Familial articular chondrocalcinosis in Spain

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Abstract

One hundred and one first degree relatives of 35 patients with chondrocalcinosis were examined for the presence of familial disease. Eleven subjects from nine families showed radiological chondrocalcinosis, a prevalence of familial disease of 26%. Two different patterns of disease were noted—the older generation was more commonly affected, and the younger generation and second degree relatives were exempt. Clinical and radiological differences were found between the early and late onset groups, but not between late onset and sporadic forms of chondrocalcinosis. These findings suggest the suggestion that the true prevalence of familial disease is underestimated. A dominant, autosomal transmission with variable penetrance is consistent with our findings, which suggests that homozygous patients with familial chondrocalcinosis may present more severe form of the disease.

Familial articular chondrocalcinosis was first reported in 1957 by Sitaj and Zitnan in Czechoslovakia (Ninth international congress on rheumatic diseases, Toronto, 1957). The term was introduced to describe a clinical entity characterised by arthritis with calcification of menisci and cartilages. The disease is caused by deposition of calcium pyrophosphate dihydrate crystals in skeletal hyaline and fibrocartilage, but the mechanisms of this deposition are unknown. The clinical picture varies from mild chronic diffuse arthralgias to recurrent attacks of acute monoarticular or polyarticular arthritis where calcium pyrophosphate dihydrate crystals are released into the joint cavity.

Calcium pyrophosphate dihydrate crystal deposition disease is currently classified into three types: hereditary, associated with metabolic diseases, and sporadic. There has been no systematic study of relatives in the last category, and no metabolic disease association has been shown.

Hereditary chondrocalcinosis has been described in families from Czechoslovakia, Chile, Holland, Canada, France, Germany, Sweden, Mexico-America, United States, Japan, Tunis (Hamza M et al, IX European congress of rheumatology, Moscow, 1983), and Spain. Two different clinical phenotypes have been noted: the first is characterised by an early onset, polyarticular involvement and variable prognosis, and the second, by a later onset and oligoarticular involvement.

Two studies have reported on 14 families from Spain, the first including only the late onset phenotype and the second, both phenotypes. We undertook our study of the Spanish population to investigate the differences between these two types.

Patients and methods

All patients seen in our clinic who met the diagnostic criteria for pseudogout proposed by McCarty were invited to participate. For inclusion in the study at least one father, brother, or son older than 60 was required in order to avoid false results deriving from study of only the younger generation. Furthermore, all first degree living members of the family older than 25 were asked to participate. Laboratory studies were performed to rule out associated metabolic disease and included complete blood count, alkaline phosphatase, calcium, phosphorus, magnesium, iron, transferrin, ferritin, triiodothyronine, and thyroxine, and 24 hour determination of urinary calcium and phosphorus.

The medical history was obtained by a questionnaire, and special attention was paid to articular symptoms, limitation of motion, age at onset, joint involvement, associated illness, total number of family members and those older than 40, birthplace, and consanguinity. Only objective signs of inflammation in joints were accepted as pseudogout; mechanical and back pain was included as chronic arthropathy.

Standard radiographs of knees, wrists, and pelvis were made in every relative and examined by two doctors. Their agreement was required for a diagnosis of chondrocalcinosis. We defined as familial disease those cases in which two or more relatives were affected, and the others were recorded as sporadic. In every patient with chondrocalcinosis radiographs of clinically affected joints were made. In the spine only intervertebral disc calcifications were accepted for diagnosis.

In cases with familial disease all members older than 20, including second degree relatives, were asked to join the study. A complete examination was made when possible. Synovial fluid was aspirated and a polarised microscopic study carried out to determine the existence of calcium pyrophosphate dihydrate crystals.

When possible, the family history was traced back and HLA typing for antigens A, B, and C carried out by a modified version of the method of Terasaki. Student’s t test and the Mann-Whitney U test were used for statistical analysis.
Results
Thirty five patients with chondrocalcinosis and no associated metabolic disease agreed to enter the study. The 35 families had 177 members aged over 25, of whom 108 were more than 40. One hundred and one (57%) and 74 (69%) subjects from each group respectively were examined.

The 101 relatives (62 women, 39 men), mean age 56 (SD 6·7) years, comprised nine parents, 47 siblings, and 45 offspring. We also studied 17 second degree relatives (10 women, seven men), belonging to two affected families of the early onset group. In one family 15 members were studied (fig 1) and in the second two members.

Eleven subjects belonging to nine different families were affected by chondrocalcinosis, showing a prevalence of familial disease of 26%. We found only one subject with more than one relative affected, the one in whom consanguinuity was shown (fig 1).

In 17/35 patients calcium pyrophosphate dihydrate crystals were found in synovial fluid by a polarised microscopic study. All three probands belonging to the early onset group had several determinations showing synovial fluid with calcium pyrophosphate dihydrate crystals. Crystals were also found in 3/6 patients in the late onset group and in 11/26 patients in the sporadic group. Calcium pyrophosphate crystals were shown in only one relative (fig 1).

As expected, no radiographic evidence of chondrocalcinosis was found in the youngest

![Pedigree of family 1. CPPD = calcium pyrophosphate dihydrate.](http://ard.bmj.com/Ann Rheum Dis: first published as 10.1136/ard.49.7.531 on 1 July 1990. Downloaded from http://ard.bmj.com/ on October 28, 2023 by guest. Protected by copyright.)
Familial articular chondrocalcinosis

Patients with: | Early onset (n=8) | Late onset (n=12) | Sporadic (n=26)
---|---|---|---
Arthralgia | 8 (100) | 7 (58) | 11 (42)
Arthritis | 7 (88) | 11 (92) | 23 (88)
Polyarthritis | 6 (75) | 1 (8) | 0
Spinal involvement | 4 (50) | 6 (50) | 17 (65)
Limitation of range motion | 4 (50) | 1 (8) | 2 (8)

Discussion

Hereditary forms of chondrocalcinosis with common features have been reported in widely separated places.1–13

There have been few studies of the prevalence of familial chondrocalcinosis. McCarty found a 25% prevalence among his patients and noted the difficulty of these investigations.1 Regnato found a high prevalence in the Chiloe Islands and suggested that the disease might have been introduced by immigrants from the Iberian Peninsula.3 Richardson also pin-pointed a Spanish man as the origin of the disease in a Mexican-American family.9 These reports suggest that familial type chondrocalcinosis might be more prevalent in Spain than in other regions.12

Chondrocalcinosis is a disease of the elderly. In Spain the prevalence in subjects over 60 was 17% in one study,16 and familial disease accounts for 11% and 27%, respectively, in two reports.12,13 In our study the prevalence was 27%. This prevalence might be falsely high because of the willingness of people with joint symptoms to cooperate;12 we found no asymptomatic subjects. As would be expected the prevalence in the older generation was higher and if all members of the older generation were studied the prevalence of familial disease might be higher.

Zitnan and Sita2 and Regnato17 described two familial chondrocalcinosis phenotypes: a severe form, with early onset, recurrent attacks of polyarticular arthritis tending to progress with time to chronic arthropathy, and severe disability, and a mild form, characterised by late onset and oligoarthritis with little or no disability. In Spain Fernandez-Dapica et al found both clinical forms,13 but Rodriguez-Valverde et al found only the late onset phenotype.12 Our group of patients had both clinical forms.

The early onset group had polyarticular and spinal involvement with severe disability in people over 60 and no sex predilection. We found no articular destruction,2 11 17 bony ankylosis,17 18 or coincidence of the two phenotypes in the same family.2 3 13 The late onset group had a female predominance, oligoarticular affectation without spinal involvement, and a mild clinical syndrome. We found no asymptomatic patients.12

There have been reports of familial chondrocalcinosis with early onset and mild disease,4–10 but all our patients over 60 with an early onset had severe functional deterioration.

Radiological findings were similar to those of previous reports.15 In the early onset group we

Table 2: Clinical characteristics of familial and sporadic chondrocalcinosis. Results are given as number (%) of patients

<table>
<thead>
<tr>
<th>Affected joint:</th>
<th>Early onset (n=8)</th>
<th>Late onset (n=12)</th>
<th>Sporadic (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee</td>
<td>8 (100)</td>
<td>12 (100)</td>
<td>24 (92)</td>
</tr>
<tr>
<td>Wrist</td>
<td>6 (75)</td>
<td>8 (67)</td>
<td>19 (73)</td>
</tr>
<tr>
<td>Symphysis pubis</td>
<td>6 (75)</td>
<td>7 (58)</td>
<td>16 (62)</td>
</tr>
<tr>
<td>Shoulder</td>
<td>5 (75)*</td>
<td>4 (33)</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Hip</td>
<td>4 (50)</td>
<td>2 (17)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Spine</td>
<td>3 (43)*</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*In this group only seven radiographs taken.
found widespread heavy joint calcification without bony ankylosis or destruction, and, commonly, soft tissue calcifications. In the early onset group the three patients over 60 studied had spinal involvement, with extensive intervertebral disc calcification both in the nucleus pulposus and in the outer fibres of the anulus fibrosus (figs 2 and 3). In the groups with late and sporadic onset only osteoporosis and degenerative changes, with disc space narrowing and osteophytes, were found. These results agree with other reports from Spain. Altogether, knees, wrists, symphysis pubis, shoulders, and hips were the most commonly affected joints, which differs little from other reports.

We found no clinical or radiological differences between late onset and sporadic chondrocalcinosis; some patients with sporadic disease, in whom a complete familial study was lacking, might have had familial disease.

A dominant, autosomal transmission with variable penetrance would explain the findings in most of the families reported. The disease is present in all generations and all affected children have affected parents. The prevalence is high in the Mexican-American' and French families, variable in Swedish families, and low in Dutch families. Zitnan and Sitai found no evidence of man-to-man transmission, and the hereditary features of their series are not clear. Reginato in Chile found both sexes equally affected, the disease present in all generations, and an incidence of affection of nearly 50%, so an autosomal dominant inheritance cannot be ruled out. Consanguinity was reported in both studies.

In the Spanish series no pattern of hereditary transmission was found. The age dependence of disease expression precludes a follow up study of the younger generation to answer this question.

In one family of our early onset group a genealogical survey disclosed several consanguineous marriages with high inbreeding. In the other two families the genealogical tree could not be drawn, but both parents came from the same small village, raising the possibility of consanguinity. This supports data suggesting that homozygous patients with familial chondrocalcinosis seem to have a more severe form of the disease. As in other Spanish series we need more information about the younger unaffected generation to discern the pattern of hereditary transmission.

HLA typing was done in 10 members of the family who underwent a genealogical survey (four with and six without chondrocalcinosis). We could not show the existence of the HLA-A2, Bw35 in our subjects, as described in the Czechoslovakian series. We, and other authors, failed to confirm such a linkage and we found no common haplotype among affected subjects.

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