

The diagnosis of calcium pyrophosphate dihydrate crystal deposition disease: the good, the bad and... ultrasonography!

G. Filippou, B. Frediani

Department of Clinical Medicine and Immunology, Rheumatology Section, University of Siena, Italy

The diagnosis of calcium pyrophosphate dihydrate crystal deposition disease (CPPD) until recent years has been mainly based on the finding of typical crystals of calcium pyrophosphate dihydrate (CPP) in the synovial fluid of affected patients and on the presence of typical calcifications on plain X-rays (1). Recently a group of experts has published, on behalf of the EULAR, a set of recommendations on the terminology, diagnosis and treatment of CPPD (2). Independently of the content of the recommendations, the only fact that a group of experts considered a rather “forgotten” but certainly very common disease (3) is a big step forward, that could give new impulses in the field of diagnosis, follow-up and pharmacological treatment. This set of recommendations for the diagnosis of CPPD, for the first time, compares ultrasonography as a valid tool for diagnosis. Further, the experts agree that synovial fluid microscopic analysis could be considered the reference method for diagnosis and that traditional x-rays may support the diagnosis of CPPD, but normal radiograms do not exclude it. But is it as simple as this?

The good - Synovial fluid analysis and CPP

In the paper published by the EULAR task force, the experts agree that “definitive diagnosis of CPPD is by identification of characteristic CPP crystals (parallelepipedic, predominantly intracellular crystals with absent or weak positive birefringence) in synovial fluid, or occasionally biopsied tissue” with a strength of recommendation (SOR) of 94 in a VAS of 0-100. In

the review by Swan et al. (4), in 2002, the authors expressed their scepticism on the diagnostic capacity of the technique as they noticed a worrying variability among different readers and laboratories in the identification of CPP crystals. They suggest that further studies are necessary in order to assess the real diagnostic value of synovial fluid analysis. A more recent study (2005) by Lumbreras et al. (5) tried to assess the inter-reader agreement in identifying CPP crystals. In that paper, trainees without previous experience in synovial fluid analysis, observed prepared slides previously classified by the expert, after a course held by the same expert. In this study, specificity and sensitivity for detecting crystals was 92% and the inter-reader agreement was between 86% and 96% towards the reference standard, but the agreement between the trainees was not calculated. In other words, in this study the authors demonstrated that after training, a trainee can identify the same “things” as the trainer but is this enough to assert that everyone can perform diagnosis of CPPD after 3-4 months of training? More appropriate study designs and further data are necessary in order to assign the role of main diagnostic tool to synovial fluid analysis. As Blondie (the good) said in the famous movie “The good, the bad and the ugly”: “Two hundred thousand dollars is a lot of money. We’re gonna have to earn it.”

The bad - Plain radiograms

Even though the statement “radiographic CC supports the diagnosis of CPPD, but it’s absence does not exclude it” (SOR

Corresponding author:
Dr. Georgios Filippou
Dipartimento di Medicina Clinica
e Scienze Immunologiche
Sezione di Reumatologia
Policlinico Santa Maria alle Scotte
Viale Bracci - 53100 Siena, Italy
E-mail: g_filippou@virgilio.it

97) has not been demonstrated by specific studies, but only by small studies or as an observation in studies with other endpoints, the finding of negative X-rays with positive synovial fluid analysis is a common experience between rheumatologists. The main reasons for this discrepancy have been identified and discussed by the group of experts. Furthermore, a recent study by Abhishek et al. presented at the EULAR congress of Berlin (6) demonstrated that although the knee joint is the most common site of CPPD involvement, almost 40% of people with CC do not present CPPD in the knee in radiograms. Additionally, only around 80% of people with CC can be identified if radiographs of knees and pelvis, or knees and wrists/hands are performed. For this reason, in order to obtain a more accurate radiographic diagnosis of CPPD, multiple sites should be screened, with obvious exposure of harmful radiations. So, as Angel Eyes (the bad) said, we have to remember: "People with ropes around their necks don't always hang."

And... ultrasonography

US is a harmless, rapid, non invasive and widely available tool. The experts confirm that "ultrasonography can demonstrate CPPD in peripheral joints, appearing typically as thin hyperechoic bands within hyaline cartilage and hyperechoic sparkling spots in fibrocartilage. Sensitivity and specificity appear excellent and possibly better than those of conventional x-rays" with a SOR of 78, definitively lower with regard to the other recommendations. This proposition has been mainly based on our previous studies (7, 8) where we tried to define the sensitivity and specificity of the technique and the US aspect of CPP crystals in US. Unfortunately, inter-reader agreement studies are lacking in this field so a real agreement has not been calculated in specific studies but only as a secondary end point. In the study by Filippucci et al. (9) an expert and a non expert sonographer reached an agreement of 90% in identifying CPP deposits in the hyaline cartilage of the knee. Even in this case, as it happened in the paper of Lumbreras et

al. (5) regarding the synovial fluid analysis, the gold standard for diagnosis was the expert's reading and the non expert sonographer spent some time with the expert for defining US findings of CPP deposits in the hyaline cartilage. Almost two years ago, a group of Italian experts met in our hospital in Siena, in order to perform a study on inter-reader agreement in identifying CPP deposits in various sites (menisci, hyaline cartilage of the knee and wrist). All participants, although with at least ten years experience in US, had never shared US sessions and all of them were aware of the most recent literature and the US criteria for CPPD diagnosis. The setting was as in real life, without previous consensus on the interpretation of the findings, and every sonographer was asked to use the most appropriate scanning technique according to his opinion. The results demonstrated an extreme variability between readers with values between 0 to 100% of agreement (10). The variability of our data was due to the different "sensitivity" of the readers in defining every small hyperechogenic deposit as a CPP deposit or not. Obviously the problem in this case was to determine who was right, as fluid analysis cannot always be performed (for example in the absence of effusion) or it may be negative in the very initial phases of the disease and, as we said before, the sensitivity of radiology is too low to use it as a gold standard. So, the question is how can we be sure that a hyperechoic deposit within the cartilage or fibrocartilage is due to CPP crystals? We tried to respond to this question by using the microscopy of joint structures as the gold standard. We examined by US, the menisci of patients that underwent knee replacement surgery, just the day before. Then we retrieved the menisci and we examined them again by US and by microscopic analysis of small samples of every meniscus. We found out that US is not as sensitive and specific as we thought (11) if we consider a single structure of a joint (meniscus in this case) and if we use a severe gold standard such as microscopic analysis of joint structures, capable of identifying CPP crystals in a

very early stage before they could reach US detectable dimensions. Sensitivity and specificity values were better in the *ex vivo* US diagnosis than in the *in vivo* examination, in part because of the possibility to perform more accurate scans in all planes. We also identified some pitfalls that could mislead a diagnosis and should be recognized as they can increase the specificity and sensitivity of the method (under submission). Fortunately, US can be performed in various sites in just a few minutes and sensitivity and specificity values can raise if we assess all cartilage and fibrocartilage structures of the knee and wrist joints. Also, we have to consider that studies comparing synovial fluid analysis versus a severe gold standard for the presence of CPP deposits in the joint (as tissue microscopic analysis is) are lacking.

In conclusion, more studies are necessary in order to assess the real sensitivity and specificity of the available tests for the diagnosis of CPPD. We believe that interaction between experts and dedicated workshops either on synovial fluid analysis or US could at least increase the diffusion of the techniques and the homogeneity of the findings. The lack of an accessible, non invasive and severe “gold standard” makes it difficult to truly assess the efficacy of the tests to diagnose CPPD. US, seems to play a very important role in the diagnosis, as it can be easily performed, it’s harmless and non invasive and could, in theory, be valuable in the follow-up of the disease, when hopefully specific treatment options will be available. So, as Tuco (the ugly) said to Blondie (the good): “If I get my hands on the two hundred thousand dollars, I’ll always honour your memory. I swear.”

■ REFERENCES

1. Ryan LM, McCarty DJ. Calcium pyrophosphate crystal deposition disease, pseudogout and articular chondrocalcinosis. In: McCarty DJ, Koopman WJ, editors. Arthritis and allied conditions. 13th ed. Philadelphia: Lea and Febiger. 1997; 2103-25.
2. Zhang W, Doherty M, Bardin T, Barskova V, Guerne, P-A, Jansen TL, et al. European league against rheumatism recommendations for calcium pyrophosphate deposition. Part I: terminology and diagnosis. *Ann Rheum Dis.* 2011; 70: 563-70.
3. Ciancio G, Bortoluzzi A, Govoni M. Epidemiology of gout and chondrocalcinosis. *Reumatismo.* 2012; 63: 207-20.
4. Swan A, Amer H, Dieppe P. The value of synovial fluid assays in the diagnosis of joint disease: a literature survey. *Ann Rheum Dis.* 2002; 61: 493-8.
5. Lumbreras B, Pascual E, Frasquet J, González-Salinas J, Rodríguez E, Hernández-Aguado I. Analysis for crystals in synovial fluid: training of the analysts results in high consistency. *Ann Rheum Dis.* 2005; 64: 612-5.
6. Abhishek A, Doherty S, Maciewicz R, Muir K, Zhang W, Doherty M. Chondrocalcinosis frequently occurs at the wrists and hips in the absence of knee involvement. *Ann Rheum Dis.* 2012; 71 (Suppl. 3): 442.
7. Frediani B, Filippou G, Falsetti P, Lorenzini S, Baldi F, Acciai C, et al. Diagnosis of calcium pyrophosphate dihydrate crystal deposition disease: ultrasonographic criteria proposed. *Ann Rheum Dis.* 2005; 64: 638-40.
8. Filippou G, Frediani B, Gallo A, Menza L, Falsetti P, Baldi F, et al. A “new” technique for the diagnosis of chondrocalcinosis of the knee: sensitivity and specificity of high frequency ultrasonography. *Ann Rheum Dis.* 2007; 66: 1126-8.
9. Filippucci E, Riveros MG, Georgescu D, Salaffi F, Grassi W. Hyaline cartilage involvement in patients with gout and calcium pyrophosphate deposition disease. An ultrasound study. *Osteoarthritis Cartilage.* 2009; 17: 178-81.
10. Filippou G, Delle Sedie A, Filippucci E, Iagnocco A, Valesini G, Grassi W, et al. Agreement tra esperti nell’identificazione ecografica dei depositi di cristalli di CPPD in pazienti affetti da condrocalcinosi Reumatismo. 2010; 62 (Suppl. 1): 236. (Abstr.).
11. Filippou G, Bozios P, Gambera D, Lorenzini S, Bertoldi I, Adinolfi A, et al. Ultrasound detection of calcium pyrophosphate dihydrate crystal deposits in menisci: a pilot in vivo and ex vivo study. *Ann Rheum Dis* 2012 [Epub ahead of print].