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Calcium pyrophosphate deposition disease: points to be considered for quality assurance in clinical practice

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Abstract

Calcium pyrophosphate deposition disease is known as crowned dens syndrome or peripheral arthritis, especially of knees, hips and shoulders. The disease course is asymptomatic, with acute or chronic disease activity related to osteoarthritis, especially in the elderly. Other risk factors are joint injury, osteoarthritis and metabolic conditions such as primary hyperparathyroidism, hemochromatosis, hypophosphatasia and hypomagnesemia. Genetic background should be considered before the age of 55 years. Only recently was the value of signs and symptoms weighted, allowing the introduction of classification criteria. Biomarkers include compensated polarized light microscopy findings, laboratory values and imaging. Imaging evidence refers to calcification of the fibrocartilage or hyaline cartilage. Chondrocalcinosis defined as such cartilage calcification is most commonly due to calcium pyrophosphate deposition disease. Calcification of the synovial membrane, joint capsule, or tendon should not be scored. Ultrasonography detects calcium pyrophosphate deposits with more than 80% sensitivity rates, which is superior to conventional radiography. In the future, dual-energy computerized tomography and Raman spectroscopy are promising new techniques to assess disease activity. Currently, the primary therapeutic goal is controlling inflammatory reactions and preventing further episodes. However, only hydroxychloroquine and magnesium carbonate have shown some efficacy and reduction of pain intensity so far. As patients report more significant unmet treatment needs than patients with gout, education is an essential issue of care. The new classification criteria will allow the validation of standardized outcome parameters with the definition of remission and low disease activity for developing treat-to-target strategies to perform well-designed interventional trials evaluating new treatment options and strategies.

Keywords

Quality index, chondrocalcinosis, imaging, biomarker, diagnostic, management

Introduction

Calcium pyrophosphate deposition (CPPD) disease is frequently observed in the elderly. Using ultrasonography (US), fibrocartilage and hyaline cartilage CPPD are rarely seen under age of 50 years, but is more frequent in elderly people, with the prevalences of fibrocartilage and hyaline cartilage CPPD rising up to 46.7% and 23.3%, respectively, after age of 80 years [1]. Such CPPD may remain asymptomatic, present as acute or chronic inflammatory arthritis, as severe joint degeneration, together with osteoarthritis (OA), or with spinal involvement [2]. Acute inflammatory CPPD arthritis had been traditionally named as "pseudo-gout". Compared to gout, CPPD arthritis preferentially affects the larger joints, while gout is caused by urate crystals and preferentially affects the smaller joints. Also contrary to gout, CPPD arthritis occurs more frequently in women than in men. Although radiographic and mechanistic associations between knee OA and knee CPPD arthritis have been described, little is known about possible associations in the hips, hands, and ankles [3].

Acute CPPD arthritis most often involves the knee, wrist, shoulder, and hip. Ligaments, tendons, bursae, bone and the spine are rarely involved. CPPD disease of the atlanto-occipital joint (crowned dens syndrome) can cause not only periodic attacks of cervico-occipital pain but also fever and neck stiffness, together with laboratory signs of inflammation [4]. In rare cases of insufficient treatment after several acute arthritis flares, even palpable and visible masses of CPP crystals, which even resemble gouty tophi, may occur [5]. These masses may even lead to local destructions and compressive symptoms if they accumulate in synovium and adjacent joint structures.

Quality assurance for the management of CPPD disease appears to be necessary. It should include identifying quality indicators for clinical routine, using treat-to-target as a treatment strategy, a specified role of nursing in the care of these patients, data acquisition to provide quality indicators and other quality aspects like polypharmacy [6]. As most of these aspects have not been addressed in clinical trials or recommendations for the management of CPPD disease so far, this narrative review summarizes current evidence, including the recommendations for the management of CPPD by the European Alliance of Associations for Rheumatology (EULAR) from 2011 [2] and the recently reported classification criteria by the American College of Rheumatology (ACR) together with EULAR [7] in view of current literature.

Points to be considered for the quality of CPPD diagnosis

Diagnosis of CPPD disease

Early and accurate diagnosis is essential to allow adequate treatment of CPPD. After EULAR had agreed in 2011 that CPPD 'should be the umbrella term that includes acute CPP crystal arthritis, OA with CPPD and chronic CPP crystal inflammatory arthritis', chondrocalcinosis was defined as cartilage calcification most commonly due to CPPD and detected by imaging or histological examination [2]. Consequently, CPPD disease was diagnosed based on clinical signs and symptoms in combination with CPP crystals within leucocytes in synovial fluid samples or typical signs of chondrocalcinosis in conventional X-rays of joints not necessarily restricted to those clinically involved [8].

Only recently were classification criteria reported by ACR and EULAR, which weighed the different signs and symptoms of CPPD disease to increase the specificity of the classification [7]. These new criteria should be applied only if the patient ever had at least one episode of joint pain, swelling, or tenderness, and after exclusion of alternate conditions including rheumatoid arthritis, gout, psoriatic arthritis, and OA, which are less likely to explain all symptoms. A patient can immediately be classified as having CPPD disease in case of a crowned dens syndrome or a synovial fluid analysis demonstrating CPP crystals in a joint with swelling, tenderness or pain. Otherwise, a patient is classified as CPPD if the sum of specific weighted items (Table 1) exceeds 56 points. Imaging of at least one symptomatic joint is required by conventional radiography (CR), US, computerized tomography (CT), or dual-energy CT (DECT).

Table 1. List of items typical for CPPD ever present during a patient's lifetime [7]. The highest weighted item (n) should be scored for each domain

	Domains and levels	n
A	Age > 60 years at onset of joint pain, swelling, tenderness	4
B	Time-course and symptoms of inflammatory arthritis[1]	
	Persistent inflammatory arthritis	9
	1 typical acute arthritis episode	12
	> 1 typical acute arthritis episode	16
C	Sites of episode(s) with peripheral arthritis and acute onset/worsening that resolves irrespective of treatment	
	1st MTP-joint	−6
	Joint(s) other than wrist/knee/1st MTP-joint	5
	Wrist	8
	Knee	9
D	Related metabolic disease (hereditary hemochromatosis, primary hyperparathyroidism, hypomagnesemia, Gitelman syndrome, hypophosphatasia, or familial history of CPPD)	6
E	Synovial fluid crystal analysis from a symptomatic joint[2]	
	CPP crystals absent on 1 occasion	−1
	CPP crystals absent on ≥ 2 occasions	−7
F	OA of hand/wrist on imaging*	
	Bilateral radio-carpal joints	2
	≥ 2 of the following: STT joint OA without 1st CMC joint OA; 2nd MCP joint OA; 3rd MCP joint OA	7
G	Imaging evidence of CPPD in symptomatic peripheral joint(s)[3]	
	None on US/CT/DECT and absent on CR/CR not performed	−4
	None on CR and US/CT/DECT not performed	0
	Present on either CR/US/CT/DECT	16
H	Number of peripheral joints with CPPD signs on any imaging regardless of symptoms	
	1	16
	2−3	23
	≥ 4	25

* : osteoarthritis is defined as present if Kellgren and Lawrence score ≥ 2 [8, 9]. [1] Persistent inflammatory arthritis defined as ongoing joint swelling with pain and/or warmth. Typical episode defined as acute onset or worsening of joint pain with swelling and/or warmth that resolves irrespective of treatment; [2] synovial fluid analysis performed by individual trained in the use of compensated polarized light microscopy for crystal identification; [3] imaging of at least one symptomatic peripheral joint by CR, US, CT, or DECT required to be considered for classification if sufficient criteria are not met. Imaging evidence of CPPD refers to calcification of the fibrocartilage or hyaline cartilage. Do not score calcification of the synovial membrane, joint capsule or tendon. MTP: metatarso-phalaneal; CMC: carpo-metacarpal; CPPD: calcium pyrophosphate deposition; OA: osteoarthritis; STT: scapho-trapezio-trapezoidal; MCP: metacarpo-phalangeal; CR: conventional radiography; DECT: dual-energy computerized tomography

Typical signs and symptoms ever present during a patient's lifetime must be considered for diagnosis of CPPD disease. The rapid development of severe joint pain, swelling and tenderness that reaches its maximum within 6–24 h, especially with overlying erythema, is highly suggestive of acute crystal inflammation, though unspecific for acute CPP crystal arthritis.

After the exclusion of more probable diagnoses, imaging of a crowned dens syndrome or synovial fluid analysis demonstrating CPP crystals in a peripheral joint with swelling, tenderness or pain can lead to a rapid diagnosis of CPPD. As CPPD disease has a predilection for knee and wrist joints, several differential diagnoses have to be considered, like gout, psoriatic arthritis and rheumatoid arthritis of the elderly. Gout, as the primary differential diagnosis of acute CPPD arthritis, classically involves joints in the feet, especially the first MTP joints. Besides, OA is common in CPPD disease, with a modestly increased rate of radiographic OA in those images with chondrocalcinosis (relative risk = 1.52) [10]. However, the proportion of radiographic OA potentially attributable to CPPD was only 4.4% [10].

As acute CPPD arthritis and sepsis may coexist, microbiological investigation should be performed as soon as infection is suspected, even if CPPD is diagnosed.

Assessment of risk factors

Ageing is the most prominent risk factor for CPPD disease. Another risk factor is a history of joint injury, which may predispose to CPPD disease. In a retrospective cohort study, the risk of CPPD disease in knees was described to be five times higher after meniscectomy than in the contralateral unoperated knees without surgery [11].

Besides, risk factors for CPPD include OA and metabolic conditions such as primary hyperparathyroidism, hemochromatosis, hypophosphatasia, and hypomagnesemia [2]. Also, chronic intestinal failure may be more frequent in CPPD disease of the elderly by 13.5-fold, and the use of diuretics may be a risk factor for CPPD disease by medication-induced hypomagnesemia [12]. All these risk factors should be assessed and discussed with the patients at the time of first diagnosis of CPPD disease.

Genetic counseling is rarely needed

In clinical practice, genetic predisposition with familial forms is rare. Familial predisposition should mainly be considered in younger patients under the age of 55 years if there is polyarticular CPPD arthritis [2]. The *HFE* gene mutations seem to be associated with the polyarticular disease phenotype [8] with a 6.5-fold higher frequency of CPPD in hip joints of heterozygotes for C282Y and a 4.7-fold higher risk of CPPD in hip or knee joints of patients aged < 65 years who are homozygotes for H63D [13]. Mutations in the human *ANK* gene (ANKH) have been shown in patients with familial CPPD, which may help to understand the aetiology of apparent sporadic CPPD [14]. Inorganic phosphate and pyrophosphate regulate the formation of CPP or hydroxyapatite crystals. The discovery of ANKH mutations in familial CPPD disease confirmed the importance of phosphate/pyrophosphate homeostasis in CPPD, with ANKH being a regulator of inorganic pyrophosphate transport [15].

Points to be considered for CPPD management

Few interventional trials are available

Once formed, CPP crystals cannot be dissolved, and at present, there is no specific treatment to eliminate CPPD from the tissue. Therefore, the main goals of CPPD therapy are to control the acute and chronic inflammatory reactions and prevent further episodes [4].

As confirmed by a recent review, the management of CPPD disease is still based on empirical evidence and strategies derived from gout treatment [16]. A few well-designed clinical trials evaluate the treatment of CPPD disease. So far, magnesium carbonate, hydroxychloroquine and methotrexate have been assessed in randomized, double-blind controlled trials [16]. Only hydroxychloroquine and magnesium carbonate have shown some efficacy and reduction of pain intensity. Even non-steroidal antirheumatic drugs and colchicine have not been evaluated in well-designed studies. The interleukin-1 (IL-1) receptor antagonist anakinra and the IL-6 receptor-blocking antibody tocilizumab appear promising but have not been adequately assessed [17]. Also, intramuscular and intra-articular glucocorticoids and adrenocorticotropic hormones (ACTH) may help, but direct comparisons between studies were impossible due to heterogenicity. Consequently, further trials are warranted to provide evidence for clear management recommendations. Without such studies, the costs of hospitalizations caused by CPPD arthritis may further increase with the ageing population [18].

Biomarkers for monitoring disease activity

Outcome parameters provide insights into the functional status of patients and their perception of CPPD disease activity and allow comparisons of these aspects with other diseases. As for other rheumatic diseases, the role of outcome parameters should be evaluated for CPPD disease to assess and monitor disease activity during follow-up. However, there is still no internationally agreed recommendation on the optimal outcome parameters for CPPD disease.

First initiatives use outcome parameters already validated for other rheumatic diseases. For example, the pain visual analogue scale (VAS) scores during a flare of CPPD disease showed pain levels comparable

with gout, although the Routine Assessment of Patient Index Data 3 (RAPID-3) scores were better in CPPD disease than in gout and similar to OA [19]. Patients with CPPD disease had worse Western Ontario and McMaster Universities Arthritis Index (WOMAC) stiffness scores than patients with mild OA but better WOMAC function scores than patients with severe OA [19].

From the laboratory perspective, C-reactive protein levels and erythrocyte sedimentation rate are undoubtedly helpful in assessing systemic inflammation. Besides, low serum magnesium and high ferritin levels were associated with CPP arthritis and may be beneficial in monitoring patients with CPPD disease [8].

The patients' perspective

For the patients, remission or low disease activity is the primary goal of any disease management, with a low rate of disease- and management-related complications. However, in line with the lack of well-designed interventional studies, patients with CPPD report more significant unmet treatment needs than patients with gout ($P = 0.04$) [19].

Education about CPPD disease and its treatment options is undoubtedly a big issue for patients with CPPD disease, which the treating physicians and nurses specialized in the care of inflammatory arthritis should provide, as proposed by EULAR [20]. Besides patient education, nurses will be able to focus specifically on timely access to care, efficiency of care, psychosocial support, and the promotion of self-management with early recognition of adverse effects.

Points to be considered for quality care in CPPD

Assessing the quality of CPPD patients' care is a challenging task. According to Donabedian's conceptual model, quality indicators refer to the three components of the health system's structure, process, and outcome [21–23].

Quality standards

A list of quality standards is proposed by the authors which was adapted from the standards developed for axial spondyloarthritis by the Assessment of SpondyloArthritis International Society (ASAS) (Table 2) [24]. Quality standards should be assessed regularly to improve healthcare quality, preferably using an appropriate software tool for the physicians' documentation.

Table 2. Proposed list of quality standards and indicators for CPPD

Quality aspects		Quality standards
1	Organization	Time from referral to rheumatologist (< 1 week)
		Time from referral to diagnosis (work-up < 2 months)
2	Treatment	Monitoring disease activity/use of scores (VAS, RAPID-3)
		Disease control/treatment escalation (out of indication!)
3	Management	Education and self-management (shortly after diagnosis)
		Rapid access (flare or possibly drug-related adverse event)
		Review by rheumatologist (at least annually if in remission)

VAS: visual analogue scale; RAPID-3: Routine Assessment of Patient Index Data 3

Quality issues for the diagnostic process

Gold standard for diagnosis

A practical gold standard for diagnosing CPPD disease does not exist in clinical settings. Using the ACR/EULAR classification criteria for CPPD, the validation cohort demonstrated a sensitivity of 99.2% and a specificity of 92.5% to classify CPPD. Assessment of risk factors and comorbidities as well as genetic counselling—at least in patients before the age of 55 years—has to be recommended after diagnosis of CPPD disease.

Synovial fluid analysis

According to the ACR/EULAR recommendations, an individual trained in using compensated polarized light microscopy for crystal identification should perform synovial fluid analysis [23]. Initially, non-polarized light microscopy should be used to screen for the characteristic morphology of CPPD crystals, followed by compensated polarized light microscopy, showing the crystals to be weakly positive birefringent for definitive identification in about 20% of samples [4]. Besides compensated polarized light microscopy, Raman microscopy could be used as an alternative method for crystal identification in synovial fluid analysis. Raman microscopy is a non-destructive technique that uses laser light to identify the chemical composition of a sample [25]. It has been found to be effective in identifying various types of crystals, including CPPD crystals, in synovial fluid analysis [26]. One advantage of Raman microscopy is that it can identify crystals even in the presence of interfering substances, such as blood or bacteria, which can be difficult to remove completely from synovial fluid samples. However, Raman microscopy requires specialized equipment and expertise, which may not be available in all laboratories. Therefore, while Raman microscopy may be a valuable alternative to compensated polarized light microscopy for crystal identification in synovial fluid analysis, the equipment's availability and the technician's expertise should be considered before choosing this method. A routine search for CPP crystals is recommended in all synovial fluid samples obtained from undiagnosed inflamed joints, especially from the knees or wrists of older patients.

Imaging procedures

Concerning the role of imaging for diagnosing CPPD disease, imaging of at least one symptomatic peripheral joint by CR, US, CT, or DECT is recommended if sufficient criteria are not met [14]. CR, especially of the wrists and the knees, has to be considered. Also, a CR of the pelvis frequently shows cartilage calcification. Imaging evidence of CPPD refers to the calcification of the fibrocartilage or hyaline cartilage. Calcification of the synovial membrane, joint capsule, or tendon should not be scored. Compared to OA without CPPD, OA with CPPD may be associated with an atypical distribution of findings (e.g., radiocarpal or mid carpal, glenohumeral, hindfoot or midfoot involvement) and prominent cyst and osteophyte formation on radiographs [2]. US can demonstrate CPPD in peripheral joints, typically as thin hyperechoic bands within hyaline cartilage and hyperechoic sparkling spots in fibrocartilage. A recent review suggests that US detects CPPD crystals in peripheral joints with more than 80% sensitivity rates, which is superior to CR [27]. However, evidence levels of the studies were low, and DECT has only marginally been explored for CPPD. Nevertheless, US, DECT and Raman spectroscopy are emerging new techniques despite significant unmet needs.

Quality issues for the patients' management

Concerning the few clinical trials to guide the management of CPPD disease, patients' education is essential both on the disease and possible disease and drug-induced complications. Rapid access to care is essential, especially in case of a flare or a suspected drug-related adverse event. More well-designed studies are warranted to increase the levels of evidence for pharmaceutical approaches and efficient treatment strategies. At present, patients have to be informed about the low level of evidence from well-designed clinical studies.

Because of the lack of long-term studies assessing the efficacy and safety of emerging therapies and treatment strategies, and the complexity of CPPD arthritis, patients will certainly benefit from a multidisciplinary approach. Therefore the collaboration of rheumatologists, radiologists, physiotherapists, and other healthcare professionals in an integrated care management program for CPPD patients should be established.

Conclusions

Only recently were the roles of signs and symptoms in CPPD disease weighted to allow the definition of classification criteria. This has to be considered a significant and essential step forward in developing

standardized outcome parameters, performing well-designed pharmaceutical trials, and defining remission and low disease activity to develop treat-to-target strategies. With the expected boost of additional trials, the awareness of this frequent disease of the elderly will rise and allow more clinical research in well-defined cohorts. Because of the relevance of deficient calcification inhibitors such as the inorganic pyrophosphate-generating ectoenzyme PC-1/nucleotide pyrophosphatase phosphodiesterase 1, inflammatory cytokines and a disordered calcium and inorganic phosphate homeostasis both for arterial and articular cartilage calcification, also comparative studies will further provide important information for controlling chondrocalcinosis in the future [28].

Abbreviations

ACR: American College of Rheumatology

ANKH: human *ANK* gene

ASAS: Assessment of SpondyloArthritis International Society

CPPD: calcium pyrophosphate deposition

CR: conventional radiography

CT: computerized tomography

DECT: dual-energy computerized tomography

EULAR: European Alliance of Associations for Rheumatology

OA: osteoarthritis

US: ultrasonography

Declarations

Author contributions

MS: Conceptualization, Investigation, Writing—original draft, Writing—review & editing, Supervision. JDP: Investigation, Writing—review & editing. Both authors read and approved the submitted version.

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The authors declare that they have no conflicts of interest.

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Consent to participate

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