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Original article

Comparison of three imaging techniques in diagnosis of chondrocalcinosis of the knees in calcium pyrophosphate deposition disease

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Abstract

Objective. To study the role of different imaging modalities, ultrasonography, conventional radiography (CR) and CT, in visualization of chondrocalcinosis of the knees in patients with CPDD.

Methods. Twenty-five patients (14 males and 11 females) with CPDD were enrolled in the study. Diagnosis was made according to D.J. McCarty classification criteria. All patients had arthritis of the knee and underwent aspiration of SF from the knee and microscopic investigation of SF samples. Diagnosis of CPDD was crystal proven. Three imaging methods were performed in patients: CR, CT and US of the knees.

Results. CR of the knee confirmed cartilage calcification (CC) in 13 patients, CT in 18 patients and US in 25 patients. No difference in age or disease duration between patients with CC detected by different imaging methods was found.

Conclusion. US appeared to be a helpful tool, possibly better than CR or CT, in revealing CC in patients with CPDD. Informativity of CT and CR in the detection of CC is almost equal.

Key words: CPDD, chondrocalcinosis, imaging, ultrasonography, computed tomography, conventional radiography.

CLINICAL SCIENCE

Introduction

Calcium pyrophosphate deposition disease (CPDD) is a metabolic arthropathy due to deposition of calcium pyrophosphate (CPP) crystals in the joints, most common in articular hyaline or fibrocartilage [1]. Diagnosis of CPDD is based on clinical and/or radiographic findings and on microscopic identification of CPP crystals in SF [2]. Crystal visualization is a cornerstone in the diagnosis of crystal-associated diseases such as gout and CPDD. EULAR recommended that definitive diagnosis of CPDD should be crystal proven [3].

Conventional radiography is a well-known imaging method of visualization of cartilage calcification (CC) in joints since 1927, when Mendl first emphasized heterogeneity of meniscal chondrocalcinosis and differentiated primary (asymptomatic, bilateral CC without cartilage damage, predominating in the elderly) from secondary CC (often post-traumatic, occurring in younger subjects as localized, symptomatic CC with cartilage fibrillation) [1]. Roentgenographic evidence of CPDD includes detection of hyaline and/or fibrocartilage calcification, seen as linear deposits parallel to and separate from subchondral bone. One of the studies has shown that the prevalence of knee CC in the Nottingham community aged $\geqslant$40 years, standardized for age and sex, with knee pain was 6.9%, while the prevalence of pyrophosphate arthropathy (PA) was only 3.4% in this community. No difference in frequency of CC and PA was found between women and men [4]. CR is a fast, simple, applicable and inexpensive imaging method of joints examination and revealing chondrocalcinosis. However, data concerning specificity and

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sensitivity of radiographic CC of the knee are not known. The specificity and sensitivity of radiographic CC is shown only for the wrists in one small case–control study, where this imaging method appeared to have low sensitivity (0.29, 95% CI 0.05, 062) and specificity (0.20, 95% CI −0.15, 0.55) [5].

Detection of chondrocalcinosis by plain radiography in patients with crystal-proven CPP arthritis varies from 29% to 93%, depending on population and joint examined [5–7]. There are several factors that may influence the diagnostic value of CR in detecting CC: localization of calcium deposits, significant cartilage loss or the technique used [8]. According to EULAR recommendations for terminology and diagnosis of CPDD, radiographic chondrocalcinosis supports the diagnosis of CPDD, but its absence does not exclude it. Thus, one of the propositions, obtained by the Delphi technique, was to determine the usefulness of ultrasonography in detecting CC in different joints in order to study other than CR diagnostic options in the diagnosis of CPDD [3].

US of joints is a relevantly new method of detection of CC but positioned as an actual, sensitive and specific technique for detection of calcium-containing deposits in cartilage and soft tissues [9, 10]. Frediani *et al.* [11] in 2005 with the use of US investigated the appearance of CPDD calcifications in the most typical sites, such as knees, wrists and shoulders. They demonstrated a definitive correlation between US patterns of CPP deposition in joints and the presence of CPP crystals in SF, while standard radiographic examination failed to show chondrocalcinosis in two patients with crystal-proven CPDD.

CT arthrography is a well-known method of visualization of bone changes. Though CT is a rather expensive imaging method and has perfect ability to show bone erosions in RA and subcutaneous and intraosseous tophi in gout, the usefulness of CT in detection of chondrocalcinosis is unknown. The value of CT in the diagnosis of the crowned dens syndrome in CPDD is well described [12, 13]. CT shows the ability to depict the shape and site of calcification and osseous abnormalities, such as bone erosions and subchondral cysts. Besides, CT appeared to be helpful in imaging calcium pyrophosphate deposition in the temporomandibular joint [14]. Also, CT provides specific imaging of gouty tophi in the knee joints, seen as masses of about 160 HU density, compared with MRI and US [15]. Therefore, the main idea of this study was to determine the diagnostic value of different imaging methods in revealing CC in the knee in patients with CPDD.

Patients and methods

Twenty-five patients (14 males and 11 females) aged $\leqslant$60 years with diagnosis of CPDD were enrolled. Diagnosis was defined according to D.J. McCarty classification criteria. Identification of CPP crystals in SF was an obligate inclusion criterion. Patients older than 60 years were not included in the study in order to avoid the influence of age and significant cartilage loss that occurs in older patients with pre-existing OA. All patients had arthritis of the knee and underwent aspiration of SF from the knee and microscopic investigation of SF samples (Olympus CX31-P). Three imaging methods were performed in all patients: CR, CT and US of the knees. US was performed with a Volusion-I (GE) using 4–13 MHz linear-array transducer. We took into consideration the US feature chondrocalcinosis, defined as linear hyperechoic deposits in the hyaline cartilage, which could be identical to CC phenomena revealed by CR [11]. Standard radiographs were made in antero-posterior and lateral projections by Stephanix (France). CT was performed with a lightspeed 9800 high speed advantage scanner VCT (DORSAL, LATERAL, 3D VIEW, GE, Medical systems LLC, USA). Roentgenographic as well as CT evidence of chondrocalcinosis included detection of hyaline and/or fibrocartilage calcification, seen as thick, linear deposits parallel to and separate from subchondral bone. All three methods were performed for both knees (bilaterally). Presence of another rheumatic disease in our patients was an exclusion criterion. The study was approved by the ethics committee of the Research Institute of Rheumatology, Federal State Budgetary Institution (part of the Russian Academy of Medical Sciences). Patients provided informed written consent before enrolment into the study.

Results

Our group consisted of 14 males and 11 females. The mean age of patients was 49.8 (28-60), mean disease duration was 5.6 years (range 0.8-18.0). The mean number of inflamed or painful joints at the moment of entry was 5 (1-20). Clinical description of patients according to EULAR recommended terminology for CPDD is presented in Table 1.

OA with CPP crystals was the most frequent clinical phenotype presented in 13 patients. Acute arthritis was diagnosed in eight patients and in five cases coexisted with OA with CPP crystals. In nine patients, chronic arthritis was recorded. Patients with chronic arthritis had more joints involved [8 (1–18) *vs* 2 (1–6) in OA with CPP, $P = 0.008$]. In addition to chronic arthritis, the pseudoneuropathic form of CPDD with destruction of the olecranon was diagnosed in Patient 6.

Trauma of the knees was one of the most frequent risk factors, presenting in 14 patients. Hyperparathyroidism (HPT) was recorded in eight patients. Five patients had coincidence of two risk factors—HPT and trauma. Two patients had haemochromatosis. Only one young woman aged 28 years had family history of CPDD. Data regarding evidence of CC in 25 patients obtained with the use of three imaging methods are summarized in Table 2.

CR revealed chondrocalcinosis of the knee in 13 patients (52%), in six of them bilaterally. CT evidence of chondrocalcinosis occurred in 18 patients (72%), most frequently bilaterally (15 patients). CR and CT were shown to reveal chondrocalcinosis in the same joints. Chondrocalcinosis was verified by US in all patients (100%) and was bilateral in 19 cases. So, in 13 patients, chondrocalcinosis was confirmed by three imaging methods. In seven patients, CC was verified only by US. We did

Table 1 Clinical description of patients

No. of patient	Sex/age (years)	Clinical presentations associated with CPDD			Disease duration (years)	Number of joints involved at the moment of entry	Possible predisposing factors
		Acute arthritis	OA with CPDD	Chronic arthritis			
1	M/54		+		6.0	6	Haemochromatosis
2	M/58			+	12.0	5	ND
3	F/55	+	+		1.5	3	HPT
4	F/58	+	+		1.0	3	ND
5	M/43	+	+		1.0	1	Trauma
6	M/52			+[a]	1.0	1	HPT, trauma
7	F/40		+		18	2	HPT, trauma
8	M/54		+		3.3	3	Trauma
9	F/49			+	6.0	9	HPT
10	F/28			+	10.0	18	Hereditary/familial
11	M/59	+	+		9.8	1	Trauma
12	M/48		+		0.8	2	Trauma
13	M/57	+	+		6.5	2	HPT, trauma
14	M/56			+	1.6	9	ND
15	F/54	+			4.4	7	HPT, trauma
16	F/53		+		3	2	OA
17	M/60	+			3	4	OA, trauma
18	M/58			+	11	11	Haemochromatosis, trauma, OA
19	M/41		+		2	2	Trauma, hypoparathyroidism
20	F/44			+	7	10	ND
21	M/39			+	10	6	HPT, trauma
22	F/39		+		5	2	Trauma
23	M/52		+		1.7	1	Trauma
24	F/43	+			7	20	HPT
25	F/52			+	7	4	OA

ND: not detected. [a]Pseudoneuropathic form.

not find statistically significant differences in age and disease duration between patients with or without CC diagnosed by CR, CT or US.

Discussion

CPDD was considered to be a rare disease, most common in the elderly, and pre-existing OA is a recognized risk factor for CPP formation [16–18]. Nevertheless, the frequency of CPDD could be underestimated. The MAPPING study showed that CPP-associated arthritis is the third most common reason for all inflammatory musculoskeletal conditions in an Italian population sample [19]. Another study showed that the prevalence of knee PA in the Nottingham community older than 40 years was 2.4% [20]. Indeed, radiological CC is a frequent finding in elderly healthy individuals, and its frequency varies from 15% between 65 and 74 years to 44% in those aged 85 years and older [16, 21, 22]. Possible explanations for the rare diagnosis of CPDD could be the absence of radiographic investigations, inaccessibility of US for joint examination and microscopy for detecting crystals in SF in undifferentiated arthritis [23]. Besides, as CPDD is known to develop mostly in older subjects, there could be an absence of clinical alarm in terms of occurrence of CPDD in younger ones. The mean age in our group of patients was 50 years, except one 28-year-old woman with familial history of CPDD.

The small number of patients in our study was due to the introduction of an age limit. We did not include patients older than 60 years and those with end-stage OA, because significant cartilage loss can be the reason for missing CC phenomena.

There are several problems in the diagnosis of CPDD. First, CPDD is a multisymptomatic disease presenting with different clinical phenotypes from clinically typical OA to acute or chronic CPP crystal arthritis [3]. A wide spectrum of clinical symptoms was the reason for using the prefix pseudo in the description of different forms of CPDD due to their apparent similarity to other forms of arthritis [24]. Recently it became obvious that using pseudo and relying only on the clinical symptoms of the disease is incorrect. According to the new classification, 13 of our patients presented with OA with CPP crystals clinical phenotype of CPDD, 8 with acute and 9 with chronic arthritis. In addition to chronic arthritis, one patient had the pseudoneuropathic form of CPDD with destruction of the olecranon.

The second problem is that detection of CPP crystals in SF is more difficult than urate crystals due to their small size, different shapes and because it also depends on

TABLE 2 Detection of chondrocalcinosis of the knee by three imaging techniques

No. of patient	CR	CT	US
1	None	None	Bi
2	Bi	Bi	Bi
3	None	Bi	Bi
4	None	Bi	Bi
5	None	Uni	Bi
6	None	None	Uni
7	Uni	Bi	Bi
8	Uni	Uni	Bi
9	Bi	Bi	Bi
10	None	None	Bi
11	Bi	Bi	Bi
12	Bi	Bi	Uni
13	None	None	Bi
14	Uni	Bi	Bi
15	None	Bi	Bi
16	None	None	Uni
17	None	Uni	Uni
18	Uni	Bi	Bi
19	None	None	Uni
20	None	None	Uni
21	Bi	Bi	Bi
22	Bi	Bi	Bi
23	Uni	Bi	Bi
24	Uni	Bi	Bi
25	Uni	Bi	Bi

None: no CC; Uni: unilateral CC; Bi: bilateral CC.

microscopic magnification and investigator's experience [25]. Nevertheless, diagnosis of CPDD should be crystal proven [3]. In our study, the presence of CPP crystals in SF was obligatory.

Third, roentgenological phenomena of CC may not be revealed in all patients with CPDD. There are at least two possible explanations for low sensitivity and specificity of CR for diagnosis of chondrocalcinosis: the small size of CPP deposits and significant cartilage loss due to OA [8]. Though CR still remains the gold standard imaging technique in daily clinical practice and in clinical trials for the evaluation of patients with OA and chondrocalcinosis due to its low cost and accessibility, sensitivity and specificity of this imaging marker are not clear. Radiographic chondrocalcinosis of the wrist is a useful imaging marker, but with low sensitivity (0.29, 95% CI 0.05, 0.62) and specificity (0.20, 95% CI −0.15, 0.55) [5]. Similar data about specificity and sensitivity of CC of the knee are not known. Our study showed that CR revealed CC in 52% of patients with CPDD. But, CR provides only a two-dimensional picture of three-dimensional structures, so there may be a risk of losing abnormalities if they are not caught in the plane beam [26].

The value of CT as an imaging marker of CC is unknown. There are no data regarding comparison of CT with CR in terms of revealing CC of the joints. CT enabled us to reveal CC in 20% more patients than were detected by CR. Still we suppose that informativity of these imaging methods is almost equal. CT advantages concern revealing cysts and erosions of the joints. So, due to its expensiveness and high radiation level, CT may be beneficial in cases where revealing of bone structure abnormalities is required.

There are few publications studying the role of US in detection of CC. Nevertheless, US was shown to have excellent sensitivity (0.87, 95% CI 0.69, 1.04) and specificity (0.96, 95% CI 0.90, 1.03) to reveal CC in the knees, which could be better than those for CR [10, 11]. In our study, we took into consideration linear calcium deposits in cartilage in all patients. We suppose that linear intra-articular calcium deposits, proposed by Frediani *et al.* [11], could be identical to CR cartilage calcification phenomena. In our study, US revealed CC in the knees of all patients. This imaging method could be an important tool in detecting CC and possibly act as a substitute for CR in the diagnosis of CPDD. US has some definite benefits (compared with CR and mostly with CT) in joint and cartilage visualization. They are absence of radiation, low cost, the possibility of performing multiplanar and dynamic joint evaluation and a high level of reproducibility. The main limitations of US in CPDD concern the small number of investigations in patients with CPDD [10, 11]. Of interest is study of the monitoring and dynamics of US changes over several years of disease. This could possibly make clear when and at what stage of the disease changes of the knee cartilage, visible only by US, become visible on CR. Absence of follow-up data leaves this question theoretical.

The diagnosis of CPDD should be accurate. Definitive diagnosis can help us to improve management of patients with CPDD. By separation of patients with CPDD from patients with OA and undifferentiated arthritis, we would be able to improve management of patients with CPDD. Our data showed advantages of US in revealing CC in patients without evident CC by CR. A limitation of our study is the small number of patients. Further investigations are desirable to understand the value of US in diagnosis and follow-up in patients with CPDD.

Rheumatology key messages

- Chondrocalcinosis and the presence of CPP crystals in the synovial fluid are the main features of CPDD.
- Radiographic imaging may not detect chondrocalcinosis in patients with CPP crystals in their synovial fluid.
- Ultrasonography of the joints can assist in the diagnosis of CPDD.

Disclosure statement: The authors have declared no conflicts of interest.

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