Hereditary chondrocalcinosis in an Ashkenazi Jewish family

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Abstract
A hereditary chondrocalcinosis is described for the first time in an Ashkenazi Jewish kindred. Of 34 family members in five generations, seven had medical history suggesting the disease. Five of 25 members of generations III-V had direct evidence for their disease. Characteristically, symptoms started at a fairly early age (third decade) while radiological evidence of chondrocalcinosis was delayed to the fourth decade. Joints commonly affected were knees, wrists, and elbows. The course was chronic with acute, exercise induced exacerbations.

Calcium pyrophosphate dihydrate (CPPD) crystal arthropathy is a disease characterised by the deposition of these crystals in the joint cartilage.1 The exact factors responsible for such deposition are still unknown. Three main forms of disease may be defined: (a) a hereditary form; (b) a form associated with endocrine or metabolic disorders; and (c) a sporadic form, by far the most common.

Several hereditary series have been reported to date.1-13 The series differ in many aspects, including the presumed genetic transmission, although autosomal dominant inheritance was suggested in most.12 Sporadic chondrocalcinosis in a Jewish home for the aged has been described in 27-6% of the residents14; no hereditary CPPD deposition was reported in this ethnic group, however. We report here for the first time a Jewish kindred with a clustering of chondrocalcinosis.

Materials and methods
The family of the propositus (fig 1, IV-4) was studied. It included 34 members in five generations, 25 of whom (generations III-V) were available for direct examination. Radiographs of knees, wrists, hands, and cervical spine were performed in symptomatic subjects. In one patient (the propositus) an elective arthrocentesis was done on a visit to Philadelphia and the fluid studied by routine analysis, compensated polarised microscope, and alizarin red S staining.

Routine laboratory tests from symptomatic subjects included blood count, fasting blood sugar, calcium, phosphorus, alkaline phosphatase, uric acid, free thyroxine concentrations, rheumatoid factor, and antinuclear antibodies. A more detailed laboratory study is presented in the case report.

Results
A family of Ashkenazi Jewish origin including 34 members in five generations was studied (fig 1). The family had lived in West Prussia and migrated to Berlin at the time of the first world war and to Israel between 1930 and 1940. Data before 1860 are unavailable. Medical history for generations I and II was collected from living relatives. Two sisters (II-1, II-5) had significant joint symptoms affecting their knees and other non-specified joints before the age of 30, and in the absence of more data are considered as suspected chondrocalcinosis.

Twenty-five family members of generations III-V were available for questioning and examination, five of whom were found to have been affected from a mean age of 24 years (range 19-30). The table contains their clinical and radiological data. The above mentioned laboratory tests were normal in all five living subjects. In six additional asymptomatic members (III-4, III-6, IV-2, IV-6, V-4, V-8) various x rays taken for unrelated reasons (trauma, low back pain, medical investigations) were traced. Joints included in the films were not found to have chondrocalcinosis. Patient No IV-4 is reported in detail.

Case report
A 43 year old doctor was referred for our observation because of protracted pain in his knees. The patient's father had gout and he had other relatives with hyperuricaemia. The patient was well and very fit until the age of 23 when he started to experience knee pain induced by exercise, sometimes accompanied by local swelling. At the age of 28 a right meniscectomy was performed at another centre where 'diffuse osteochondritis' was described. Calcium and routine laboratory results were normal. During the following 12 years he experienced exacerbations and remissions with gradual progression of both the severity and frequency of his symptoms, extending to the elbows, proximal and distal interphalangeal joints, and cervical spine. In 1986 arthroscopy of the left knee disclosed degenerative changes which were more prominent in the medial meniscus and the patellofemoral joint.

On general physical examination the patient was well. His cervical range was moderately limited. Heberden nodes were evident. The knees had 10° flexion contractures, weakened quadriceps muscles, and well preserved stability. Effusion was present on some occasions. Other joints were normal.
Serial x rays (fig 2) showed progressive osteoarthrosis of medial, lateral, and patellofemoral compartments of both knees with chondrocalcinosis of both meniscal and articular hyaline cartilage. Osteoarthrosis of the cervical spine with multiple subluxations and suspected congenital fusion of C3 to C4 were also evident. The intervertebral discs did not show calcification. Hands and wrists seemed normal.

Serum calcium was slightly raised on a single occasion, but repeated determinations, as well as phosphorus, magnesium, and alkaline phosphatase, were normal. Further laboratory tests were normal and included uric acid, creatinine, creatinine clearance, 24 hours cyclic AMP, serum iron and total iron binding capacity, caeruloplasmin, free thyroxine, parathyroid hormone, growth hormone, insulin, urine free cortisol, rheumatoid factor, and antinuclear antibodies. Knee joint fluid examined by one of us (HRS) during a quiescent phase, using polarised microscopy and alizarin red S screen stain, disclosed clear viscous fluid with 0.2×10⁶ white blood cells/l, small positively birefringent CPPD-like crystals in synovial fluid cells, and occasional clumps of alizarin red S positive material suggestive of apatites.

The patient found partial relief with aspirin or piroxicam. During the past 12 months colchicine 0.5 mg three times a day has reduced the rate of his relapses and also the baseline daily pain.

Clinical and radiological data on five symptomatic members in a kindred with familial chondrocalcinosis

<table>
<thead>
<tr>
<th>Family member</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Age of onset (years)</th>
<th>Joints affected (C=clinically; R=radiologically)</th>
<th>Knee</th>
<th>Wrist</th>
<th>MCP*</th>
<th>Spine</th>
<th>Elbow</th>
<th>Shoulder</th>
<th>Other</th>
<th>Osteoarthrosis on x ray</th>
<th>Course</th>
<th>Acute episodes</th>
<th>Chronic pain</th>
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<tr>
<td>III-2</td>
<td>F</td>
<td>78</td>
<td>19</td>
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<td>III-3</td>
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<td>IV-4</td>
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*MCP=metakarpophalangeal joints; PIP=proximal interphalangeal joints; ND=not determined.
†=deceased, medical notes and x rays available.
Discussion
This report is the first description of familial chondrocalcinosis in an Ashkenazi Jewish
kindred. Sporadic chondrocalcinosis was ob-
served radiographically in 27-6% of volunteer
subjects in a Jewish home for the aged.14 In
our survey five family members had a strong clinical
history and findings suggestive of CPPD crystal
deposition disease. In the patient who under-
goed joint aspiration CPPD-like crystals were
found. Four had radiographic evidence of
chondrocalcinosis. The fifth subject, without
such evidence, is only 23 years old. Radi-
ographic chondrocalcinosis appeared years after
joint pain started in the propositus (fig 2).
Onset of symptoms occurred early during the
third decade of life in all affected patients. The
clinical course in our patients is characterised by
recurrent attacks, commonly triggered by exer-
cise, superimposed on moderate chronic arth-
ralgia. The knee was the most affected joint,
followed by the wrist, and showed degenerative
changes beginning at age 30. Although meni-
sectomy may accelerate degenerative changes and
CPPD deposition,15-16 the unilateral pro-
cedure in our patient cannot explain bilateral
involvement. No metabolic abnormality was
 detected among the symptomatic family
members. Laboratory tests were not carried out in
asymptomatic subjects.
Familial or hereditary CPPD disease has
been reported from various geographical regions
and ethnic groups. Since the original description
of Hungarian familial chondrocalcinosis by
Zitnan and Sitaj in 1963,17 ten series, none of
them Jewish, have been published from the
Netherlands,7 France,8 Spain,9 Sweden,10
Canada,11 Chile,6 Germany,5 the United States of
America,4 10 and Japan.13 No further studies
have been reported during the past six years.
Tracing the exact origins of the present
Jewish Ashkenazi family is hampered by his-
torical events and the emigration to Israel.
The oldest known members lived in West Prussia
during the 19th century. Our patients when
compared with previously published series show
clinical similarity to the Hungarian group.3
The inheritance pattern seems to be dominant
with varying expressivity. Without a systematic
radiological study of all family members,
however, a firm conclusion on the inheritance
pattern cannot be reached. Because this family,
as in the Hungarian series,3 does not show man
to man transmission, an autosomal versus sex-
linked transmission cannot be excluded.

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