

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 support 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 a 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 hyalin 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 when calcium pyrophosphate dihydrate crystals are released into the joint cavity.¹

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.¹

Hereditary chondrocalcinosis has been described in families from Czechoslovakia,² Chile,³ Holland,⁴ Canada,⁵ France,⁶ Germany,⁷ Sweden,⁸ Mexico-America,⁹ United States,¹⁰ Japan,¹¹ Tunis (Hamza M *et al*, IX European congress of rheumatology, Moscow, 1983), and Spain.^{12 13} 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,^{12 13} 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 McCarty¹⁴ 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, tri-iodothyronine, 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, joints involved, 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.¹⁵

Student's *t* test and the Mann-Whitney U test were used for statistical analysis.

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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 consanguinity 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

generation. Of those studied, 5/9 parents (56%) and 6/47 (13%) siblings were affected, but we found no disease in second degree relatives of the patients. This finding suggests that if the older generation were studied the prevalence would be higher.

The nine families with familial disease had 29 members older than 40, 19 (66%) of whom were studied; from the 26 families with sporadic chondrocalcinosis a similar proportion, 55/79 (70%), were studied.

The clinical characteristics of the 20 subjects with familial articular chondrocalcinosis (nine index cases, 11 relatives) were different. Two patterns of disease were defined (tables 1 and 2). In eight patients (five men, three women) belonging to three families there was an early onset (<35 years), always as polyarthralgias and pseudogout. These episodes, which lasted from several days to weeks, affected almost all joints; attacks were self limited and tended to progress with time to chronic arthropathy resembling

Table 1: Age, sex, and first clinical symptom

	Early onset	Late onset	Sporadic
No of families	3	6	26
No of members affected	8	12	26
Women/men	5/3	8/4	16/10
Age at onset (mean±(SD))	30 (3.2)*	52 (7.8)**	60 (8.4)
First symptom			
Pseudogout	7	3	6
Arthralgias	0	4	10
Arthritis and arthralgias	1	5	10

*p<0.001 early onset v late and sporadic; **p<0.05 late onset v sporadic.

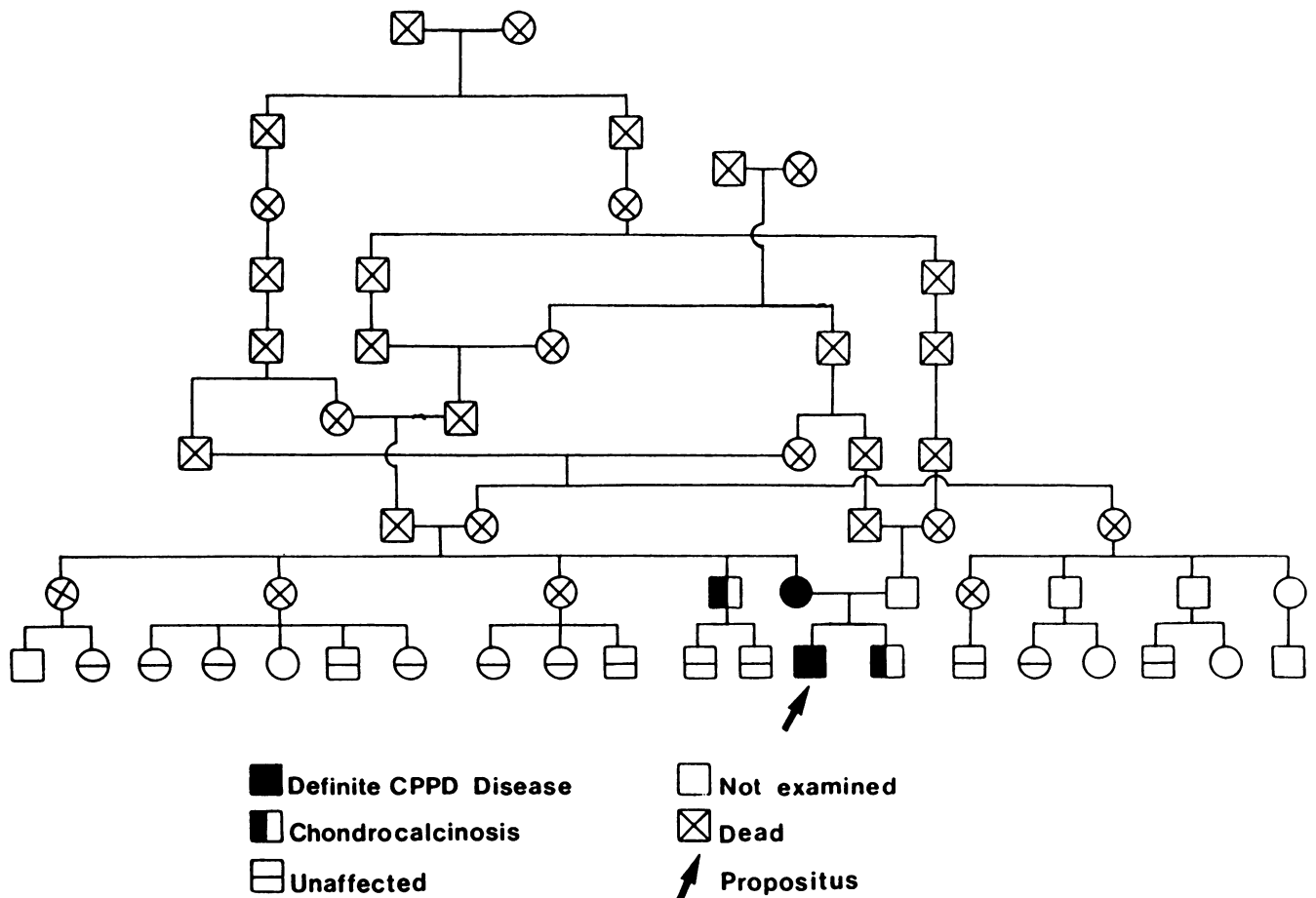


Figure 1: Pedigree of family 1. CPPD=calcium pyrophosphate dihydrate.

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

Patients with:	Early onset (n=8)	Late onset (n=12)	Sporadic (n=26)
Arthritis	8 (100)	7 (58)	11 (42)
Arthralgias	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)

degenerative joint disease. Patients over 60 had severe neck and back pain and stiffness with limitation of articular range of motion. There was no articular destruction or bony ankylosis in any joint studied. In the other 12 (eight women, four men), belonging to six families, there was a late onset (>45 years) with arthralgias, sometimes with pseudogout attacks, affecting mainly knees and wrists; no radiographic spinal involvement was found despite the fact that some patients complained of mechanical lumbar or cervical pain. None was asymptomatic, but the disease produced little or no disability.

In 19 of the 20 patients radiological studies were made. In a 64 year old woman with early onset disease and severe limitation of motion the diagnosis was based on x ray films of the knees, pelvis, and hips made two years earlier. In two patients of the early onset group over 60 years old, a complete articular series showed that every peripheral and axial joint was affected. We found spinal involvement in the three subjects over 60 in the early onset group; one of them had evidence of cervical and lumbar calcifications. In 11 patients aged 60 or more belonging to the other two groups six cervical and seven lumbar x ray films were obtained. In five patients osteoporosis and degenerative changes were found and in six only late findings.

We found radiological differences between patients with early and late onset chondrocalcinosis—namely, in the number and extension of joints affected, in the principal osteoarthritic changes, and in the presence of soft tissue calcifications in the early onset group. We found no differences between the groups with late onset and sporadic chondrocalcinosis (table 3).

Laboratory investigations showed normal values in all subjects, excluding the possibility of secondary forms of the disease. No other inflammatory rheumatic disease was found in the study.

In one family of the early onset group a genealogical survey showed several consanguineous marriages and a high rate of inbreeding

Table 3: Radiological involvement in familial and sporadic chondrocalcinosis. Results are given as number (%) of patients

Affected joint:	Early onset (n=8)	Late onset (n=12)	Sporadic (n=26)
Knee	8 (100)	12 (100)	24 (92)
Wrist	6 (86)*	8 (67)	19 (73)
Symphysis pubis	6 (75)	7 (58)	16 (62)
Shoulder	5 (71)*	4 (33)	5 (19)
Hip	4 (50)	2 (17)	4 (15)
Spine	3 (43)*	0	0

*In this group only seven radiographs taken.

(fig 1). In the other two families of the same group it was not possible to delineate the genealogical tree, but both parents came from the same village, raising the possibility of consanguinity.

HLA typing was carried out in 10 members of the family surveyed genealogically (four with and six without chondrocalcinosis). No HLA associations were found and no HLA-A2, Bw35 antigens were identified in the patients.

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 Reginato 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 cooperate¹²; 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 Sitaj² and Reginato¹⁷ 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 Fernández-Dapica *et al* found both clinical forms,¹³ but Rodríguez-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 13}

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.¹⁹ In the early onset group we

found widespread heavy joint calcification without bony ankylosis or destruction, and, commonly, soft tissue calcifications.^{2 11 17 18} 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 annulus fibrosus (figs 2 and 3). In the groups

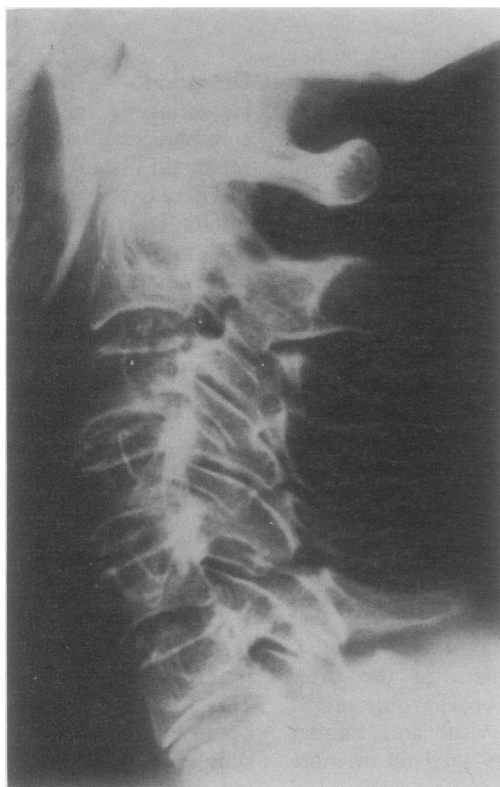


Figure 2: Cervical chondrocalcinosis in early onset group.

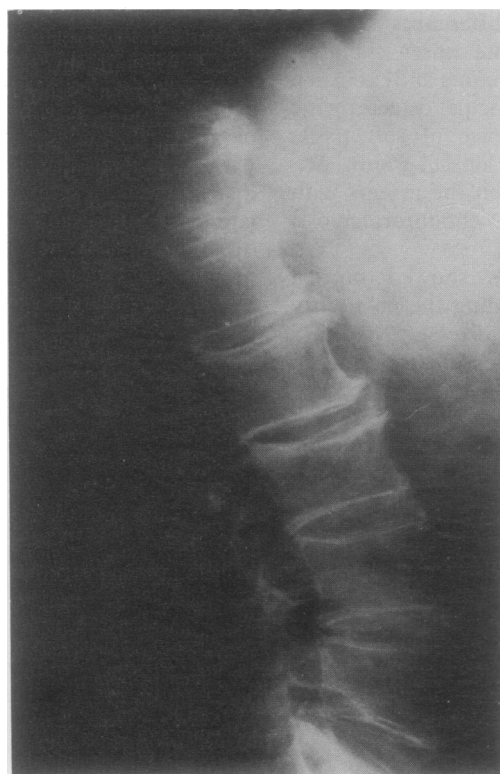


Figure 3: Lumbar chondrocalcinosis in early onset group.

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.¹² Altogether, knees, wrists, symphysis pubis, shoulders, and hips were the most commonly affected joints, which differs little from other reports.^{2 4 9 10}

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.⁴⁻⁹ The disease is present in all generations and all affected children have affected parents. The prevalence is high in the Mexican-American⁹ and French families,⁶ variable in Swedish families,⁸ and low in Dutch families.⁴ Zitnan and Sitaj found no evidence of man-to-man transmission,² 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.¹⁸ Consanguinity was reported in both studies.^{18 20}

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.^{12 13}

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.²¹ We, and other authors,^{5 6 9 18} failed to confirm such a linkage and we found no common haplotype among affected subjects.

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