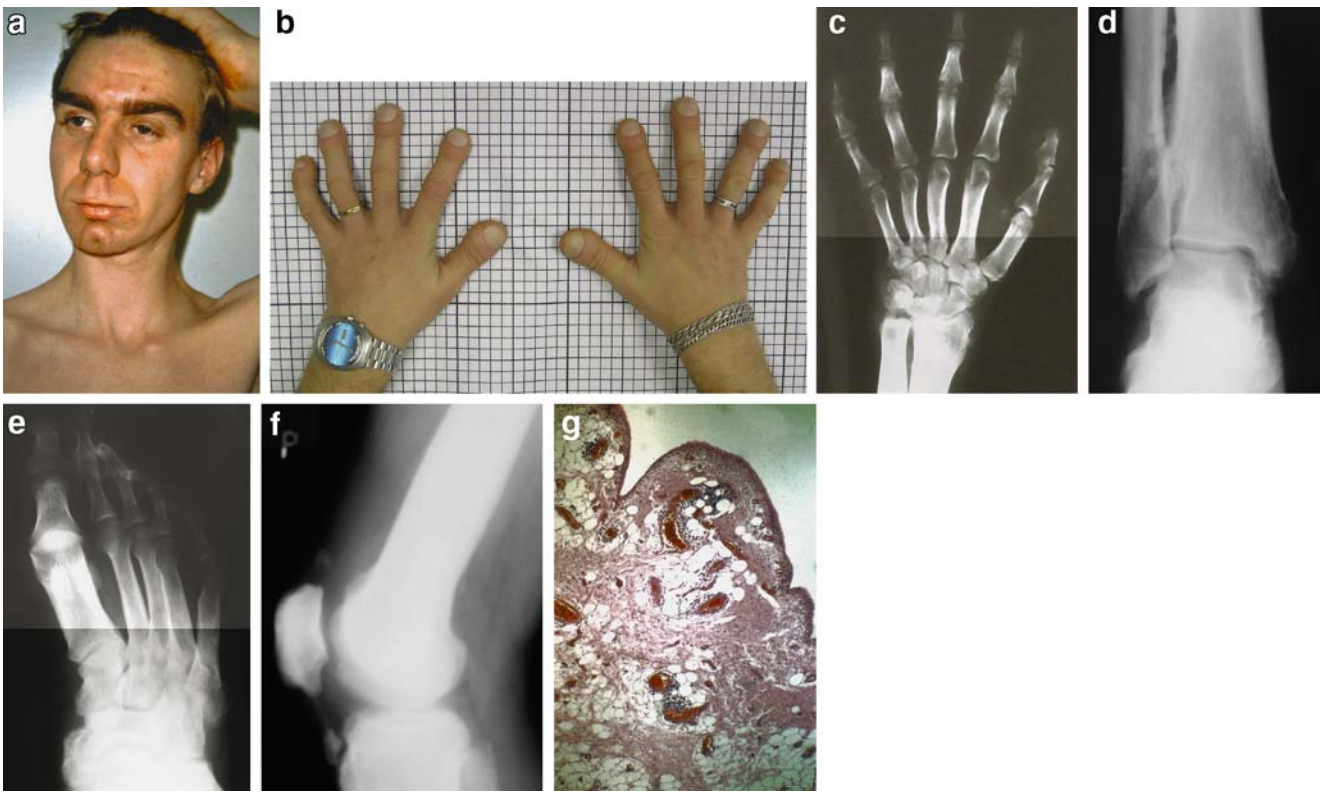

Fig. 1 Patient 1. **a** Deep frontal and nasolabial folds, heavy eyelids, ptosis of the left eyelid, oily facial skin. **b** Broad hands. Clubbing of fingers, swollen interphalangeal joints, round turtle-back-shaped nails. **c** Narrowing of the joint space. Irregular outline of the carpal bones and proximal end of the metacarpals. Periosteal thickening of the metacarpals. Widening of the proximal end of the middle phalanges. **d** Periosteal new bone formation at the distal right tibia and in the interosseous membrane. **e** Extensive periosteal new bone formation at the metatarsals. **f** Soft tissue swelling. Erosion at the lower aspect of patella and anterior aspect of distal femur. Separation of tibial apophysis. **g** The lesion shows villous hypertrophy of the synovium consistent with villonodular synovitis. The villi contain large amounts of fat and loose fibrous tissue. There is synovial epithelial hyperplasia. A focal lymphocytic infiltrate that is predominantly perivascular is present (125×HE)

Anti-inflammatory therapy with nonsteroid drugs (nimesulid and diclofenac) was introduced. Therapy with anti-resorptive drugs such as bisphosphonates was not considered because of higher bone density of proximal femora and normal bone density of the spine at densitometric examination (DEXA). Partial synovectomy of the right knee was performed at the age of 22 years. Villonodular synovitis was diagnosed with light microscopy (Fig. 1g). After the operation there was relief of pain and decrease of swelling of the right knee, but restriction of movements of the knee as well as other big joints progressed. The CRP levels remained high (62.7–33.3 mg/l) in spite of continuous anti-inflammatory therapy. At the age of 29, the patient was incapacitated and received an invalid pension.

Patient 2

This 19-year-old man is the brother of Patient 1. He was born after a normal pregnancy and delivery. His development was normal until the age of 17 years when painful swelling of the right knee appeared, and clubbing of the digits similar to that of his brother was noted. At the age 19 years, radioisotope synovectomy of the right knee was carried out. There was temporary relief of symptoms. Because of the progression of the right-knee swelling with arthralgia and limitation of movements, arthroscopy was performed. It showed advanced inflammatory changes in synovial membrane and hypertrophied villi.

The patient was examined at the Ambulant Centre for Defects of Locomotor Apparatus at the age of 19.5 years. His height was 178 cm, weight 64 kg. He complained of pain and swelling of the right knee. His phenotype and clinical examination were similar to those of his brother. Additionally he had pectus excavatum. The right knee was painful and swollen. Mild restriction of the joint movements was present. Biochemical tests and radiographic examination documented changes similar to those of his brother. Partial synovectomy of the right knee was performed at the age of 20. Villonodular synovitis was diagnosed. There was relief of knee pain but no improvement of knee movement. In spite of treatment with anti-inflammatory drugs, CRP remained increased. Densitometry showed similar results as for his brother, and treatment with anti-resorptive drugs was not introduced.

Family II

Patient 3

This 18-year-old man was presented at the Department of Medical Genetics for diagnosis. He was born to a 28-year-old C1P1AO mother and 29-year-old father after a pregnancy of 36-weeks gestation and normal delivery. The parents were healthy, not related but from the same geographical area. The family history was negative. Specifically there were no members in the family who showed any features of pachydermoperiostosis. Birth weight was 2,500 g. The amniotic fluid was green. The fluid was not analyzed, but there was no evidence of infection.

Immediately after birth it was noted that the child had "too much skin." The anterior fontanelle was about 6 cm in length. It closed after the second year of life. Since birth, increased perspiration was noted. Insidious enlargement of the hands and feet with clubbing of the distal ends of the digits appeared at the age of four. As a teenager, the patient complained of pain on movement in the knees, ankles and wrists. This was associated with enlargement of the joints. Increasing thickening of the skin at the palms and soles appeared during adolescence.

On examination at the age of 18 years, his height was 179 cm (50th percentile), weight 56 kg (below 10th percentile), HC 56.5 cm (25–50th percentile). He showed a marfanoid habitus with poor development of the muscles and subcutaneous tissue. Seborrhea was noted. His facial skin was oily and devoid of expression. The facial folds were prominent. He looked older than his age (Fig 2a). There was funnel deformity of the chest. The knees, ankles and wrists were enlarged and of decreased mobility. The hands and the feet were large and wet with clubbing of digits. The nails were turtle-back shaped with longitudinal striations. There was palmoplantar hyperkeratosis. The hair and teeth were normal. He walked with a clumsy gait. Radiographic examination documented generalized osteoporosis. The diaphyses and metaphyses of the long bones were expanded. The cortex of the long bones was thin and there was little periosteal thickening (Fig 2b). There was acroosteolysis of the distal phalanges of the hands and feet.

Patient 4

This 17-year-old man was more severely affected than his older brother, Patient 3. He was born after a pregnancy of 36-weeks gestation and normal delivery. The fetal movements during the pregnancy were noted to be decreased. The amniotic fluid was green. Birth weight was 2,800 g. His knees and ankles were enlarged and his feet were large. There was also limitation of knee movements. Like his brother, he had "too much skin" and a large anterior fontanelle which closed after the second year of life. Increased perspiration was present since birth.

Insidious enlargement of the hands with clubbing of the distal end of the fingers appeared soon after he started to walk. Eruption of the primary teeth was delayed. The first teeth appeared at the age of 12 months. In spite of early physiotherapy, he started to walk after the second year of life. His gait was always clumsy and by the time he finished

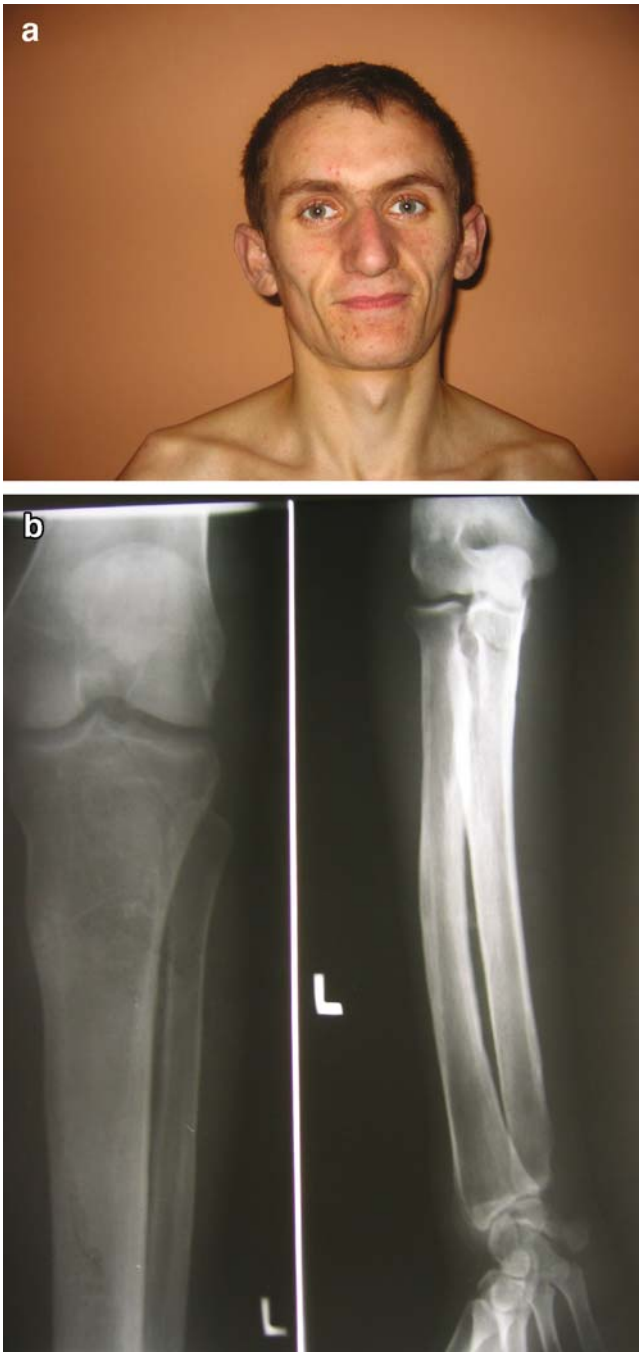

Fig. 2 Patient 3, 18 years old. **a** Similar facial appearances to his brother (see Fig. 3a). **b** Similar appearances to his brother (Fig. 3e and f)

primary school, he walked on his toes. Since early childhood, he complained of pain on movements and stiffness in the knees, ankles and wrists. This was associated with enlargement of the respective joints, which were painful on palpation. Increased thickening of the skin at the palms and soles appeared early during adolescence.

On examination at the age of 17 years, his height was 178 cm (50th percentile), weight 58 kg (below 10th percentile), HC 55 cm (below 10th percentile). He showed a marfanoid habitus with poor development of the muscles and subcutaneous tissue (Fig. 3). Seborrhea was noted. His facial skin was oily with prominent folds and devoid of expression. He looked older than his age. His palate was high, and the teeth were crowded. There was scaphoid deformity of the chest. The knees, ankles and wrists were enlarged and of decreased mobility. The hands and feet were large with clubbing of digits. There were contractures in the interphalangeal joints resulting in paw-like appearance of the hands. The nails were thick and turtle-back shaped. There was palmoplantar hyperkeratosis, and the palms and soles were wet. Scattered hyperkeratosis foci were present at the dorsum of the hands. He walked on his toes. Radiographic examinations showed changes similar to those of his brother (Fig. 3d–f).

Patient 5

This 10-year-old girl was less affected than her brothers. She was born after a pregnancy of 36-weeks gestation and normal delivery. The amniotic fluid was green. Birth weight 2,000 g. Like her brothers she had "too much skin" and a large anterior fontanelle which closed after the second year of life. Increased perspiration was noted soon after birth.

At the age of 3 years, it was noted that she had relatively large hands and feet. Clubbing of the distal end of the digits and nail changes were noted later than in her brothers. On examination at the age of 10 years, her height was 147 cm (75th–90th percentile), weight 46.5 kg (above 90 percentile), HC 53 cm (50th percentile). Her muscles and subcutaneous tissue were well developed. Her face was devoid of expression, and she looked older than her age. There was mild funnel deformity of the chest. She did not have joint complaints, and her walking was normal. The hands and feet were large with clubbing of the digits. There were thick, turtle-back nails (Fig. 4). There was palmoplantar hyperkeratosis but no seborrhea. Radiographic examination documented generalized osteoporosis, thin cortex of the long tubular bones and minimal acroosteolysis of the distal phalanges of the hands.

In all the siblings of the second family the mental development, the routine blood and urine examinations, serum calcium, phosphorus, alkaline phosphatase and karyotype were all normal.

Discussion

We do not discuss the history of PP research or differential diagnosis between PP and secondary hypertrophic osteoarthropathy (secondary to pulmonary neoplasms and a variety of other intrathoracic and extrathoracic disorders) as they have been described at length in numerous papers and textbooks [1, 2, 5, 7, 8, 11, 13–31].

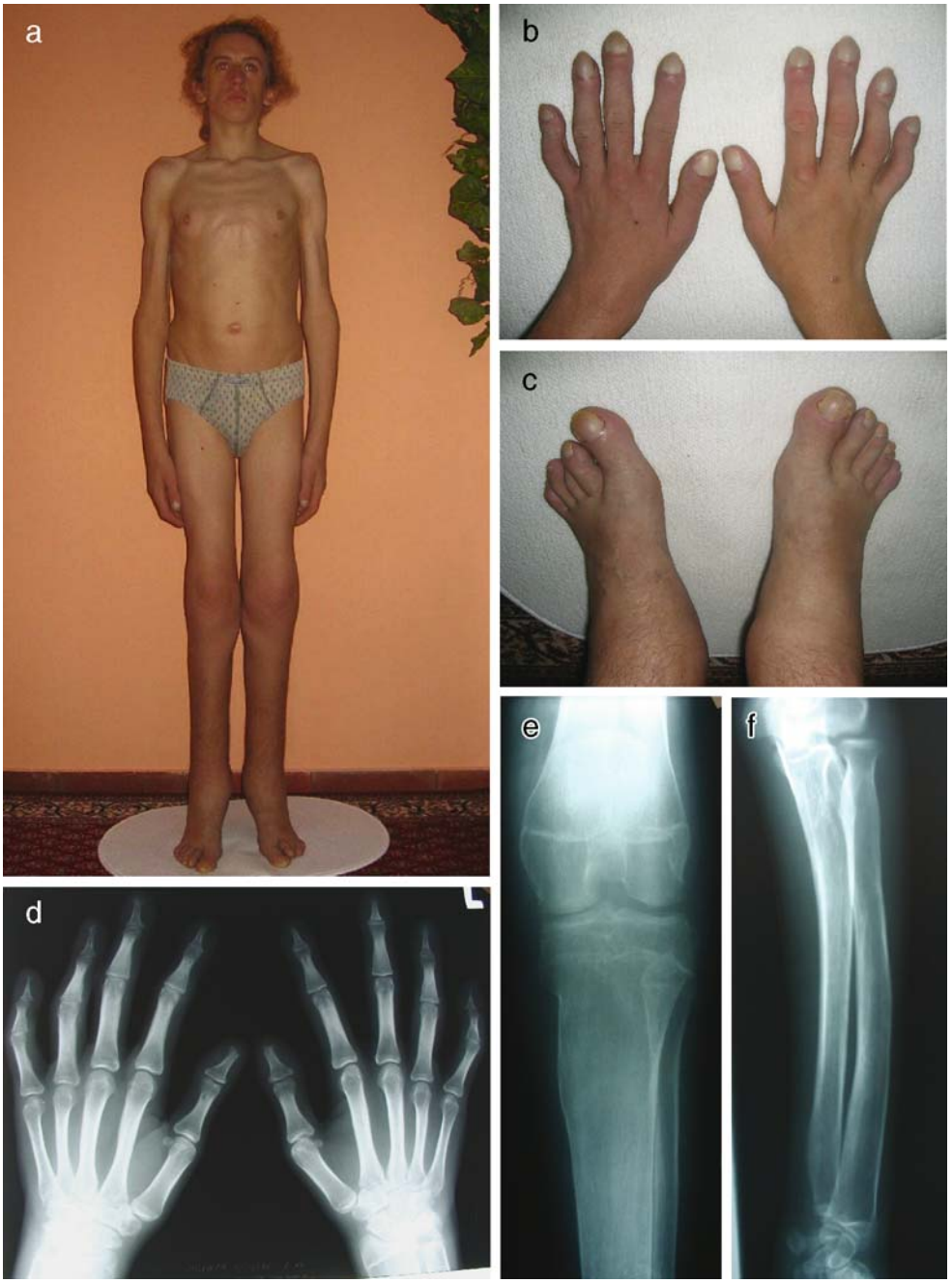

Fig. 3 Patient 4, 17 years old. **a** Marfanoid habitus. Poor subcutaneous and muscular development. Swollen knee and ankle joints. Deep frontal and nasolabial folds. Looks much older than his age. **b** Claw deformity of the hands. Swollen and deformed proximal interphalangeal joints. Clubbing of the fingers. Turtle-back-shaped nails. **c** Swollen ankle joints and clubbing of toes. Turtle-back-shaped nails with longitudinal striations. **d** Narrowing of the joint spaces. Hypoplasia of the fourth and fifth metacarpals. Acroosteolysis. **e** Osteoporosis. Abnormal trabecular pattern. Thin cortex. Periosteal thickening at the proximal, medial aspect of the left tibia. **f** Osteoporosis. Loss of normal trabecular pattern. Periosteal thickening at the proximal end of ulna

PP predominantly affects soft connective tissue (digital clubbing), skin (pachydermia) and bone (periosteal thickening). Arthralgia or arthritis is present in 20–40% of all cases. Major joints are usually affected. Most often hands and feet are spared. After the active phase during adolescence, articular manifestations may become stationary or even resolve spontaneously [15].

Severe progressive arthalgia and arthritis in knees, ankles, wrists and proximal interphalangeal (PIP) joints were distinctive signs and symptoms in our first family. Because of the severity of knee involvement, subtotal synovectomy was performed in both brothers. The younger brother had temporary relief of right knee pain after radioisotope synovectomy. After recurrence of symptoms, surgical subtotal synovectomy in the right knee was carried out. Surgical joint procedures are rarely performed in patients with PP, but in rare cases, in which synovial biopsy has been done, lymphocytic and plasmacytic infiltration of the synovial membrane has been reported. Villonodular synovitis has rarely been observed in PP. Villonodular synovitis has locally aggressive behavior and capacity to invade bone, joint capsule, tendons and adjacent soft tissues. There was invasion of bone in patient 1. Although villonodular synovitis usually affects only one

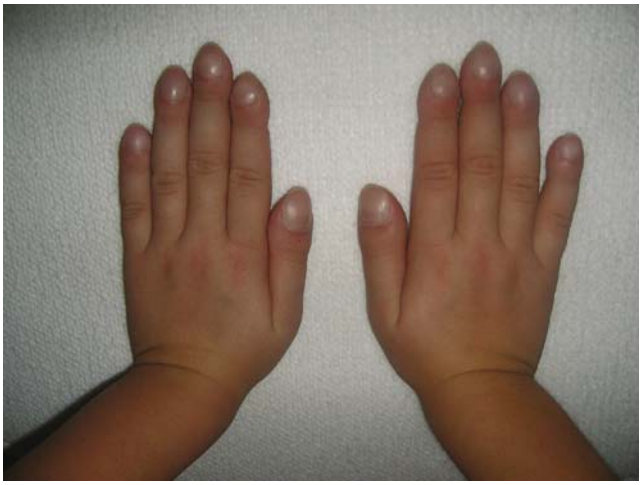

Fig. 4 Patient 5. Clubbed fingers with turtle-back-shaped nails

big joint, both knees were affected in the older brother [33]. Eyelid ptosis was another sign of the severity of the disease.

Distinctive features in the second family present in all the siblings were green amniotic fluid, "too much skin," large anterior fontanelle with late closure and increased perspiration since birth. Decreased fetal mobility of patient 4 was an unusual finding not yet reported in PP. Cardinal features of PP, such as large hands and feet, abnormal nails, increased perspiration, palmoplantar hyperkeratosis and joint pains appeared in this family much earlier than is usually reported in the literature. Some were present at birth, others were noted in the first few years of life. It is notable that although our patients did not show thickening of the skin of the face, their faces were devoid of expression, and they looked much older than their ages. The different radiographic features in families I and II are also interesting. In family I, the density of the skeleton was normal, and there was irregular periosteal bone formation. In family II, there was generalized osteoporosis with cortical thinning, little cortical reaction and acroosteolysis.

Genetics

The genetics of PP is best explained as autosomal dominant inheritance with marked variability in expression [29]. Recessive inheritance is suggested by instances of affected sibs with apparently normal consanguineous parents [5]. Clinical history, absence of incomplete forms in the families and a severe course of the disease suggest that PP in our families was the result of recessive inheritance. The chromosomal location and gene abnormality of PP are unknown.

Nomenclature

Variability in expression in dominantly inherited form causes confusion in the nomenclature of PP. We believe that the name of PP should be used only for cases with three major characteristics: digital clubbing, pachydermia and periosteal thickening. The name "incomplete form" of PP should be limited to patients with two major characteristics and "forme fruste" to patients with one major characteristic who have relatives affected with PP. We do not agree with the diagnosis of PP in patients with one or two characteristics, without relatives affected with PP [4, 12, 22].

Differential diagnosis

Diagnosis of PP is easy when all three major characteristics —**clubbed digits**, **pachydermia** and **periostosis**—are present. As a rule, PP remains unrecognized in the early stages of the disease, that is when the symptoms are mild and uncharacteristic and the phenotypic abnormalities are not yet fully developed. In these early stages of the disease, skin disorders, rheumatic conditions, or idiopathic digital clubbing are diagnosed. Presence of PP in the family makes the early diagnosis of "incomplete" or "fruste forms" possible.

According to some authors [1, 5, 19], onset of PP is bimodal with the first peak of incidence during the first year of life and the second in adolescence. In the recent paper "PP: an update," Castori et al. [5] stated the age of PP onset at birth in 5.9% of cases, 0–2 years in 11.7% of cases, and 3–11 years in 25% of cases. We believe that these statistics are erroneous. They include patients with uncertain or unproved diagnosis ("incomplete forms"—isolated, without familial association) [4, 12, 22], and cases of familial idiopathic osteoarthropathy (FIO) (Currarino syndrome) [3, 6, 9, 10, 32]. According to Maroteaux [20], childhood cases of PP are exceptional. We infer that the authors are assuming that patients reported as having FIO have PP, and these patients represent the first peak of incidence.

We regard FIO as a disorder different from PP. However the relationship between PP and FIO of Currarino [10] will remain debatable until the gene for PP is found. Early infantile presentation of our second family with PP was quite different from that of FIO. DNA investigations may also help to explain the differences in the history, phenotype, and radiographic appearances in our families with PP.

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