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RELIABILITY OF CONVENTIONAL RADIOGRAPHY OF THE KNEE FOR THE ASSESSMENT OF CHONDROCALCINOSIS: AN ANCILLARY STUDY OF THE OMERACT ULTRASOUND – CPPD GROUP

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Background: Conventional Radiography (CR) has been widely used in the assessment of knee chondrocalcinosis (CC) and is still considered one of the most important diagnostic methods for the diagnosis. However, there are no studies on the reliability of CR for CC.

Objectives: To assess the reliability of CR of the knee in the assessment of chondrocalcinosis (CC).

Methods: This is an ancillary study of the Criterion Validity of Ultrasound in Calcium Pyrophosphate Deposition Disease (CPPD) study [1]. Consecutive patients with knee osteoarthritis (OA) that were planned for total knee replacement surgery were enrolled in 4 centres from Romania, Italy, USA and Mexico. All patients underwent CR of the knees taken maximum 6 months before surgery, in posterior-anterior weight bearing and lateral projections. DICOM files of the radiographs were retrieved, anonymised and read independently by two musculoskeletal radiologists with experience in microcrystalline arthropathies. Each reader performed a second evaluation 3 weeks after the first one to calculate the inter- and intra-reader agreement. For each patient a dichotomic score was assigned (absence/presence of CC) at the level of the medial and lateral menisci, tibiofemoral hyaline cartilage, quadriceps and patella tendons, synovial membrane/joint capsule. The definitions of the ACR/EULAR taskforce for identification of CPPD in conventional radiography were used in this study [paper in preparation]. According to these definitions CPPD in CR appears as "linear or punctate opacities in the region of fibro- or hyaline articular cartilage/synovial membrane or joint capsule/within tendons or entheses that are distinct from denser, nummular radio-opaque deposits due to basic calcium phosphate deposition". Cohen's kappa was used to calculate the agreement between the two readers.

Results: We enrolled 33 patients with knee OA (60.6% female, mean age 69yo $\pm$ 8). The kappa values of the inter-reader and intra-reader agreement in the various sites of the knee are indicated in Table 1. Inter-reader agreement was substantial at the level of both menisci but only moderate or fair at the other sites of assessment. This had a negative impact on the overall evaluation of the knee joint that proved to be unreliable (k of 0.16 – none to slight agreement) if all anatomical structures are included for assessment, and moderately reliable (kappa 0.41) when both menisci and hyaline cartilage are considered. On the other hand, intra-reader kappa values were substantial or higher in all sites (except for synovial membrane/joint capsule for one reader). The striking difference of the intra-reader compared to the inter-reader kappa values, highlight a different interpretation and application of the definitions used for most of the sites with the exception of the menisci.

Table 1. kappa values for intra- and inter-reader agreement. Values from 0.01–0.20 are considered as none to slight agreement, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement.

	Medial meniscus	Lateral meniscus	Hyaline cartilage	Quadriceps tendon	Patellar tendon	Capsule/synovia	Menisci + cartilage	Entire joint
Inter-reader	0.67	0.71	0.34	0.47	NA	0.37	0.40	0.17
Intra-reader	0.67	0.90	0.84	0.65	NA	0.53	0.71	0.76
1 st assessor					(insufficient number of categories)			
Intra-reader	1	0.80	1	1	1	0.91	0.86	0.94
2 nd assessor								

Conclusion: CR has been extensively used for diagnosis of OA and CPPD. The results of our study raise some concerns on the reliability of CR in identification of CPPD. Assessment of calcium crystals at the menisci level should be used for identification of CC as other sites of the knee seem to present low reliability.

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COMPARATIVE ANALYSIS OF THE CLINICAL AND LABORATORY PROPERTIES OF GOUT, OSTEOARTHRITIS, AND CALCIUM PYROPHOSPHATE DEPOSITION DISEASE

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Background: The clinical differentiation between gout, osteoarthritis (OA), and calcium pyrophosphate deposition disease (CPPD) still remains a hurdle in daily practice without imaging or arthrocentesis. Although a plethora of clinical data exists, reliable predictor biomarkers for all but gout are still missing.

Objectives: To explore an association between common physical examination, ultrasound and laboratory findings and gout, OA, and CPPD, which can in turn provide reliable diagnostic predictions.

Methods: 277 patients were retrospectively analysed using ANOVA with Scheffe's post hoc tests and conditional inference trees regarding biomarkers such as age, sex, body mass index, hypertension, renal status, cumulative affected joint size, number of afflicted joints, double contour sign, intracartilaginous double contour sign, degree of vascularization on ultrasound (DoV), uric acid, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, and leucocyte count. Simple linear regressions were carried out to explore associations between increased inflammatory parameters and the above-mentioned biomarkers. Statistically significant associations were defined as p values < 0.05.

Results: The male sex was associated with gout (p value < 0.05 vs CPPD and < 0.05 vs OA). OA affected younger patients than CPPD (mean 64.5 vs 73.1 years, p < 0.05). Hypertension was correlated with gout (p < 0.05) and CPPD (p < 0.05), impaired renal status with gout when compared to OA (p < 0.05) but not compared to CPPD (p 0.21). A higher number of involved joints was associated with gout (mean 2.2 joints) compared to OA (1.0, p < 0.05) and CPPD (1.6, p 0.01). The double contour sign was not able to differentiate gout and CPPD with a sensitivity/specificity of 71%/55% for gout and 59%/39% for CPPD. The intracartilaginous double contour sign was specific for CPPD (99%) but with a low sensitivity of 26%. DoV was significantly associated with gout (vs OA, p < 0.05) and CPPD (vs OA, p < 0.05). Unsurprisingly, uric acid was associated with gout while ESR and CRP were increased in gout and CPPD, but not in OA. Some associations were statistically significant but arguably clinically unimportant. Conditional inference trees were able to exclude OA (specificity 97.5%) and CPPD (specificity 94.0%) as possible differentials based on just uric acid, CRP, hypertension,

and sex, and diagnose gout with a sensitivity of 95.1%, summarized in Figure 1. Linear regressions demonstrated an elevated CRP response in people suffering from type II diabetes, higher cumulative joint points score, number of affected joints, as well as elevated uric acid, ESR, and leucocyte count.

Figure 1. Conditional inference tree using unbiased recursive partitioning to reliably differentiate between gout, osteoarthritis, and calcium pyrophosphate deposition disease.

Conclusion: Gout can be reliably diagnosed, simultaneously excluding OA and CPPD as differential diagnoses by conditional inference trees using just four biomarkers. A correlation between inflammatory reaction severity based on CRP levels was found in patients suffering from type II diabetes, more or larger joint involvement and elevated uric acid levels. The double contour sign remains a questionable differentiator between gout and CPPD with a sensitivity/specificity of 71%/55% for gout and 59%/39% for CPPD, similar to findings reported by Löffler et al (1) with a sensitivity/specificity of only 64%/52% for gout.

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POS1136 MONOSODIUM URATE CRYSTALS REDUCE SCHWANN CELLS VIABILITY

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Background: The prevalence of peripheral neuropathy in patients with gout almost reaches 25%[1]. Demyelination caused by Schwann cell (SCs) injury and apoptosis is the major pathological feature of peripheral[2]. None of study has focused on the effects of monosodium urate (MSU) crystals on SCs.

Objectives: To assess the effect of MSU crystals on SCs.

Methods: Mouse-derived Schwann cells (RSC96) are stimulated with different concentrations of MSU crystals (0mg/ml, 0.25mg/ml, 0.5mg/ml) and time (24h, 48h, 72h). The migration ability of Schwann cells is evaluated by scratch assay, the proliferation level is assessed by the cell counting kit-8 (CCK-8) assay, and the apoptosis rate is detected by flow cytometry.

Results: The scratch assay showed that the migration ability of SCs was worsened, CCK-8 assay suggested that proliferation of SCs was reduced in a dose-dependent manner ($P < 0.05$). According to the result of flow cytometry, the survival rate of SCs at 0.5mg/ml ($78.60\% \pm 2.26\%$) was lower than that 0.25mg/ml ($87.50\% \pm 0.95\%$) and 0mg/ml ($98.80\% \pm 0.26\%$) ($p < 0.05$) at 24h. When the stimulation time increased to 72h, the survival rate at 0.5mg/ml ($47.90\% \pm 11.70\%$) dropped significantly, which was significantly different from the other two groups ($p < 0.05$).

Conclusion: MSU crystals can cause damage to Schwann cells. It may help to explain the reason of peripheral neuropathy in gout patients.

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Figure 1. Flow cytometry assays of RSC96 on MSU crystals at 72h

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POS1136 PHARMACOKINETICS OF PEGLOTICASE AND METHOTREXATE POLYGLUTAMATE(S) IN PATIENTS WITH UNCONTROLLED GOUT RECEIVING PEGLOTICASE AND CO-TREATMENT OF METHOTREXATE

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Background: In an open-label, single-arm trial in adult patients with uncontrolled gout (MIRROR open-label [OL] trial) evaluating pegloticase co-treatment with methotrexate (MTX); 78.6% patients were responders, defined as maintenance of serum uric acid < 6 mg/dL for at least 80% of the time during month 6 [weeks 20, 22, and 24]. In comparison, 42% patients achieved a response during month 3 and 6 in historical Phase 3 monotherapy trials of pegloticase (C0405 and C0406)¹. MTX co-treatment is shown to improve the pharmacokinetics (PK) of biologics by attenuating the formation of anti-drug antibodies².

Objectives: To determine the systemic exposures of pegloticase and methotrexate polyglutamate(s) (MTX-PGs) in uncontrolled gout patients receiving pegloticase and MTX; to evaluate the effect of MTX on the PK of pegloticase in comparison to historical pegloticase monotherapy trials (C0405 and C0406)³; and to evaluate the immunogenicity of pegloticase in co-treatment with MTX.

Methods: In the MIRROR OL trial, MTX (15 mg/week) was given orally 4 weeks prior to the first pegloticase dose and continued weekly, in combination with pegloticase 8 mg given intravenously every 2 weeks, for a treatment duration of up to 52 weeks. Pre-infusion samples were collected to measure MTX-PGs in red blood cells. Pre- and post-infusion blood samples were obtained to measure the peak (C_{max}) and trough (C_{min}) concentrations of pegloticase at multiple visits. Anti-drug antibody blood samples were collected at multiple visits. The impact of MTX on pegloticase PK was evaluated by comparing pegloticase exposures with MTX from this trial to historical monotherapy data (C0405 and C0406)^{3, 4}. The observed pegloticase concentrations with MTX were also overlaid with the 90% prediction interval based on the population PK model⁵ from C0405 and C0406.

Results: Pegloticase and MTX-PG levels were determined in 14 patients. The 11 responders were generally associated with higher pegloticase exposures than the non-responders, especially C_{min} (Figure 1). Concomitant treatment of MTX resulted in fewer patients with C_{min} below quantitation limit (BQL) (5/14 [36%] with MTX vs 6/32 [77%] without MTX), and higher overall C_{min} (median: 1.03 μ g/ml with MTX vs BQL without MTX); C_{max} was slightly higher (median [Q1, Q3]: 2.11 [1.65, 2.59] μ g/ml with MTX vs 1.51 [BQL, 2.48] μ g/ml without MTX). Pegloticase co-treatment with MTX resulted in more concentrations above the predicted median value of pegloticase, compared to monotherapy. ADA data is consistent with pegloticase PK and efficacy. Significant increase in ADA titers were only observed in 2 subjects (both were non-responders) at time corresponding to the loss of pegloticase exposure and increases in sUA levels. Concentrations of MTX-PGs were maintained during the treatment course, suggesting compliance of MTX administration. There was no apparent difference in concentrations of MTX-PGs between responders and non-responders.

Conclusion: Pegloticase 8 mg IV every 2 weeks co-treatment with MTX 15 mg weekly resulted in fewer patients with pegloticase C_{min} below the quantification