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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
Pachyonychia Congenita

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Synonyms and related keywords: PC, Jadassohn-Lewandowsky syndrome, polykeratosis congenita (Touraine), palmoplantar keratoderma, PPK, keratosis disseminata circumscripta, leukokeratosis linguae, PC-1, Jadassohn-Lewandowsky type, PC-2, Jackson-Lawler type, pachyonychia congenita tarda, MIM 167200, MIM 167210

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Background: Pachyonychia congenita (PC) is a rare form of hereditary palmoplantar keratoderma (PPK). Müller made the first documented observation in 1904 (Müller, 1904). The next reports were published in 1905 by Wilson (Wilson, 1905) and in 1906 by Jadassohn and Lewandowsky (Jadassohn, 1906). In the dermatologic literature, PC is better known as Jadassohn-Lewandowsky syndrome.

The condition is rare, but more than 250 cases have been reported. Certain reports include large series of cases: Moldenhauser and Ernst reviewed 93 cases and described 6 new cases (Moldenhauser, 1968). Puente reported 26 cases (Puente, 1955), Kumer and Loos reported 23 cases (Kumer, 1935), and Su reported 12 cases (Su, 1990). Fourteen cases from Slovenia (Franzot, 1981) and 25 cases from Croatia (Videni, 1991) are reported.

Various classifications for PC have been proposed. Currently 2 distinct syndromes of PC are recognized in the United States: (1) PC-1, or the Jadassohn-Lewandowsky type, which is designated as Mendelian Inheritance in Man (MIM) entry 167200 (McKusick, 1994), and (2) PC-2, or the Jackson-Lawler type, which is designated as MIM entry 167210.

For a definitive classification of PC, more data about genotypic-phenotypic correlation in the same patients is needed.

Pathophysiology: PC results from mutations in the genes encoding epidermal keratinocyte keratins, specifically K6a, K6b, K16, and K17. In most cases, an autosomal dominant mode of inheritance is described; however, autosomal recessive inheritance is also mentioned in the literature.

Sporadic PC cases in which no family linkage can be established may be the result of new mutations. However, another interpretation seems to be probable. The interpretation of this observation is that, in addition to the mutation of the keratin gene, a second mechanism (an additional mutation) is needed for the expression of PC. Cockayne studied the pedigrees of patients with PC that were available at the time and was the first to introduce this concept (Cockayne, 1933).

Findings from the present authors’ clinical studies of a relatively large series of patients with PC support Cockayne’s theory.
Frequency:

- **In the US:** The disorder is rare. In the United States, only a few reports exist.

- **Internationally:** No data about the incidence in various countries are available. However, in Slovenia, an incidence of 0.7 case per 100,000 inhabitants is reported. In Croatia, a comparable incidence of 0.53 case per 100,000 persons is reported.

**Mortality/Morbidity:** The lesions in PC do not endanger the patient’s life.

**Race:** Most likely, all races can be affected.

**Sex:** PC affects both sexes equally.

**Age:**

- The affected nails are usually present at birth, but they may appear later, as they do in PC tarda.

- Paller et al described 5 patients in whom the disfigured nails appeared when they were aged 10-30 years. However, molecular biologic analysis was not available to verify the diagnosis.

**History:**

- Parents notice the lesions soon after their child’s birth.

- Paller et al described 5 patients in whom the disfigured nails appeared when they were aged 10-30 years, as they do in PC tarda.

**Physical:**

- Jadassohn-Lewandowsky type, or PC-1, is the most common variant. Mutations of the genes
encoding keratins K6a, K6b, and K16, which disrupt the keratin filament assembly, characterize the disorder.

- In the nails, the most prominent feature is a substantially thickened, brownish gray nail plate with a rough surface. Usually, all fingers are affected; the toenails may also be affected, but this finding is less characteristic. The thickened fingernails may expand into periungual tissue, causing a pressure-provoked paronychia.

- Circumscribed or diffuse hyperkeratoses are expressed on the palms and soles. Periodically, blisters may appear in hyperkeratotic areas, especially in children. Hyperhidrosis often accompanies the hyperkeratoses.

- Follicular hyperkeratosis is observed on the face (eg, temples, front eyebrows) and on the extensor aspect of the proximal parts of the extremities.

- Leukokeratosis of the oral mucosa is a prominent sign. Patchy whitish areas may be seen on the back of the tongue; the buccal mucosa; and sometimes, the gingiva. Some patients have early tooth decay.

- In PC, oral leukokeratosis is not a precancerous lesion. It is differentiated from leukoplakia or cancer either by performing oral biopsy or by recognizing its presence in patients with other expressions of PC.

- In certain patients with PC-1, steatocystoma multiplex may appear later in life.

- **Jackson-Lawler type, or PC-2, is rare.**
  - Patients have a thickened nail plate and, eventually, the other symptoms appear. The symptoms are the same as those in PC-1; however, PC-2 is characterized by natal teeth and the consistent presence of steatocystoma multiplex.

  - Hair anomalies (eg, unruly hair) are also described.

  - The disorder is linked to mutations in the genes for keratin K17.

  - Sebaceous cysts may appear later in life.
- Corneal opacities and cataracts are rare. Reports of such findings were made prior to the classification of PC into PC-1 and PC-2 types.

- Cicatricial alopecia is an uncommon symptom.

- A thickened nail plate may occasionally be observed in the dominant form of dystrophic epidermolysis bullosa.

**Causes:** An autosomal dominant mode of inheritance is observed in most cases of PC, but sporadic cases do occur. An autosomal recessive mode of inheritance has also been mentioned.

- Cockayne was the first to express the opinion that the presence of an additional factor, probably a second genetic mutation, is necessary for the expression of the disease (Cockayne, 1933).

- Munro was the first to propose that the genetic defect in PC is linked to the keratin gene cluster on chromosome 17 (Munro, 1994).
  - In a detailed molecular biologic analysis, McLean et al found that PC is caused by mutations on chromosomes 16 and 17.
  - More detailed molecular analysis revealed that PC was caused by mutations in the genes encoding the epidermal keratinocyte keratins K6a, K6b, K16, or K17 (McLean, 1995); these mutations are responsible for the clinical manifestations.

- Bowden found the following genetic changes (Bowden, 1995):
  - Mutations in the 1A helical encoding region of K6a in Slovenian patients with PC-1
  - A deletion in one codon in 2 adjacent asparagine residues (N170/N171) in 5 patients
  - A mutation of F174S phenylalanine to serine in one patient

- Rare genetic variants are described in each syndrome. Some of these appear to be due to mutations that occur elsewhere in the keratin genes.
Most well-studied mutations occur at the ends of the helical-rod domains and probably disrupt keratin filament assembly.

Phenotypic variations in some of the clinical manifestations can be explained by means of a detailed study of point mutations, but the expression of other aspects of the phenotype may depend on unidentified factors.

**Differentials**

- Candidiasis, Mucosal
- Epidermolysis Bullosa
- Keratosis Follicularis (Darier Disease)
- Onychomycosis
- Pityriasis Rubra Pilaris

**Workup**

**Lab Studies:**

- Molecular DNA analysis reveals deletion mutations, substitution mutations, and other mutations of keratin genes K6a, K6b, K16, and K17.

- Oral leukokeratosis is differentiated from leukoplakia or cancer either by performing oral biopsy or by recognizing its presence in patients with other expressions of PC.

- In babies, PC can be misdiagnosed as candidiasis; PC can be misdiagnosed as onychomycosis later in life.

  - The occasional detection of *Candida* spores can be confusing.
- To confirm candidal infection, mycologic investigation should reveal multiple spores and hyphae.

- A detailed investigation of the fingernails in 8 patients with PC-1 in whom the diagnosis was verified by molecular biologic analysis did not reveal infection. A few spores and no hyphae were seen in 4 patients, but no spores and no hyphae were found in the other 4 (Kansky, 1998).

**Histologic Findings:** The hyperkeratotic lesions of the skin and oral mucosa show acanthosis, hyperkeratosis, and parakeratosis. Premalignant changes are not observed.

Electron microscopy can be performed by using plantar or palmar skin samples. Electron microscopy shows thickened and clumped intermediate filaments, as well as enlarged keratohyaline granules. In the broadened granular layer, thick masses of tonofilaments and large, irregular keratohyaline granules are present. In the spinous layer, thick masses of tonofilaments are found at the periphery of the cells.

<table>
<thead>
<tr>
<th>TREATMENT</th>
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**Medical Care:** Currently, no ideal treatment for the thickened nail plate is available, although a few therapeutic options have been suggested.

- The thickened nail plate can be softened by using 20% salicylic acid ointment or 20% urea and 10% salicylic acid in emulsifying ointment with occlusion changed at weekly intervals.

- After the nail is softened, it can be abraded. Mechanical abrasion, which is sometimes performed by patients themselves, may be helpful. This abrasion may be followed by additional softening of the nail plate.

- A 5% 5-fluorouracil cream can be applied twice daily. 5-fluorouracil cream can be applied after thinning or abrasion of the nail plate to suppress the hyperproliferative activity of the nail matrix.

- Systemic treatment with acitretin in a daily dose of 1 mg/kg is partially effective; the nail plate becomes thinner, and its surface becomes smoother. Generally, the adverse effects, including teratogenicity and hyperostosis, do not justify its use.

**Surgical Care:** The affected nails can be removed under local or general anesthesia; however, unless the nail matrix is removed, nails regrow with the original abnormality.
Consultations:

- A psychiatrist may be consulted if the patient has psychiatric problems related to the abnormal nails.
- A geneticist may be consulted for genetic counseling.

Activity: Certain leisure activities (eg, bowling) or occupations that require the use of fine motor skills in limited spaces may be difficult.

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<thead>
<tr>
<th>MEDICATION</th>
<th>Section 7 of 11 [Back Top Next]</th>
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<td>Author Information Introduction Clinical Differentials Workup Treatment Medication Follow-up Miscellaneous Pictures Bibliography</td>
<td></td>
</tr>
</tbody>
</table>

Medications are used to reduce the morbidity associated with this syndrome.

Drug Category: Retinoids -- Retinoids regulate the differentiation and proliferation of epithelial cells. Some also possess antitumoral activity.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Acitretin (Neotigason, Soriatane) -- Retinoic acid analog such as etretinate and isotretinoin. Etretinate is main metabolite. Has clinical effects similar to those of etretinate. Mechanism of action is unknown.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>0.5-1 mg/kg/d PO; after 1-2 mo, reduce dose to one half or one third of initial dose</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity</td>
</tr>
<tr>
<td>Interactions</td>
<td>Increases toxicity of methotrexate (avoid concomitant use); interferes with effects of microdosed progestin minipill; coadministration with alcohol may enhance synthesis of etretinate, which has much longer half-life (&gt;120 d)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>X - Contraindicated in pregnancy</td>
</tr>
</tbody>
</table>

Do not use in severe obesity; women of childbearing age must be capable of complying with effective contraceptive measures; recommended that contraception be continued for at least 2 y
### Precautions

After stopping treatment; etretinate may form from acitretin, which takes about 2-3 y to clear from body; caution in impaired renal or liver function; perform AST, ALT, and LDH tests prior to therapy at 1- to 2-wk intervals until levels stable; thereafter perform tests at intervals as clinically indicated.

### Drug Category: Antineoplastic agents -- These agents inhibit cell growth and proliferation.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Fluorouracil (Carac, Efudex, Fluoroplex) -- Interferes with DNA synthesis by blocking methylation of deoxyuridylic acid, inhibiting thymidylate synthetase and subsequently cell proliferation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>Apply 5% formulation topically bid</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; potentially serious infections</td>
</tr>
<tr>
<td>Interactions</td>
<td>None reported</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>X - Contraindicated in pregnancy</td>
</tr>
<tr>
<td>Precautions</td>
<td>Incidence of inflammatory reactions may occur with occlusive dressings; porous gauze dressing may be applied for cosmetic reasons without increase in reaction; patients should expect inflammatory reaction with crusting</td>
</tr>
</tbody>
</table>

### Drug Category: Keratolytic agents -- These agents cause cornified epithelium to swell, soften, macerate, and then desquamate.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Salicylic acid (20%) ointment -- By dissolving the intercellular cement substance salicylic acid produces desquamation of the horny layer of skin, while not affecting structure of viable epidermis. Hydrate skin and enhance effects of medication by soaking affected area in warm water for 5 min prior to use. Remove any loose tissue with brush, washcloth, or emery board and dry thoroughly. Improvement should generally occur in 1-2 wk.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>Apply to affected area and cover with occlusive dressing</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Precautions</td>
<td>Documented hypersensitivity; prolonged use in infants, diabetics,</td>
</tr>
</tbody>
</table>

http://www.emedicine.com/derm/topic812.htm
<table>
<thead>
<tr>
<th><strong>Contraindications</strong></th>
<th>and patients with impaired circulation not recommended; use on moles, birthmarks, or warts with hair growing from them, genital or facial warts, or warts on mucous membranes, irritated skin, or any area infected or reddened also contraindicated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interactions</strong></td>
<td>None reported</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>C - Safety for use during pregnancy has not been established.</td>
</tr>
<tr>
<td><strong>Precautions</strong></td>
<td>Avoid contact with mucous membranes, normal skin surrounding warts, and eyes; immediately flush with water for 15 min if contact with eyes or mucous membranes occurs; avoid inhaling vapors</td>
</tr>
<tr>
<td><strong>Drug Name</strong></td>
<td>Urea (Ureacin-40) -- Promotes hydration and removal of excess keratin in conditions of hyperkeratosis.</td>
</tr>
<tr>
<td><strong>Adult Dose</strong></td>
<td>Apply to affected area and cover with occlusive dressing</td>
</tr>
<tr>
<td><strong>Pediatric Dose</strong></td>
<td>Not established</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Documented hypersensitivity; viral skin disease</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>None reported</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>C - Safety for use during pregnancy has not been established.</td>
</tr>
<tr>
<td><strong>Precautions</strong></td>
<td>Do not use near eyes; caution if applied to broken or swollen skin</td>
</tr>
<tr>
<td><strong>Drug Name</strong></td>
<td>Salicylic acid (20%), urea (40%), and hydrophilic ointment compound -- Compounded in the pharmacy. Promotes hydration and removal of excess keratin in conditions of hyperkeratosis.</td>
</tr>
<tr>
<td><strong>Adult Dose</strong></td>
<td>Apply to affected area and cover with occlusive dressing</td>
</tr>
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<td><strong>Pediatric Dose</strong></td>
<td>Not established</td>
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<td><strong>Contraindications</strong></td>
<td>Documented hypersensitivity; prolonged use in infants, diabetics, and patients with impaired circulation not recommended; use on moles, birthmarks, or warts with hair growing from them, genital or facial warts, or warts on mucous membranes, irritated skin or any area infected or reddened also contraindicated; viral skin disease</td>
</tr>
</tbody>
</table>
### Interactions

None reported

### Pregnancy

C - Safety for use during pregnancy has not been established.

### Precautions

Do not use near eyes; caution if applied to broken or swollen skin; avoid contact with mucous membranes, normal skin surrounding warts, and eyes; immediately flush with water for 15 min if contact with eyes or mucous membranes occurs.

### Further Outpatient Care:

- Patients receiving systemic retinoids require appropriate laboratory monitoring, including serum pregnancy testing.

### Complications:

- Paronychia may occur due to the ingrowing of the thickened nail plate.
- Adverse effects observed during treatment with retinoids include dryness of the skin and mucous membranes, dry eyes, and transient hair loss.

### Prognosis:

- Nail findings persist, while other manifestations may become less severe later in life.

### Patient Education:

- Patients and their relatives should be informed that PC does not endanger an individual's life, but it may impair his or her quality of life.
- The patient may be informed that, at present, no effective treatment is available; however, gene therapy treatment may be available in the future.
- A genetic counselor should inform the carrier that this gene has an autosomal dominant inheritance pattern and that PC
can affect one half of his or her progeny.

Medical/Legal Pitfalls:

- Failure to correctly diagnose PC may result in the inability to provide genetic counseling, correct treatment, or adequate treatment.
- PC can be misdiagnosed as candidiasis or onychomycosis, and unnecessary treatment with antifungals might result.

Caption: Picture 1. Pachyonychia congenita. The most prominent feature is a substantially thickened, brownish gray nail plate with a rough surface.

Picture Type: Photo

Caption: Picture 2. Pachyonychia congenita. Leukokeratosis of the oral mucosa is a prominent sign. Patchy whitish areas may be seen on the back of the tongue; the buccal mucosa; and sometimes, the gingiva.
Picture Type: Photo
Caption: Picture 3. Pachyonychia congenita. Hyperkeratotic lesions of the skin may involve acanthosis, hyperkeratosis, and parakeratosis.

BIBLIOGRAPHY


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