

Pachydermoperiostosis

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Creation date: April 2004

Scientific Editor: Professor N. Stavrianeas

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[Abstract](#)

[Key-words](#)

[Disease name and synonyms](#)

[Definition/ Diagnosis criteria](#)

[History](#)

[Epidemiology](#)

[Differential diagnosis](#)

[Etiology](#)

[Clinical description](#)

[Physiopathology](#)

[Diagnostic methods](#)

[Genetic counselling](#)

[Treatment](#)

[References](#)

Abstract

Pachydermoperiostosis (PDP) is a rare hereditary disorder that is characterized by digital clubbing and subperiosteal new bone formation associated with pain, polyarthritits, cutis verticis gyrata, seborrhea, hyperhidrosis. The precise incidence of the disease is unknown. PDP is often familial and occurs predominantly in men. It is believed to be inherited in an autosomal dominant pattern with variable penetrance; autosomal recessive forms have also been reported.

Three forms of PDP are described: complete, incomplete and fruste form. PDP is manifested mainly by dermatological (pachydermia, thickening and furrowing of the facial feature, digital clubbing, cutis verticis gyrata, seborrhea, oedema, hyperhidrosis) and rheumatological symptoms (joint effusion, arthritis, acro-osteolysis, periosteal ossification). Rheumatologic symptoms can be improved by nonsteroidal anti-inflammatory drugs or corticosteroids or colchicine. Clinical improvement of the dermatological symptoms was achieved by retinoids. Plastic surgery may be helpful for complications on the face. Finger clubbing surgical reduction has been tried with success.

Key-words

idiopathic hypertrophic osteoarthropathy, pachydermia, periostosis, finger clubbing., seborrhea hyperhidrosis, nonsteroidal anti-inflammatory drugs, corticosteroids, colchicine

Disease name and synonyms

Primary hypertrophic osteoarthropathy,
Idiopathic hypertrophic osteoarthropathy,
Hereditary hypertrophic osteoarthropathy,
Touraine-Solente-Gole syndrome.

associated to several diseases and sometimes occurs as paraneoplastic syndrome. The pachydermoperiostosis (PDP) represents the primary or idiopathic form of HOA, in which the skin involvement is the main feature.

Diagnosis criteria are the followings:

Major criteria: pachydermia, periostosis, finger clubbing.

Minor criteria: hyperhidrosis, arthralgia, gastric ulcer, cutis verticis gyrata, blepharoptosis, joint

Definition/ Diagnosis criteria

The hypertrophic osteoarthropathy (HOA) is a syndrome characterized by finger clubbing, periostosis and arthritis. The secondary form is

effusion, column-like legs, edema, seborrhea, acne, hyperhidrosis, flushing.

The clinical suspicion of PDP is confirmed by radiography of the long bones.

History

Friedreich described first in 1868 a familial case of HOA (1) that he called "Hyperostosis of the entire skeleton". In 1890, Pierre Marie named this condition "Osteoarthropathie Hypertrophique Pneumique"(2). Touraine, Solente and Golé (3) in 1935 first individualized the PDP as the primary form of HOA: "la pachydermie plicaturée avec pachyperiostose des extrémités", and proposed a classification (3, 4) where the **complete form** includes pachydermia, clubbing, perisostosis; the **fruste form** has prominent pachydermia with minimal skeletal changes; and the **incomplete form** has no pachydermia.

Cutis verticis gyrata form of pachydermia of the face and the scalp, first described by Unna (5) and Jadassohn (6) in 1906-1907, is a symptom sometimes found in PDP, but described also in other conditions.

Epidemiology

The PDP is a rare syndrome and the precise incidence is unknown. There are 96 cases published from 1947 to 1990 (7) and at least 50 cases since 1990. It seems more frequent when systematically searched, with 5 cases for 1820 outpatients consulting in different specialities for a one-month period, with a prevalence of 0,16% (8). PDP occurs predominantly in men with a ratio 9:1 (9,10), and has been reported in many races. Typically, men are affected more severely than women.

Differential diagnosis

The *secondary form of hypertrophic osteoarthropathy* occurs predominantly in men aged 30-70, with bone changes that develop rapidly, and are often more painful. The skin changes may be absent or mild. In case of rapid treatment of the primary disease, the bone and skin changes can regress (31).

Cutis verticis gyrata has a primary essential form without other symptoms (52), a primary non essential form with mental deficiency syndrome and ophthalmologic abnormalities (53, 54), and a secondary form that occurs in myxoedema, in certain hematodermia, in [neurofibromatosis](#), and in [acromegaly](#) (55).

Psoriasis: The psoriatic onycho-pachydermoperiostitis is limited to the extremities and characterized by psoriatic nail involvement, thickening of the soft tissue of the fingers and toes, and osteoperiostitis of the distal phalanges, lack of clubbing, and may be associated with

psoriatic skin lesions. It is considered as a form of [psoriatic arthritis](#) (56).

Acromegaly: In acromegaly the facial skeleton, the jaw and the skull as a whole are enlarged, and radiological visual defects may be detectable.

Rheumatoid arthritis: Joint features of HOA can mimic rheumatoid arthritis, but in PDP the erythrocyte sedimentation rate is normal, and the arthrocentesis shows a non-inflammatory fluid.

Etiology

PDP is often familial. It may affect several members of the same family. A familial history of PDP is found in 25-38% of patients (10-12).

The genetic transmission is usually ruled out by a dominant autosomal gene with variable expression and penetrance (4, 11-15). PDP has been described in consanguineous marriages (16,17), and autosomal recessive transmission may also occur (18, 19) with no difference in the severity of the symptoms (17), but with presence in some cases of growth retardation, early ulcers, and acrolysis of the distal parts of the extremities (19). Chromosomal abnormalities have been reported in PDP (20), but at this date no locus has been identified. HLA-b12 has been found in 44% of 18 patients (21).

Clinical description

The onset of PDP is usually in adolescence and often presents as enlargement of the distal extremities with clubbing. The skin and bone changes become progressively more severe for 5-20 years and usually remain unchanged throughout life. Incomplete form of PDP without pachydermia (22-24), or restricted to the lower extremities (25) or to the fingers (26) is rare (27).

Dermatological symptoms

Pachydermia is the most frequent symptom occurring on the face and on the extremities (dorsum of the hands and feet), and can be graded as (4):

- grade 0: absence
- grade 1: mild to moderate involvement (cutaneous thickening without puckering)
- grade 2: severe (cutaneous thickening with puckering).

Thickening and furrowing of the facial features, with deep nasolabial folds are usually observed. In 30% to 40% (12) of the cases the skin hypertrophy involves the eyelids and provokes ptosis (13,28). These symptoms on the face give a uniform expression of weariness and despair.

Cutis verticis gyrata seems to be more rare (13,16), it affects 24% of patients with PDP in a retrospective study of 125 cases (11), and can be seen in other pathologies.

The development of *clubbing* in childhood (27) is insidious, with enlargement of the hands, feet, and fingers during adolescence. The clubbing is a very frequent symptom and occurs in 89% of the patients with PDP (10,11). Nail bed capillary microscopy shows slight capillary enlargement and increased tortuosity (29).

The *oedema* involves usually the lower part of the legs with a column-like aspect, more rarely on the forearms.

Seborrhea is found in more than 90 %, with sebaceous hyperplasia, open sebaceous pores, oily skin, and sometimes folliculitis and acneiform rash (29). The skin appears greasy on the face and the scalp.

The *hyperhidrosis* is frequent, with profuse sweating of the palms and soles in 44% to 67% (10,12), sometimes involving the big folds, and may be associated with *flushing*.

Rheumatological symptoms

The *joint effusions*, present in 41% of patients with PDP (11), are located usually at the knees, with synovial fluid of non-inflammatory nature (30), with few polynuclear neutrophils (31).

Arthritis appears in PDP in 20-40% of cases, usually symmetric (4,31), and may be severe (30).

Acro-osteolysis is not rare and affects the terminal phalanges of fingers and toes (31-33).

The irregular *periosteal ossification* affects predominantly the distal ends of the long bones (29), in 80 to 97 % of patients (11,27). A pain in the joints and along the bones can be exacerbated by intake of alcohol (29, 34).

Other symptoms

Sparse facial and pubic hair;

Gynecomastia (35);

Average intelligence (29), rarely severe;

Periodontal and bone abnormalities (36).

In the childhood, these symptoms arise the problem of the differential diagnosis between primary and secondary HOA. Secondary HOA is common in cyanotic congenital heart disease, and in cystic fibrosis, it is more rare in pulmonary metastases, especially from bone tumors.

In childhood, the clinical signs of PDP are more rheumatoid (37, 38), and this diagnosis should be considered in any child presenting with joint pain and finger clubbing (37). Although symptoms may begin at age of 7 or 8, the problem does not strike attention until near adolescence. The most common presenting symptoms are aching along the tibial shafts, and/or effusions into the knees. Sometimes appears pain at the ankles, wrists and down the forearms. Dermatological symptoms as seborrhea and hyperhidrosis of hands and feet appear in adolescence. The typical pachydermia

appears in adulthood. Therefore the classification of the type of PDP is impossible in childhood (38). In young people, the periostitis tends to extend into the epiphyseal region and may be irregular, causing alterations in the shape and growth of the epiphyses. Infants have been reported with a distinct type of idiopathic hypertrophic osteoarthropathy, characterized by enlargement and delayed closure of the cranial sutures soon after birth, followed in the childhood by progressive painful swelling of the forearms and legs (38,39).

Complications

- Osteonecrosis of the femoral head (27,79).
- Carpal and tarsal tunnel syndrome (29), which can be explained by the stenosis of the tunnels secondary to the periosteal apposition and to the megaepiphysis.
- Neurological changes due to the compression of the spinal chord and nerve roots (34) are rare.

Associated diseases

Myelofibrosis, extra-medullary hematopoiesis
The anemia seems to be multifactorial, with myelofibrosis, gastro-intestinal bleeding associated with peptic ulcer or erosions (57) and presence of a serum inhibitor of the late stage of erythropoiesis (58). The myelofibrosis may occur without extramedullary hematopoiesis (44,58,59). In 3 cases myelofibrosis has been found associated with extramedullary hematopoiesis, 2 times in hepatosplenomegaly (57,60), 1 case in paravertebral mass with medullar compression (61,62). In rare cases, an extramedullary hematopoiesis may occur without myelofibrosis (63), with solitary tumors, suggesting the possible intervention of growth factors common to the skin fibroblasts and the blood progenitor cells in the pathogenesis of primary osteoarthropathy.

Gastric hypertrophy, atrophic gastritis, peptic ulcer

Reports of PDP associated with gastric involvement have been described in families (64) and in sporadic cases. The gastro-intestinal symptoms appear usually in the twenties and are severe, with gastric and duodenal ulcer (57 64,65). Oeso-gastro-intestinal pathology was found in 25 of 52 patients with PDP (27). The levels of serum pepsinogen I and II can be found elevated (64,66).

[Crohn's disease](#)

PDP has been found associated with inflammatory bowel disease and in particular with Crohn's disease (CD) (67,68). The PDP

precedes the CD usually 7 to 10 years. No genetic link has been found (18).

Anecdotic associations

Squamous cell carcinomas (65) appearing on the face of a 46 years old man, with 15 years course of PDP, attributed to chromosomal instability.

Papular mucinosis in two cases (69,70), with common in the two pathologies disorder of the fibroblasts.

Cases of primary digital clubbing have been associated with *palmoplantar keratoderma* (71).

Pyoderma gangrenosum (72).

Multiple basal cell carcinomas (73).

Acromegaly (74).

Physiopathology

The fibroblasts are at the center of the process of fibrosis (40,41), and may be found in an activate state of proliferation and fibrillogenesis, producing and increased amount of collagen fibers (13,42). Other studies did not found proliferation of the fibroblasts but a dysregulation of the matrix molecules synthesized by the fibroblast with increased matrix deposits and increased synthesis of decorin protein (41,43). These differences could be explained with the difference of stage of the disease in the patients examined. An increased proliferation of bone marrow derived fibroblasts has been shown (44). The evidence of platelet fibrin thrombi in some vessels suggests the possible role of the platelets with their potent growth factors (11,45), with evidence of increase of platelet-derived growth factor (46,47). It is not excluded that one or several others growth factors are involved in the process (40,42). The epidermal growth factor was found increased in urinary excretion (48). The Von Willebrand factor antigen levels (marker of platelet and/or endothelial activation) and vascular endothelial growth factor levels were elevated in plasma in different studies (49,50).

The role of alcohol consumption has been described in several cases (29,34) but has not been demonstrated. It could act as revealing factor in fruste forms (51) or aggravating factor, as it is in Launois-Bensaude lipomatosis.

Diagnostic methods

Radiology

Radiologic examination reveals soft-tissue swelling, irregular periosteal proliferation with cortical thickening of the long bones, metatarsal and metacarpal bones, and phalanges, and megaepiphysis at the long bones. Erosions of the joints are very rare (31). In some cases, calcifications of musculotendinous insertions, interosseous membranes (75, 76), and Achilles

tendon (29), rarely in the joints (77) may be found.

The scintigraphy shows a more intensive tracer accumulation in the area of the affected joints, of the clubbed fingers in more than 90% of patients (27).

Biology

In the greatest series of PDP (13), there were no biological abnormalities. Hypocholesterolemia (58,60) and hypergammaglobulinemia (58,64) have been reported in patients with PDP and remain unexplained.

Liver functions tests have been found pathological in 12 patients of a serie of 52 patients (27), but the consumption of alcohol was not mentioned.

The osteocalcin blood level, marker of osteoblastic activity, could be important to determine the degree of activity of the disease (9,48,58).

Histology

Light microscopy of the bone shows apositional rates, which are increased in cortical bone but reduced in trabecular bone, resulting in trabecular osteoporosis (30).

Light microscopy of the skin:

- acanthosis of the epidermis with normal granular layer;
- in the dermis, diffuse endothelial hyperplasia, thickness of the tunica media of arterial vessels, with partial occlusion at the vascular lumen, thickening and packing of collagen fibers, variable degree of pericapillary lymphohistiocytic infiltrate (13), hypertrophy of epidermal appendages, seborrhic hyperplasia with obstructive cystic dilatation of the sebaceous gland, granulomatous reaction (90), increase of acid mucopolysaccharide and accumulation of fibrillar material in disorganized microfibrils of elastic fibers (9).

Electron microscopy

- Irregular calibre of collagen fibers (78).
- Fibroblast activation with increased fibrillogenic activity (hypertrophic Golgi complexes, and rough endoplasmatic reticulum).
- Thickening of the basement membrane, which appears multi-layered in the complete form of PDP (13), with a single basal lamina in the incomplete form.

Genetic counselling

Genetic counselling should be offered to patients with PDP and their families. Although no chromosomal abnormality has been

identified, a radiologic survey of relatives may be completed.

Treatment

Non-steroidal anti-inflammatory agents (ibuprofen, indomethacin, celecoxib) may improve the joints symptoms (31), but not always (29).

Colchicine in open cases (22, 32) and in a blind study (80) improved the articular symptoms, the folliculitis and pachydermia after 15 days of treatment at 0,5 mg per day the first week, and 1 mg the second week. It was supposed that colchicine inhibits the neutrophils chemotaxis, and reduces tissular oedema.

Some joint effusions can be improved temporarily by intra-articular steroid injections.

Rheumatologic symptoms have been improved by intra-venous treatment with **pamidronate**, a biphosphonate, 1mg/kg, with moderate to very good results, in an open study with 3 cases (81).

Isotretinoine at an initial dose of 0,5mg/kg/day showed a dramatic improvement of the skin symptoms, especially on the face in a family of 3 patients with pachydermia and cutis verticis gyrata (82,83). Clinical improvement is noted for seborrhea, acne, folliculitis and pachydermia. Retinoids have been shown to reduce procollagen production by diminishing procollagen mRNA in fibroblasts, thus inhibiting the production of collagenase (84). As the chronic therapy with isotretinoine can induced hyperostosis, a scintigraphy follow-up of the bones is needed (85).

Plastic surgery may be helpful for complications on the face, as frontal rhytidectomy (86-88), or correction of ptosis (89,90). Finger clubbing surgical reduction has been tried with success (80).

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