Exploration of Musculoskeletal Diseases

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Calcium pyrophosphate crystal deposition disease—what's new?

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Calcium pyrophosphate crystal deposition disease (CPPD) is a prevalent inflammatory rheumatic musculoskeletal disease (RMD) that has recently gained more scientific interest than before. CPPD may become clinically apparent as an acute arthritis or a chronic arthropathy. The latter includes the development of structural changes as assessed by conventional radiography or it presents as a mostly incidental radiographic finding called chondrocalcinosis (CC) [1]. The pathophysiologic basis of CPPD seems to be an imbalance between the production of pyrophosphate and the levels of pyrophosphatases in compromised cartilage. Pyrophosphate deposits in the synovium and adjacent tissues combine with calcium to form calcium pyrophosphate (CPP). Intra-articular CPP crystal deposition can occur in both sexes and all ages [1, 2]. Accordingly, CPPD has been associated with older age, but also with hemochromatosis, hyperparathyroidism, hypophosphatasia, and hypomagnesemia [3]. CPPD is rarely inherited as a monogenic autosomal dominant disease [4, 5].

The clinical presentation of patients with CPPD [2, 3] is variable. It may resemble other RMD such as rheumatoid arthritis (RA), polymyalgia rheumatica (PMR), and gout. Since there is no decisive diagnostic test for CPPD in most cases, the diagnosis often remains uncertain. There have been several international attempts to improve the recognition and standardization of CPPD. One example is the work of the European Alliance of Associations for Rheumatology (EULAR) task force that has tried to find an international agreement on the terminology and classification of CPPD [6]. Thus, CPPD has been defined as the umbrella term that includes acute crystal arthritis, chronic inflammatory polyarthritis associated with CPPD, asymptomatic CPPD, and osteoarthritis (OA) with CPPD, while CC has been defined as cartilage calcification, often due to CPPD as detected by imaging or histological examination. Eleven key recommendations were agreed on regarding clinical features, synovial fluid (SF) examination, imaging, comorbidities, and risk factors [6]. The current situation in this regard has been nicely explained some years ago [7]. More recently, an international multidisciplinary working group has studied the reliability and diagnostic accuracy of radiographic definitions for the identification of CPPD [8]. Using the new definitions, two radiologists and two rheumatologists assessed the images of patients with knee OA twice, before knee replacement for the presence or absence of CC on different joint and tissue structures. Cytological examinations under compensated polarized light microscopy were taken as reference standard. Based on a good agreement among and between radiologists, and rheumatologists, radiography was very specific for CPPD (92%) but, expectedly, the sensitivity remained low in sites and in the overall diagnosis (54%). Importantly, a negative imaging finding does not exclude the diagnosis of CPPD.

The epidemiology of manifestations and phenotypes of CPPD is in part still controversial [9, 10]. Women were more frequently affected than men in two studies [11, 12]. However, in a recent study, for the first time higher odds for acute CPPD among males have been reported [13]. In that very study with well-characterized cases of previously identified correlates of CPPD [13], OA [odds ratio (OR) 3.1], male sex (OR 1.4), RA (OR 2.1), gout (OR 2.8), proton pump inhibitors (OR 1.9), loop diuretics (OR 1.6), and thiazides (OR 1.5) were significantly associated with CPPD, while people of colour had lower odds (OR 0.5). CPPD is clearly a disease of aging and is rare in patients younger than 60 years of age.

The prevalence of CPPD reported depends much on the joints studied. In Italy, CC was among the five most prevalent musculoskeletal conditions observed with a prevalence of 0.42% [12]. In other surveys, CC was detected in 7–10% of knees together with hands, wrists, hips, and the symphysis pubis, respectively [14–18]. CPPD predominantly affects knees, but it also occurs in the absence of knee involvement by CC [19, 20]. CC does occur in association with OA [14, 15, 21]. However, the presence of hip OA is not associated with CC at the hip or distant joints [20]. CPPD also occurs in the spine [22], and that is not only in the form of the well-known crowned dens syndrome [23]. For associations with other RMDs see the paragraph below.

The diagnostic criteria proposed by McCarty and Ryan had been the only criteria defining CPPD to date but they were not widely used [3, 24]. In the *N Engl J Med* review of 2016 [3], experts still found that "until validated diagnostic and classification criteria for CPPD are available, it seems prudent to define definite CPPD as the presence of CPP crystals in SF or tissues with appropriate clinical findings". However, as recently confirmed [25], conventional radiography provides important support for the diagnosis of CPPD and may assist in distinguishing CPPD from other types of arthritis. The recently released validated American College of Rheumatology (ACR)/EULAR classification criteria include all important items of potential relevance for the classification of CPPD [26]. They are explained in more detail in this issue of *Explor Musculoskeletal Dis*.

Conventional radiography is most frequently used to diagnose CC and CPPD but, if only CC is present, this is not sufficient to classify patients as having CPPD. Therefore, clinical symptoms such as the acuteness of attacks and flares of arthritis with swollen, warm, and often reddened joints have also to be present. However, since such features also occur in other inflammatory RMDs, there are challenges regarding the differential diagnosis of CPPD.

As already mentioned, conventional radiography and SF crystal analysis are considered reference standards for CPPD but there are other imaging methods such as ultrasound, dual energy computed tomography (DECT) and magnetic resonance imaging (MRI) which are increasingly used for diagnosis and differential diagnosis of CPPD [27–30]. Ultrasound for example takes advantage of the pseudo-double contour sign to detect CPP in the hyaline cartilage but mainly in larger joints [31, 32]. However, these imaging procedures although increasingly used are not yet considered established standards to diagnose CPPD and CC to date, but a lot of research is currently being performed to shed more light on this. Again, the recent consensus definition of imaging has put the actual situation regarding imaging pulse frequency (PF) for CPPD in perspective [33].

There is one most direct method to diagnose CPPD that, however, is least sensitive: the detection of CPP crystals in the SF by polarized light microscopy. This technique has long been considered as the gold standard for diagnosing CPPD [2] but the reliability and feasibility of this approach were often challenged, and other inflammatory diseases may mimic CPPD associated findings, especially in not well-trained hands [3, 34, 35]. Importantly, the new classification criteria do also stress that there should be no evidence of another more probable explanation for patients' symptoms and diagnosis [25]. Current classification criteria for other diseases [36–38] can be taken into account for this purpose (of course without using them for making the diagnosis).

However, it is not only the differential diagnosis but also the cooccurrence of RMDs that may cause problems for diagnosis and classification. The literature on the co-occurrence of RA and gout is limited but there is some evidence that it exists [39–41]. Comparatively more work more work has been published on

RA and CPPD [42–45]. A closer look at the clinical picture and the radiographs of affected joints of patients clinically diagnosed with CPPD and CC has been recently taken to retrospectively compare them with patients diagnosed with seropositive and seronegative RA in order to determine the prevalence and the clinical differences of these rather common diseases in daily clinical practice. It was found that the combination of RA and CC occurred rather often [46]. To consider chronic CPPD in the differential diagnosis of RA was already advised in the 2011 EULAR recommendations for CPPD [3]. The co-occurrence of RA and CPPD may be simply explained by misdiagnosis which implies that CPPD was previously underdiagnosed in favor of seronegative RA. This assumption is supported by the reported higher prevalence of CC in seronegative *vs.* seropositive disease [46]. In any case, these data confirm the clinical similarity of CPPD and RA. However, seronegative RA may just be underdiagnosed in daily practice. As shown in an early arthritis cohort, using the 2010 ACR/EULAR classification criteria for RA only 51% of patients with seronegative RA were identified in early disease [47]. Another basic problem with the early diagnosis of seronegative RA is that it often cannot be confirmed over time. Indeed, in a Finnish study that included a 10-year follow-up, the diagnosis of seronegative RA had to be revised in the majority of patients [42]. Therefore, it is important to review the diagnosis of seronegative RA over time-especially since the management of RA and CPPD differs in many regards.

Furthermore, the presence of erosion was defined as being critical in these ACR/EULAR criteria for RA [36]. However, it is mandatory that other inflammatory RMD had been excluded. If patients present with symmetric arthritis of hands and wrists and their radiograph shows CC, the differential diagnosis is not so easy—especially if the onset was not sudden and did not appear as an acute attack.

The differences in treatment reported in that study [46] are consistent with current strategies in the management of CPPD but the evidence for the treatment of CPPD by commonly administered drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, colchicine [48] and methotrexate [49] had been rather limited. Very recently, the COLCHICORT study showed that colchicine and prednisone exhibited equivalent short-term efficacy for the treatment of acute CPPD with some differences in safety [50]. Furthermore, there is some evidence for an effect of the anti-interleukin 1(IL-1) biologic disease-modifying antirheumatic drugs (bDMARD) anakinra [50–52]. Although the effect of anti-IL-1 agents may argue in favor of an autoinflammatory disease, it needs to be mentioned that anakinra also works in RA [53]. In addition, there may be a role for anti-IL-6 agents such as tocilizumab [49, 54].

Thus, the comorbidity of CPPD and the prevalence of CC have been shown to be more frequent in seronegative than in seropositive RA [46]. The clinical similarity between these two diseases can make the right diagnosis difficult. Hopefully, studies using innovative imaging techniques may shed more light on this. Prospective cohort studies and randomized clinical trials are urgently needed to provide an evidence basis for the management of CPPD, this rather prevalent RMD in the elderly. The new classification criteria and the recent framework paper by the Outcome Measures in Rheumatology (OMERACT) group on core sets for short and long-term studies in CPPD [55] and agreement on standardized outcome measures [56] are a good step forward in this direction.

Abbreviations

ACR: American College of Rheumatology

CC: chondrocalcinosis

CPP: calcium pyrophosphate

CPPD: calcium pyrophosphate crystal deposition disease

EULAR: European Alliance of Associations for Rheumatology

IL-1: interleukin 1

OA: osteoarthritis

OR: odds ratio

RA: rheumatoid arthritis

RMD: rheumatic musculoskeletal disease

SF: synovial fluid

Declarations

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JB: Conceptualization, Methodology, Project administration, Formal analysis, Visualization, Writing—review & editing, Writing—original draft.

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The author declares there is no conflicts of interest.

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