Prevalence of calcium pyrophosphate deposition disease in a cohort of patients diagnosed with seronegative rheumatoid arthritis

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Abstract

Objective

We aimed to characterise the clinical and radiographical phenotype of calcium pyrophosphate dihydrate deposition (CPPD) disease in patients initially diagnosed with seronegative RA, and to increase the awareness that CPPD disease can be falsely diagnosed as seronegative rheumatoid arthritis (RA).

Methods

Altogether 435 early seronegative RA patients were clinically diagnosed in a single rheumatology centre and scheduled for a 10-year follow-up. All clinical data were collected and reviewed. CPPD-related arthritis was suspected if a patient had typical radiographical findings and suitable clinical pattern of CPPD or calcium pyrophosphate crystals were found in the synovial fluid. These patients are the subjects of this study.

Results

Among 435 seronegative RA patients, 17 patients (3.9%) (baseline mean age 71.2 years, 82% women) with CPPD disease were identified. CPPD resembling clinical patterns in these patients were: chronic CPP crystal inflammatory arthritis (9 patients), acute CPP crystal arthritis (6 patients) and OA with CPPD (2 patients). All had typical radiographical findings of CPPD: Chondrocalcinosis (CC) of triangular fibrocartilage (17 patients [100%]), CC of knee (9 patients [53%]), CC or narrowing of metacarpophalangeal joints (7 patients [41.2%]), CC of metatarsophalangeal joints (4 patients [23.5%]), CC of symphysis pubis (1 patient [5.8%]), CC of glenohumeral joint (1 patient [5.8%]) and scapholunate advanced collapse (5 patients [29.4%]). None of these patients developed typical RA-like erosions.

Conclusion

CPPD disease can mimic seronegative RA at baseline and is important in the differential diagnosis of seronegative arthritis at baseline and during follow-up. The prevalence of CPPD patients in our early seronegative RA patients was 3.9%, the percentage was 7.0% among patients ≥60 years at baseline.

Key words

rheumatoid arthritis, seronegative, calcium pyrophosphate deposition disease, differential diagnosis

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Introduction

Calcium pyrophosphate dihydrate deposition (CPPD) disease is seen mainly in the elderly (1) and is the most common cause of chondrocalcinosis (CC) (2). The most commonly affected joints in CPPD are knees, wrists, hips and symphysis pubis but CPPD in metacarpophalangeal (MCP) joints and ankles as well as in other joints can be seen (3-6). Although radiographical knee involvement is common, CPPD may be asymptomatic (6). The prevalence estimates of CPPD are usually based on radiographically detected CC and do not represent the whole spectrum of clinical CPPD disease. However, it has been reported that calcium pyrophosphate (CPP) crystal arthritis in an Italian population survey of the elderly is the third most common inflammatory rheumatic disease with the prevalence of 0.42% (1).

Clinical presentation of CPPD is heterogeneous, from asymptomatic radiographical findings to acute, inflammatory mono-/oligoarthritic attacks and chronic CPP crystal inflammatory polyarthritis (7). The latter form can be divided into two separate phenotypes; a polyarticular, osteoarthritis resembling arthritis with flares of inflammatory signs and symptoms, and a rarer form of polyarticular CPPD disease with more persistent inflammatory arthritis which can mimic rheumatoid arthritis (RA) (7, 8). The differential diagnosis of CPPD and osteoarthritis (OA) has been studied, especially with regard to distribution of radiographically affected joints (knee, wrist, scapho-trapezoid joint and MCP joints) (9-11). Since the radiocarpal, 2nd and 3rd MCP and glenohumeral joints are usually not affected in OA, OA-like changes in these locations are highly suggestive of CPPD. Other CPPD associated radiographical findings are large subchondral cysts, variable osteophyte formation, severe articular damage and scapholunate advanced collapse (SLAC) (12-14). Because of the heterogeneous group of clinical syndromes, European League Against Rheumatism (EULAR) CPPD Task Force proposed more distinct terminology for CPPD clinical outcomes, including asymptomatic CPPD, acute CPP crystal arthritis, osteoarthritis (OA) with CPPD and chronic CPP crystal inflammatory arthritis (2).

The golden standard for diagnosis of CPPD has been identification of birefringent, rhomboid CPPD crystals in synovial fluid (SF) (2). Different sensitivities (78–92%) and specificities (82–86%) for SF analysis has been reported (15, 16). However, it is possible that all crystals in a synovial samples of acute arthritis patients cannot be seen (17). Radiographic findings of CC are often used to confirm the diagnosis of CPPD, but detection rates in conventional radiographs are variable. Fisseler-Eckhoff *et al*. studied meniscal histological specimens and found that only 35.3% of cases with histologically proven meniscal CC deposits were seen in conventional radiographs (18). Overall, sensitivities vary depending on the joint studied (from 29% to 93%) (2). Ultrasound (US) seems also to be a useful tool for diagnosis of CPPD. Two recent studies reported good sensitivities for US compared to conventional radiographs (19, 20). In one study Forien *et al*. compared US and radiography of wrists in 32 patients with crystals identified in SF. In this study US had higher sensitivity (94%) than radiography (53.1%) for detecting CPP deposits (19). In another study Ottaviani *et al*. compared US and radiography of knees with respective 100% and 64% sensitivities (20). Di Matteo *et al*., however, recently reported comparable sensitivities (77.8% for US, 76.4% for x-ray) and even slightly better specificity (96.9% *vs*. 90.6%) for x-rays to detect CPPD in wrist triangular cartilage complex compared to US (21). Filippou *et al*. compared diagnostic accuracy of US, microscopic analysis of SF and radiographs in the diagnosis of CPPD of the knee. They demonstrated that US was at least as accurate as SF analysis for the diagnosis of CPPD, the reported sensitivity and specificity values were 96% and 87% for US, 75% and 93% for radiography and 77% and 100% for SF, respectively (22). Moreover, US seems to detect inflammation in the knee joints better than clinical assessment in CPPD patients (23). Finally, one systematic review and one

meta-analysis acknowledged US to be a potential tool in the diagnosis of CPPD (2, 24).

The few reported studies have considered CPPD to be rare in RA patients (25, 26). According to Doherty *et al*. the incidence of radiographical knee CC in 100 RA patients was 3% and CPPD crystals were found only in 1% of the knee synovial fluid analyses (26). Recent recommendations by the EULAR have summarised risk factors for CPPD, with inverse association of RA (2). As a contradictory finding, another analysis of 93 RA (76% rheumatoid factor positive) patients the SF for CPPD crystals showed much higher prevalence (25.8%) (27). These studies did not categorise RA patients according to serology, thus the prevalence of CPPD in seronegative RA patients remains unknown. It is known that, seronegativity is more common in elderly onset RA (>60 years) (28), the age group in which CPPD is most prevalent. The diagnosis of CPPD is often challenging and it is possible that a proportion of CPPD patients are diagnosed falsely as seronegative RA.

Our aim was to study the 10-year clinical course of patients with seronegative arthritis and perform reclassification of diagnoses when applicable (29). In total, 17 CPPD cases were found, initially diagnosed and treated as seronegative RA and are subjects of this report.

Patients and methods

Data from all 1030 adult patients with a clinical diagnosis of early RA in the Jyväskylä rheumatology clinic between 1997 and 2005 were collected, including demography, clinical characteristics, medications, patient-reported outcomes, measures reflecting disease activity and progression of radiographic joint damage. A total of 435 seronegative patients were included in the present analyses.

A structured treatment path included 4–5 multidisciplinary visits during the first two years after diagnosis (described in detail elsewhere (30)) and follow-up visits at five and ten years. Clinical monitoring included a complete clinical examination, patient-reported outcomes, laboratory tests, including haemoglobin (Hb), rheumatoid factor (IgM RF), CRP and ESR. Additional serological tests (*e.g*. HLAB27, antinuclear antibodies (ANA), antibodies against double stranded deoxyribonucleic acid (DNA), antineutrophil cytoplasmic antibodies (ANCA), myositis associated antibodies or serology for infectious agents) were tested according to treating specialist´s decisions. RF was interpreted as negative if it was <2x of the upper limit of normal level. Anticitrullinated protein antibodies (ACPAs) were measured after 2005 within follow-up visits. Radiographs of hands and feet were taken at baseline and at 2, 5 and 10 years. Radiographs of other joints were taken on demand according to the treating clinician's decision. All CPPD suspected patients' radiographs were assessed by KP and also KR, a radiologist.

Complete clinical and radiographic follow-up data were collected and reviewed retrospectively. The diagnosis of CPPD related arthritis was suspected if a patient had typical CC in radiographs of symptomatic joints, had suitable clinical pattern of CPPD during follow-up or positive CPP crystal finding in synovial fluid analysis and there was no signs of other inflammatory rheumatic diseases, such as psoriatic arthritis, spondyloarthritis, polymyalgia rheumatica or inflammatory connective tissue disorders.

Results

Among the 435 seronegative RA patients, 17 patients (3.9%) with possible CPPD disease (82.4% women) were identified. The percentage was 7.0% among those ≥60 years of age at baseline. The mean age at baseline was 71.2 years. Eleven patients attended 10-year follow-up visit, the reasons for missing the control was death (three patients), comorbidities (two patients) and refusal (one patient). The clinical characteristics of suspected CPPD patients and all seronegative arthritis patients ≥60 years of age at baseline are illustrated in Table I.

Altogether in seven (41.2%) patients the baseline inflammatory joint symptoms and signs were polyarticular. All these patients had symptoms in wrist and MCP or PIP joints, while other symptomatic joints were hip (one patient) and ankle (three patients). In six (35.3%) patients the baseline symptoms and findings were oligoarticular, including MCP and PIP joint involvement (two patients) and wrist and MCP, PIP or MTP joint symptoms (four patients). Altogether four patients had monoarticular baseline joint involvement including ankle (one patient) and wrist (three patients). In three patients inflammatory symptoms resembled polymyalgia rheumatica either at baseline or during follow-up and two patients were suspected to suffer from palindromic RA at baseline.

At baseline seven patients (41.2%) fulfilled the 1987 ACR criteria (31) for RA. The analysis of synovial fluid of four patients was available and three showed positivity for CPP crystals. Synovial fluid analyses of the other patients had not been performed. The respective mean (SD) ESR and CRP of the CPPD patients at baseline were 33 (29) and 45 (21). The corresponding, not statistically significantly different figures of the other seronegative RA patients ≥60 years of age were 42 (26) and 36 (55). In retrospect the baseline radiographs of ten patients (58.8%) showed evidence of some CC, either in wrists or knee joints. Radiographs of five CPPD patients showed no CC at baseline and the baseline radiographs of the remaining two patients were not found.

The patients' initial disease-modifying anti-rheumatic drug (DMARD) treatments were as follows: sulfasalazine (SSZ) monotherapy (three patients), hydroxychloroquine (HCQ) monotherapy (four patients), methotrexate (MTX) + small dose glucocorticoid (two patients), SSZ + small dose glucocorticoid (six patients), HCQ + small dose glucocorticoid (one patient) and MTX, HCQ and small dose glucocorticoid (one patient). The prevalence of overall prednisone use was 59% (10 patients) at baseline.

Ten (59%) patients discontinued their DMARD treatment during the follow-up period. In seven cases DMARDs were stopped during the first 5 years from the baseline (ranging from 1 month to 5 years). In the other three patients DMARDs were discontinued at 6, 10 or at 11 years from baseline. Only

Table I. Baseline and 10-year follow-up characteristics in patients with seronegative arthritis who were ≥60 years old at baseline and 16 CPPD patients (≥60 years old at baseline).

	Number available for analysis	
Age at baseline (years) mean (SD)		
≥60 year seronegative patients	211	72.2 (7.5)
CPPD patients	16	72.5 (5.7)
Female, n (%)		
≥60 year seronegative patients		144 (68.2)
CPPD patients		13 (81.3)
ACR 1987 criteria for RA fulfilled at baseline, n (%)		
≥60 year seronegative patients	197	124 (58.8)
CPPD patients	16	7 (43.8)
Baseline laboratory and clinical characteristics		
CRP, mg/l, mean (SD)		
≥60 year seronegative patients	200	36.8 (55.3)
CPPD patients	16	35.1 (28.6)
ESR, mm/h, mean (SD)		
≥60 year seronegative patients	199	42.1 (26.5)
CPPD patients	15	45.5 (21.5)
Hb, g/l, mean (SD)		
≥60 year seronegative patients	202	126.1 (14.3)
CPPD patients	16	126.0 (9.4)
HAQ, mean (SD)		
≥60 year seronegative patients	152	1.1 (0.7)
CPPD patients	12	1.1 (0.5)
SJC, mean (range)		
≥60 year seronegative patients	179	6.7 (0-22)
CPPD patients	11	5.2 (0-16)
TJC, mean (range)		
≥60 year seronegative patients	95	7.4 (0-25)
CPPD patients	10	7.7 (2-20)
DAS28, mean (range)		
≥60 year seronegative patients	127	4.8 (2.1-7.9)
CPPD patients	8	5.5 (4.6-6.6)
10-year laboratory and clinical characteristics		
CRP, mg/l, mean (SD)		
≥60 year seronegative patients	87	6.0 (9.6)
CPPD patients	10	4.5 (3.7)
ESR, mm/h, mean (SD)		
≥60 year seronegative patients	87	16.5 (16.2)
CPPD patients	10	17.8 (10.9)
Hb, g/l, mean (SD)		
≥60 year seronegative patients	83	134.4 (14.5)
CPPD patients	10	133.7 (6.7)
HAQ, mean (SD)		
≥60 year seronegative patients	73	1.1 (0.8)
CPPD patients	8	0.9 (0.6)
SJC, mean (range)		
≥60 year seronegative patients	86	2.1 (0-23)
CPPD patients	10	0.8 (0-5)
TJC, mean (range)		
≥60 year seronegative patients	86	0.8 (0-13)
CPPD patients	10	3.1 (0-19)
DAS28, mean (range)		
≥60 year seronegative patients	76	2.6 (0.5-4.9)
CPPD patients	9	2.9 (1.4-4.5)

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hb: haemoglobin; HAQ: Health Assessment Questionnaire; SJC: swollen joint count; TJC, tender joint count; DAS28: Disease Activity Score.

three patients continued their MTX treatment after the 10-year check-up visit. One patient was on SSZ treatment and one patient on HCQ treatment until their death (at 17 years and 5 years from baseline). The two patients who did not attend the 10-year check-up visit were treated with SSZ and HCQ at five years. A total of ten patients reported some adverse events (AE) *e.g.* gastrointestinal AE, rash or nausea, but no serious AEs were reported (Table II).

Altogether five patients became asymptomatic during the follow-up period, four of these cases were treated with a combination of DMARDs and small dose glucocorticoids. The other patients' outcomes (reported as the duration (years) from the last inflammatory attack after baseline) are shown in detail in Table II. Also the spectrum and the lengths of CPPD patients DMARD treatments are shown in Table II.

During follow-up all patients had typical clinical pattern for CPPD disease. According to EULAR recommendations of categorisation for CPPD disease clinical outcome terminology, chronic CPP crystal inflammatory arthritis was seen in nine patients, acute CPP crystal arthritis in six patients and OA with CPPD in two patients. All patients had radiographical findings compatible with CPPD disease during follow-up: CC of triangular fibrocartilage (17 patients [100%]), CC of knee (nine patients [53%]), CC or narrowing of MCP joints (seven patients [41.2%]), CC of metatarsophalangeal (MTP) joints (four patients [23.5%]), CC of symphysis pubis (one patient [5.8%]), CC of glenohumeral joint (one patient [5.8%]) and SLAC (five patients [29.4%]) (Fig. 1). None of these patients developed typical RA-like erosions and all patients remained seronegative for RF and ACPAs during the whole follow-up period. During the follow-up patients did not have any clinical signs of other idiopathic inflammatory rheumatic diseases, such as psoriatic arthritis, spondyloarthritis, polymyalgia rheumatica or systemic connective tissue disorders.

Discussion

One of the main findings of our study was that CPPD disease can mimic and be falsely diagnosed as seronegative RA in elderly. We found that the prevalence of possible CPPD disease in our seronegative RA patients was 3.9% and 7.0% among those >60 years old. This finding is compatible with the study by Doherty *et al*. which reported radiographical knee CC incidence of 3% in RA patients (26), but remarkably lower than in the report by Gerster *et al*. (27).

The initial diagnosis of seronegative RA of our patients was made during the 1990s and early 2000th century, prior to the era of ACPA analyses. At that time

Table II. The characteristics of CPPD patients' treatment and outcome.

Patients. Gender, Age at onset (years)	Symptoms at onset	Joints treated with intra articular glucocorticoids (injection time)	Baseline DMARD treatment	Length of DMARD use (reason for discontinuation)	Outcome at the 10-year follow-up visit: last attack of joint swelling after baseline
Patient 1 F 66	PMR+arthritis	Knee, wrist (at baseline and at 4 years), ankle (at baseline)	MTX + HCQ + GC	Prednisolon 5mg 1.5 years HCQ 2 years (GI AE) MTX 10 years (until death)	4 years
Patient 2 M 77	PMR+arthritis	MCP, PIP (at baseline), ankle (3 years)	SSZ + GC	Prednisolon 5mg 2 years and 3 months SSZ 2 months (gi AE) MTX 5 years (remission)	3 years
Patient 3 F 69	Palindromic arthritis		HCQ	HCQ ongoing	No attacks after baseline
Patient 4 F 52	Polyarthritis	MCP (at baseline), PIP (at 4 months), MTP, PIP (at 1.5 years)	HCQ	Prednisolon 5 mg 1 year (during symptom attacks) HCQ 2 months (rash) SSZ 10 years (remission) MTX 4 years (remission)	1.5 years Complaints due to OA
Patient 5 F 68	Polyarthritis	wrist (at baseline)	SSZ + GC	Prednisolon 5 mg 3 months SSZ 5 years (remission)	No attacks after baseline Complaints due to OA
Patient 6 F 70	Polyarthritis	MCP, ankle (at baseline)	SSZ + GC	Prednisolon 5 mg 6 months SSZ 4 months (GI AE) MTX 5 years (remission)	No 10-year visit (due to refusal) No attacks until the 5-year visit
Patient 7 F 80	Polyarthritis	wrists (at baseline)	MTX + GC	Prednisolon 5 mg ongoing HCQ 8 months (rash) MTX 2 months (lung AE suspicion)	No attacks after baseline complaints due to OA
Patient 8 F 62	Polyarthritis	MTP (at baseline)	SSZ	SSZ 4 years (remission)	No attacks after baseline
Patient 9 F 67	Oligoarthritis	knee (at baseline and at 1, 5 and 6 years), wrist (at baseline and at 3 months)	MTX + GC	Prednisolon 5 mg 12 years HCQ 9 months (nausea) MTX 10 years (remission)	6 years
Patient 10 F 79	Polyartrhtitis	wrist (at baseline)	SSZ + GC	Prednisolon 5 mg (on demand) HCQ 1.5 years (rash) SSZ 1 months (rash)	No 10-year visit (due to comorbidity) No attacks until the 5-year visit
Patient 11 M 74	Monoarthritis		SSZ	SSZ 1 month (nausea)	No 5- or 10-year visit (due to death)
Patient 12 M 65	Palindromic	MCP, wrist (at 5 years) GH-joint, MCP (at 6 years)	HCQ	Prednisolon 5mg ongoing HCQ 8 months (no effect) im gold 3 months (proteinuria) leflunomide 2 months (rash) Adalimumab 6 months (loss of efficacy) MTX ongoing	7 years complaints due to OA
Patient 13 F 77	Polyarthritis	wrist, knee (at baseline and at 5 years)	SSZ + GC	Prednisolon 5mg 3 months SSZ 6.5 years (remission)	No 10-year visit (due to death) knee symptoms at 5-year visit
Patient 14 F 76	Polyarthritis	wrists, knee (at 4 and 12 months, 2 years), MTP (at 12 months)	SSZ	SSZ ongoing	2 years
Patient 15 F 79	Palindromic	wrist (at baseline)	HCQ	HCQ 4 years	No 5- or 10-year visit (due to death) no attacks during 2-year follow-up
Patient 16 F 75	Polyarthritis	wrist, PIP, MCP (at baseline)	GC	Prednisolon 5mg 6 months HCQ 1 month (rash) SSZ 5 days (GI AE) MTX 2 years (remission)	No attacks after baseline
Patient 17 F 76	PMR+ arthritis		SSZ + GC	Prednisolon 10 mg 3 months and 5 mg 4 years (remission) SSZ 1 month (rash) MTX ongoing	sporadic attacks during MTX and Prednisolon interruption during 10-year follow-up

F: female; M: male; PMR: polymyalgia rheumatic; PIP: proximal interphalangeal joint; MCP: metacarpophalangeal joint; GH: glenohumeral; HCQ: hydroxychloroquine; SSZ: sulpha-salazine; MTX: methothrexate; GC: glucocorticoids (small dose, p.o.); GI: gastrointestinal; AE: adverse event; OA: osteoarthritis

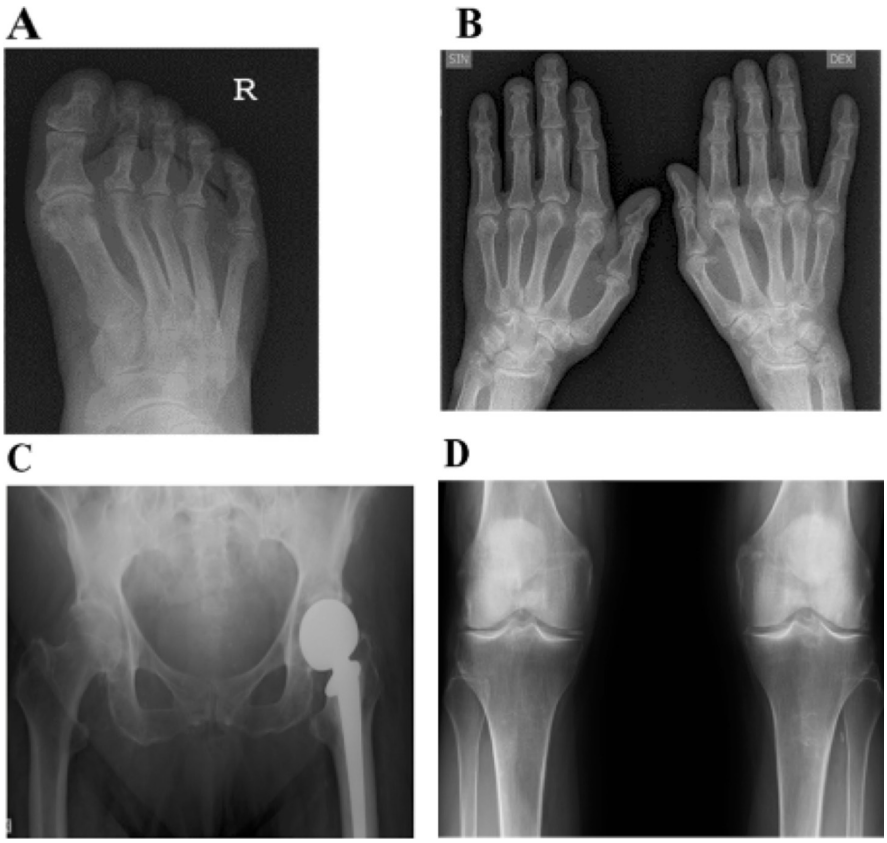

Fig. 1. Examples of radiographical CPPD findings in our patients.
A: Chondrocalcinosis of MTP I joint. **B**: Chondrocalcinosis of triangular fibrocartilage, MCPJ narrowing. **C**: Chondrocalcinosis of symphysis pubis. **D**: Chondrocalcinosis of the knee.

the diagnosis of seropositive RA was limited only to the presence of positive rheumatoid factor (RF). Positive serology receives special emphasis in the current diagnostic criteria of RA and especially ACPA positivity is considered as an indicator of severe disease. In these RA patients, the thresholds for earlier and more intensive DMARD treatment are lower (32). However, before the availability of ACPA analyses, a proportion of RF negative RA – perhaps ACPA positive cases – demonstrated an erosive disease course. Even during that era the rheumatologists in Finland were encouraged to treat polyarticular arthritides, irrespective the serology, actively with DMARDs. The trend enabled the inclusion of initially wrongly diagnosed arthritides, *e.g.* the patients with CPPD disease, into these treatment protocols. The same treatment practice was followed regarding the patients initially not fulfilling the ACR criteria for RA, but with a potential to advance to polyarthritis.

Our patients were initially treated with DMARDs and followed as RA exposing a proportion of patients to unnecessary treatments with potential harms. The majority (59%) of our CPPD disease patients stopped their antirheumatic drug treatments during the follow-up period. Further, the benefit of DMARDs in the patients continuing their treatment remains arguable, taking into consideration the limited evidence of possible benefits of DMARDs in CPPD (33, 34). The majority of our patients were treated with small dose glucocorticoid and/or with intra articular glucocorticoids, and it is possible that especially the patients who suffered from a single joint attack only and were asymptomatic after baseline were symptom-free because of the initial glucocorticoid treatment. However, part of our patients continued their DMARDs for years, and it is possible that these treatments may have influenced positively on their outcomes, considering that most of the patients were asymptomatic for years after baseline (Table II). However, we intend to emphasise the importance of the correct diagnosis within a group of seronegative (rheumatoid) arthritis.

Since the 1960s, polarised light microscopy analysis of SF has allowed identification of CPPD crystals as the definitive way of diagnosing "pseudogout" or CPPD disease (35). Earlier proposed diagnostic criteria for definite CPPD includes both the identification of CPP crystals in SF by compensated polarised light microscopy and presence of typical CC in radiographs (2). In our CPPD patients, only four patients' synovial fluids were analysed during follow-up; all the samples were from the knee joint. One sample showed non-inflammatory leucocyte count probable due to knee OA and the remaining SF showed positive CPP crystals. However, certain difficulties in obtaining SF samples can be identified. First of all, it is difficult to get SF from smaller joints like MCP and wrist. The clinical picture of chronic, polyarticular form of CPPD disease is described as more persistent but less symptomatic than acute, "pseudogout"-like CPPD form, and it mostly affects small joints. Secondly, in some of our study patients the inflammatory symptoms were palindromic, and not present during the check-up visits. Most likely these palindromic joint symptoms were due to "pseudogout" form of CPPD disease, but interpreted as palindromic RA. Thirdly, clinicians as a rule are content with the existing diagnosis and have no interest in obtaining new diagnostic SF samples at the follow-up visits.

In a review article Swan *et al*. questioned the reliability of detecting CPP crystals in SF analyses. They pointed out that crystal concentration is of great importance – the higher the crystal load in the SF, the more likely the analysts will get it right (36). Further, Filippou *et al*. also demonstrated that not all SF analyses show positivity for CPP crystals in knee OA patients with histological proven CPPD (22).There is also evidence that in an acute form of CPPD disease the smallest crystals may not be seen. One can conclude that SF analysis is not 100% sensitive to find all CPPD cases (15-17). Further, in the chronic forms of CPPD disease joint effusions

are infrequently found. In such cases, in real life, the presumed diagnosis of CPPD often relies on typical clinical pattern and radiographical signs of CPPD, defined as probable CPPD according to the proposed diagnostic criteria (2). Thus, only the long-term follow-up of patients can reveal the genuine diagnosis. Nowadays also US and dual energy computed tomography (DECT) scanning may be of additional use when conventional radiographs are difficult to interpret or when crystals cannot be examined (2, 12). In fact, US has proven to be at least as accurate as SF analysis for the diagnosis of CPPD and also its reliability has been shown in different joint areas (22, 37).

By now we know that CPPD disease can mimic RA symptoms and signs at baseline, particularly if involving the joints commonly seen in RA such as wrists as 2nd and 3rd MCP joints. Typical CPPD related radiographic findings can help clinicians to diagnose such cases correctly. However, the x-ray findings are not always present when first inflammatory symptoms of crystal arthritis begin, perhaps because conventional radiographs are not sensitive enough to find all CPPD disease cases. In our study, the baseline radiographs of ten patients showed evidence of CPPD disease. Only the radiographs of hands and feet were taken at baseline, and no systematic radiographic screening for other joint areas typical for CPPD disease, such as knees or symphysis pubis was done. Probably more extensive radiographical screening could have helped clinicians earlier towards the right diagnosis. However, during the follow-up, all patients did develop typical CPPD related findings in radiographs and no one developed typical erosive findings seen in radiographs of seropositive RA patients.

One must also bear in mind that in emerging phenotype of seronegative RA has been described as protean, distinctly different from that of a classical, seropositive, symmetrical polyarthritis phenotype of RA. For example, Pratt and Isaacs in their review of seronegative RA, described a particular clinical presentations of seronegative RA in elderly patients including a rapid onset with polymyalgic features and elevated acute phase markers (38) – a condition, which can in real life easily be mixed up with an acute CPPD disease form.

This study has some weaknesses concerning the retrospective way it was conducted concerning the re-evaluation of the diagnoses, although patients were followed and monitored with a prospective plan made back in 1997. The clinicians were not same during all check-up visits which could have influenced the way they re-evaluated patients' differential diagnosis. This must have partly influenced the lack of confirmative SF analyses for CPPD, the initial diagnosis of RA was thought to be the correct diagnosis option and therefore, SF samples was taken only in a minority of patients. Finally, our study patients were examined and diagnosed with suspected early RA during the era when US was not a daily diagnostic tool in our rheumatology clinic. Nowadays, US is increasingly used in rheumatology clinics to direct towards reliable diagnosis of CPPD and with better availability than any other imaging. The strength of our study is the long follow-up time of our patients and the extensive clinical data collected during the follow-up years. Therefore, taking into account the typical clinical symptoms and radiographical signs of CPPD in our patients as well as the lack of symptoms of other differential diagnoses and clues for other seronegative inflammatory arthritis diseases, such as psoriatic arthritis, other spondyloarthritis diseases, polymyalgia rheumatica or inflammatory connective tissue disorders, we are convinced that our patients represent CPPD. Our long-term follow-up results of patients initially diagnosed as seronegative RA suggest that when suitable clinical picture of crystal arthritis is seen with radiographic signs of CPPD, the diagnosis of RA should be questioned, even in the absence of SF findings. Nevertheless, all clinicians are encouraged to get SF samples whenever available. The analysis may result as an unveiling of the wrong initial diagnosis.

In conclusion, we found that the prevalence of CPPD in our seronegative RA patients was 3.9%, the proportion was 7.0% among those >60 years of age at baseline. Our study increases the awareness that CPPD disease belongs to the syndromes which should be considered when diagnosing seronegative arthritides in the elderly. In fact, we have shown, that in real life rheumatology it is possible to misdiagnose CPPD disease as seronegative RA. These findings also remind us of the broad clinical spectrum of CPPD disease and the importance of long-term follow-up of seronegative arthritis patients, which may disclose their correct diagnosis.

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