Does acute synovitis (pseudogout) occur in patients with chronic pyrophosphate arthropathy (pseudo-osteoarthritis)?

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Abstract

Objective

Pyrophosphate arthropathy has been linked to diverse clinical subtypes. The two most common are: acute synovitis (pseudogout) and chronic pyrophosphate arthropathy ("pseudo-osteoarthritis"). We have conducted a study to examine whether these are overlapping syndromes.

Methods

We reviewed all synovial fluid (SF) analyses performed in our laboratory from January 1988 to May 1997 to determine if patterns of SF leukocyte counts and Alizarin red stains in patients with repeated samples suggest that some patients were prone to acute attacks and some to chronic pyrophosphate arthropathy and whether acute attacks superimposed on chronic symptoms were common. Joint x-rays were screened for osteoarthritis (OA) and chondrocalcinosis.

Results

We identified 67 patients who had Calcium pyrophosphate dehydrate (CPPD) in their SF and had more than one SF examined (185 SF). We divided the patients into 2 groups. Group A (n=25) had at least one SF leukocyte count > than 2000 per mm^3 and group B (n=42) had SF leukocyte counts always < than 2000 per mm^3. Chondrocalcinosis detected on x-ray was more common in group A versus group B, 48% versus 19% ($p<0.05$, Fisher's exact test). OA was mild (grades 0-1) in 39% of group A versus 12.5% of group B patients, but the difference between groups was not significant. CPPD crystals were not detected in 13.5% SFs previously having CPPD crystals. Alizarin red staining for suspected hydroxyapatite was more often 2+ to 3+ in group B (31.6%) compared to group A (15.5%; $p<0.05$, Fisher's exact test).

Conclusion

Acute synovitis and chronic pyrophosphate arthropathy are often two distinctive syndromes with some patients never having inflammatory attacks. Acute synovitis is more common in patients with chondrocalcinosis while chronic pyrophosphate arthropathy is associated with increased alizarin red staining and a trend suggestive of increased severity of OA.

Key words

Pseudogout, pyrophosphate arthropathy.

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Introduction

Calcium pyrophosphate dihydrate (CPPD) crystals can deposit in articular and periarticular connective tissues. McCarty classified pyrophosphate arthropathy into diverse clinical subtypes. These include: Type A which resembles acute gout (pseudogout) (20% of cases); Type B which mimics rheumatoid arthritis (pseudo-rheumatoid-arthritis) (5% of cases); Types C and D present as pseudo-osteoarthritis: Type D includes patients who have joint degeneration resembling osteoarthritis (OA) and no acute attacks. In these patients wrist, carpal, MCP, elbow and shoulder joint involvement is much more common than in primary 'nodal' osteoarthritis. (50% of cases), Type C includes patients with Type D who have superimposed acute attacks (1). Type E includes asymptomatic joints; Type F includes neuropathic joints. Other rarer subtypes included joints post trauma and hemarthrosis. The usefulness of this classification has been felt by some to be limited by overlap between subsets (2-4). Doherty *et al*. have more simply categorised pyrophosphate arthropathy into acute and chronic (3).

Doherty *et al*. (3) suggested that acute attacks superimposed on chronic symptoms are not uncommon, while McCarty *et al*. (1, 5) described a subset of patients with Pseudo OA (Type C) who have acute attacks superimposed on a chronic degenerative arthropathy.

Our aim was to examine whether acute synovitis (pseudogout) and chronic pyrophosphate arthropathy (pseudo-osteoarthritis) occur in the same patients based on our collection of synovial fluid (SF) analyses.

Methods

We reviewed all SF analyses performed routinely on all in the Arthritis-Immunology Center at the Philadelphia VA Medical Center during 1988 to May 1997 (n=4976) and identified 67 patients who had CPPD in their SF and had more than one SF examined (185 SF). All patients met diagnostic criteria for CPPD disease (pseudogout) proposed by Ryan and McCarty (6) in which a case is considered "definite" if CPPD crystals are demonstrated in tissues or synovial fluid or if crystals compatible with CPPD are demonstrated by compensated polarised light microscopy (as was seen in all our patients), Due to the retrospective nature of this study, synovial fluid studied were those aspirated when thought necessary by the staff Rheumatologist taking care of the patient and sent to the synovial fluid laboratory. The CPPD crystals were visualised under ordinary light microscopy (x400) and with a compensated polarised light microscope (x400). Alizarin red stains were performed as described by Paul *et al*. (7). Basic calcium phosphate (hydroxy-apatite) compounds were seen as large round or irregular aggregates that rapidly develop a bright orange-red color. The degree of synovial fluid alizarin staining of apatite-like material was graded from 0 (none) to 4 (maximal) (7).

CPPD crystals are square, rhomboid or rod-like and show a paler and more slowly developing stain.

We divided the patients into two groups. Group A (n=25) had at least one SF leukocyte count greater than 2000 per mm^3 and group B (n=42) had SF leukocyte counts always less than 2000 per mm^3. Retrospective chart review of patients was performed to confirm a clinical picture of acute versus chronic pyrophosphate associated arthropathy at the time of the SF fluid analysis. Due to the retrospective nature of this study patient charts were available on 23 (92%) in Group A and 33 (79%) in group B.

All available joint x-rays were screened for signs of OA and chondrocalcinosis. Forty-two sets of joint x-rays from patients with synovial samples with CPPD crystals were obtained (18 in group A and 24 in group B) and were read by a bone radiologist (LN) and by one of the authors (NS). These included: 1 shoulder, 13 wrist, 4 hand, 3 hip, 24 knee and 4 foot x-rays.

We used the grading method of Kellgren and Lawrence (8) to score the severity of OA.

Grade 0 (none): Absence of roentgenographic changes of OA.

Grade I (doubtful): Asymmetric narrowing of joint cartilage associated or not associated with sclerosis of subchondral bone.

Grade II (minimal): Narrowing of joint cartilage associated with subchondral bone sclerosis, and small osteophytes on the joint margins.
Grade III (moderate): Increased narrowing of joint cartilage, subchondral sclerosis, larger osteophytes and pseudocystic areas with sclerotic walls in the subchondral bone.
Grade IV (severe): Same as grade III, but with subluxation and gross deformity of the bone ends.

Statistical analysis
The data were analysed using SPSS (version 16.0) statistical software package (SPSS Inc., Chicago IL). Two-sided Fisher's exact tests were calculated to compare the group with acute inflammatory joint fluids and the clinical picture of pseudogout to the group with non-inflammatory SF and chronic pyrophosphate associated arthropathy on the dependent variables: the presence of chondrocalcinosis, OA severity and alizarin red staining for suspected hydroxyapatite. Probabilities equal to or less than 0.05 were considered to indicate statistically significant differences.

Results

All patients were males. Mean patient age in our study was 70. Patients in group A tended to be younger (mean age of 67) as compared with group B (mean age of 74). No differences were found between patients in group A and group B in underlying systemic diseases. One patient in group A was found to have hemochromatosis. No other metabolic predisposition was found.
One hundred and eighty-five SFs were examined. SF WBC range was 50 per mm^3 to 88100 per mm^3. SF WBC range in group A was 100 per mm^3 to 88100 per mm^3 and in group B 50 per mm^3 to 1750 per mm^3.
Seventy-six percent of all SFs were considered noninflammatory based on SF WBC less than 2000 per mm^3. (33% of SFs in group A and 100% of SFs in group B). Nineteen percent of patients had both inflammatory and noninflammatory fluids at different times (Table I). Seven of these also had MSU crystals and most likely had acute gout; one had active RA that may have explained the inflammatory SF WBCs. Not all SF with MSU crystals were inflammatory (Table II).
SF WBC counts varied in no predictable pattern being higher, lower or the same in SF without CPPD as when CPPD crystals were present. CPPD crystals were absent or not detected in 25 (13.5%) fluids from the same joints previously having CPPD crystals. (Ten [15%] of these SFs were in group A and 15 [12.6%] in group B) (Table II).
Acute synovitis was observed at least once in all group A patients. The synovitis lasted several hours (n=7) to 1- 5 days (n=15) with a maximal length of time of 10 days in a patient who had total knee replacement. The involved joints were: knees (n=21), elbow (n=1) and wrist (n=1). Three of these SFs in group A were from knees of three different patients with a total knee replacement. One patient had a septic knee (Staphylococcus aureus). MSU crystals were found in 7 patients along with CPPD crystals.
Among patients in group B the symptoms lasted from weeks to months (n=10) to years (n=23). Clinical diagnoses for OA were found in 24 group B patients of whom charts were reviewed. Among these patients 16 (60%) had repeated intra-articular (IA) corticosteroid injections (SFs were aspirated prior to IA injection). The aspirated joints were: knees (n=32) and wrist (n=1).

Table I. Patients with both inflammatory and non-inflammatory range SF WBCs at different times.

Patient n.	WBC1	WBC2	WBC3	WBC4
4	350	100	**4900**	**700**
32	**1950**	**29000**		
39	950	5600		
41	**150**	**16250**		
42	700	40950		
50	7500	7950	300	
54	100	350	18500	12950
56	4550	**1900**		
58	500	**11300**	**1450**	300
60	5600	250	200	
64	400	**250**	**350**	2150
65	1350	5250		
67	11450	1250	**1350**	1430

SFs with MSU crystals (n=7) (in bold print).

Table II. Patients with SFs with CPPD crystals and other SFs from which the CPPD crystals were absent or not detected.

Patient n.	WBC1	WBC2	WBC3	WBC4	WBC5
2	50	50	**600**		
4	350	100	4900	**700**	
7	23350	**16300**			
15	170	50			
21	**31450**	19700			
22	50	50	**150**	50	200
27	50	100	**100**		
29	300	50	**900**	**850**	**150**
30	100	150	**50**		
35	150	**700**			
41	150	**16250**			
46	5500	**4750**			
49	1350	**300**			
54	100	350	**18500**	12950	
55	250	**50**	**50**	**300**	400
57	350	**50**	**50**		
58	500	**11300**	**1450**	**300**	
64	400	**250**	350	2150	

SFs without CPPD (n=25) (in bold print).

Chondrocalcinosis was more common in group A patients as compared to those in group B, 48% versus 19% ($p<0.05$, Fisher's exact test). Three patients in group B had grade 0-1, while 9 patients had grade 2 and 12 had grade 3–4. In group A, on the other hand, 7 had grade 0–1, 6 had grade 2 and 5 had grade 3–4. Thus, OA was mild (grade 0–1) in 39% of group A versus 12.5% of group B patients, while in 50% of group B patients, OA was moderate to severe (grade 3–4) compared to only 27.7% of patients in group A. However, these differences between groups were not significant. Alizarin red staining for suspected hydroxyapatite was more often 2+ to 3+ in group B (OA or chronic arthropathy) (31.6%) compared to group A (15.5%; $p<0.05$, Fisher's exact test).

Discussion

Doherty and Dieppe (9) defined chronic pyrophosphate arthropathy as a structural abnormality of cartilage and bone associated with intra-articular CPPD deposition while pseudogout was defined as acute synovitis associated with intra-articular CPPD deposition. In our study, acute synovitis was more common in patients with chondrocalcinosis detected on plain x-rays, while chronic pyrophosphate associated arthropathy was associated with increased alizarin red staining associated with apatite crystals and a tendency toward greater OA severity.

Chondrocalcinosis occurs in up to 5–10% of adults (10). Chondrocalcinosis shows a marked increase with age, with a prevalence of as high as 30% in persons older than 75 years (11). Although, patients in group B tended to be older than those in group A, chondrocalcinosis was more common in group A compared to group B, 48% versus 19%. This suggests that, factors other than age, such as osteoarthritis, contribute to the higher prevalence of chondrocalcinosis in group A. Chondrocalcinosis is more common in osteoarthritic knees (12-14).

Radiographic studies have shown that chondrocalcinosis is associated with OA (15, 16). Some grade 3–4 OA was seen in patients with acute synovitis. This is in accordance with Fam's study (17) in which 33% of patients with pyrophosphate arthropathy had severe OA based on x-ray findings. Chronic pyrophosphate arthropathy may be a subset of OA. The strong association between CPPD crystals and OA has led many to consider CPPD presence as a process marker for articular insult (9). Up to 35% of patients presenting for total knee arthroplasty for OA have CPPD arthropathy in the surgical pathology specimens (18). In these patients it is unclear whether alterations in cartilage matrix precede, follow, or are coincidental with CPPD crystal deposition. We did not have enough x-rays of the atypical joint involvement reported in pyrophosphate arthropathy such as glenohumeral, metacarpophalangeal, ankle and elbow joints to permit distinction in this group between OA and pyrophosphate arthropathy changes. It is important to note that, the sensitivity of magnetic resonance imaging (MRI) for chondrocalcinosis is extremely low (19) and as low as 39% for plain radiographs (20). Ultrasonography allows the assessment of patients with crystal induced arthropthies. Ultrasound images show synovitis, bone erosions, tendon, bursal and cartilage pathology. The conformation and anatomical location of crystals may help distinguish the different crystal induced arthropathies (21). We found ultrasound to be more sensitive than plain radiographs in the detection of chondrocalcinosis in the knees (22). MRI was not useful in detecting chondrocalcinosis in the elbows or knees. We found plain radiographs and ultrasound to be better suited than MRI in detecting chondrocalcinosis in hyaline cartilage.

Alizarin red staining was more prominent in group B with lower SF WBC compared to group A. A relationship between the severity of radiographic changes and the presence of apatite in the synovial fluid has been described for the knee joint (23) and with OA severity by x-ray (24). Alizarin red staining has been recommended as a way of screening synovial fluids for the presence of apatite. Although, the technique is not specific the possibility of finding apatite-like crystals by transmission electron microscopy is much higher in SFs with strongly positive tests (77%) as compared with SFs with weakly positive tests (25%) (7). In this earlier study, no apatite was found in synovial fluid with negative staining.

We did not demonstrate any higher SF median leukocyte counts in fluids (groups A and B) with CPPD crystals versus those without. SF WBC counts varied in no predictable pattern being higher, lower or the same in SF without CPPD as when CPPD crystals were present. This is in agreement with data published by Gibilisco *et al*. (25). Gibilisco's study did not offer an explanation for the lack of correlation between the intraarticular presence of pro-inflammatory CPPD crystals and synovial fluid WBC. Possible explanations previously proposed for the consistently lower SF WBC counts observed in group B include: subtle differences in the CPPD crystals such as a lesser ratio of monoclinic to triclinic CPPD crystals; smaller crystals and lower Ca: P ratio as compared to those seen in patients in group A. It is suspected that monoclinic CPPD crystals are more inflammatory than triclinic CPPD crystals (26,27). MSU crystals and rheumatoid arthritis coincident with the CPPD also explained some of the inflammation episodes in group A. As is the case with MSU crystals in gout (28) and apatite crystals found in aging articular cartilage (29) CPPD too can exist in synovial effusions with little readily detectable inflammatory cell response. In addition, an inhibitory effect of the apatite crystals might be considered as factor in the lesser inflammation in group B, since alizarin red staining could be seen more often in this group. Previous studies suggested lower SF WBC in patients with non-inflammatory SFs (30) in patients who had SF apatite crystals versus those who did not.

Only one patient in group A was found to have hemochromatosis. No other metabolic predisposition was found. This is in support of the rarity of known metabolic predispositions to CPPD associated disease.

Three of the SFs in group A were from knees of three different patients who had previous total knee replacements. This was an important and unexpected finding.

Due to the retrospective nature of this study patient charts were available on 92% in Group A and 79% in group B and not all x-rays were available for our review. In addition it is possible that not all patient "flares" were either aspirated or included in the study, although patients in our hospital usually had their joint fluids aspirated and sent to our synovial fluid lab, even if their diagnosis was already known. All patients were men and therefore no data are presented for women. This may be important given the different prevalence of OA in men and women. Lastly, our study consisted of a small number of patients making smaller effects more difficult to detect. Larger cross-section and prospective studies are needed to replicate and expand the findings presented herein.

Acute synovitis was seen in group A patients while among patients in group B the symptoms lasted from weeks to months in 30% to years in 70%. The chronic nature of symptoms predicted the SF white count. We did not encounter any patients with chronic inflammatory effusions. The knee was the most involved joint in both groups. The frequent involvement of the knee joint in our series may be due to the greater availability of SF from the more readily accessible knee joint, compared to other joints.

This study contributes to our understanding of important clinical aspects of CPPD deposition disease. Acute synovitis (pseudogout) and chronic pyrophosphate crystal associated arthropathy ("pseudo-osteoarthritis") are often two distinctive syndromes with some patients never having inflammatory attacks in this study. Acute synovitis is more common in patients with chondrocalcinosis while chronic pyrophosphate associated arthropathy is associated with increased alizarin red staining associated with apatite crystals and a trend suggestive of increased severity of OA. (Which could have been statistically significant had the number of x-rays included been larger). We question whether the consistently low SF WBC counts observed in group B can be due to some subtle differences in the CPPD crystals or some inhibitory effect of the apatite crystals seen more often in this group.

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