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Prevalence of monosodium urate deposits in a population of rheumatoid arthritis patients with hyperuricemia☆

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ABSTRACT

Objectives: To investigate the prevalence of monosodium urate (MSU) crystal deposits, indicative for gout, in a population of rheumatoid arthritis (RA) patients with concomitant hyperuricemia and to analyze the clinical and disease-specific characteristics of RA patients who exhibit MSU crystal deposits.
Methods: Overall, 100 consecutive patients with the diagnosis of RA and a serum urate level above 6 mg/dl underwent dual energy computed tomography (DECT) of both feet and hands to search for MSU crystals in a prospective study between October 2011 and July 2013. Presence and extent of MSU crystal deposits on DECT was assessed by automated volume measurement. Demographic and disease-specific characteristics were recorded and included into two logistic regression models to test for the factors associated with MSU crystal deposits in RA.
Results: Hyperuricemic RA patients were mostly male (55%), over 60 years of age (63 $\pm$ 11 years), had established disease (8.7 $\pm$ 10.5 years) and a mean disease activity score 28 (DAS 28) of 3.2. In total, 20 out of 100 patients displayed MSU crystal deposits in DECT. Interestingly, the majority (70%) of the RA patients positive for MSU crystal deposits were seronegative RA patients. Hence, every third seronegative RA patient had MSU crystal deposits. According to logistic regression model analysis, seronegative status correlated positively with presence of urate deposits ($p = 0.019$).
Conclusions: These data show that a considerable number of RA patients display periarticular MSU crystal deposits. Seronegative patients were shown to be predominantly affected with every third patient being positive for urate deposits.

Introduction

Little is known about the prevalence of gout in patients with the diagnosis of rheumatoid arthritis (RA). This situation is surprising since RA affects roughly 1% of the population [1] and gout is the most frequent form of inflammatory arthritis in men [2,3]. Gout affects 3.22% of adults in the United Kingdom and 3.9% in the United States with an increasing tendency [4,5]. In contrast to RA, the prevalence of gout among adults is significantly higher in men than in women with a male to female ratio of 3.6:1 [3,4]. Despite the relatively high prevalence of RA and gout, the interrelation of RA and gout is poorly investigated and considered to be rare [6–8]. In their systematic literature research, Kuo et al. [7] reported only 32 cases where RA and gout were found in the same patient. In addition, McCarty [9] reported that gout and RA are negatively correlated. However, clinical experience suggests that a considerable proportion of RA patients are hyperuricemic, a prerequisite for the deposition of monosodium urate (MSU) crystals in the tissue. This observation is endorsed by a recently reported 25-year cumulative prevalence of 5.3% for the coexistence of RA and gout [10].

Gout is defined as an aseptic inflammation caused by interaction of MSU crystal deposition and adjacent tissue [11,12]. Hence, detection of such deposits is the key to diagnosing gout. The gold standard method for the diagnosis of gout remains the microscopic demonstration of negatively birefringent, needle-shaped MSU crystals under polarized light in the synovial fluid or tophi [2,13]. However, this approach requires aspiration of fluid from the affected joint, which is frequently not feasible due to the location of urate deposits, adverse clinical conditions or lack of patient's consent and therefore can only be accomplished in a subset of patients, mostly limited to acute gouty attacks. Moreover, MSU deposits in the tendons or ligaments are usually not

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accessible by aspiration [14–17]. Thus, in clinical practice, the diagnosis of gout is often made on a presumptive basis [18]. Recently, dual energy computed tomography (DECT) has enabled rheumatologists to at least partly overcome this challenge as it can rapidly detect MSU crystal deposits *in vivo* in a non-invasive manner. DECT uses X-ray beams of two different energies to differentiate MSU crystal deposits from connective tissues and from calcium containing structures by their absorption properties [15,18,19]. The sensitivity and specificity of DECT to detect MSU crystals is reported to be 90% and 83%, respectively [16], or 84% and 93% according to an earlier study [20]. Additionally, specialized software allows for accurate and standardized determination of tophus volumes [19–22]. Based on the advances in detecting MSU crystal deposits *in vivo* using DECT, our aim was to investigate the prevalence of monosodium urate (MSU) crystal deposits, indicative for gout, in a population of rheumatoid arthritis (RA) patients with concomitant hyperuricemia and to analyze the clinical and disease-specific characteristics of RA patients who exhibit MSU crystal deposits.

Patients and methods

Patient characteristics

In total, 100 consecutive patients diagnosed with RA according to the 2010 ACR/EULAR classification criteria and a serum urate level of 6 mg/dl or higher were recruited prospectively, when presenting to the outpatient rheumatology department at the University Hospital Erlangen, Germany, between October 2011 and July 2013. Pregnant women and patients under 18 years of age were not to be included into the study. Three patients already had a concomitant diagnosis of gout before the inclusion in the study. Also, patients on urate lowering medication were not excluded from the study if they were still hyperuricemic. Due to the radiation exposure and with monosodium urate deposits not forming below a serum urate level of less than 6 mg/dl, we did not perform DECT scans of a normouricemic control group. Patients' informed consent was obtained and the study was approved by the ethics committee of the University of Erlangen-Nuremberg (No. 4503-CH).

At baseline, demographic background information on gender, age, height, weight, and body mass index were documented. Clinical data regarding RA such as duration of disease, disease activity based on DAS 28, previous and current anti-rheumatic drug treatment were obtained as was autoantibody status, too. Seronegativity was defined as negative rheumatoid factor and negative anti-CCP2 antibody test, while a positive rheumatoid factor or/and positive anti-CCP2 antibodies was considered seropositive. Apart from serum urate level, the following parameters were obtained: Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP) and serum creatinine level. Additionally, the presence of co-morbidities which are known to be associated with gout, such as obesity (defined by BMI of 30 kg/m^2 or higher), hypertension, diabetes mellitus, hypertriglyceridemia, chronic renal insufficiency, and a diagnosis of metabolic syndrome were recorded [23–25]. The latter was defined by a BMI of 30 kg/m^2 or higher and two out of the following: hypertension, diabetes mellitus type II, hypertriglyceridemia, and low HDL [26]. The use of medications that can potentially increase serum urate levels was identified and documented (i.e., diuretics, β blockers, non-losartan angiotensin II receptor blockers, and ACE inhibitors). The use of urate lowering medications like calcium channel blockers and losartan was assessed for evaluation of a possible inverse effect [27]. Furthermore, comorbidity with hyperuricemia as an independent risk factor was documented, including cardiovascular disease, stroke, COPD, and sleep apnea [25,28,29]. Diagnostic arthrocentesis was performed in seven patients with positive DECT in whom clinical circumstances allowed to do so. The results of the synovial fluid analysis as well as clinically apparent tophi were recorded.

DECT imaging

As a standard procedure, DECT scans were performed of ankle joints and feet, as these sites, especially the first metatarsophalangeal joint (MTP 1), are most likely to show the presence of MSU deposits [30,31]. In addition, scans of the hands of nine patients and scans of the knees of one patient were obtained because of clinical presentation of these patients.

Images were generated by a second-generation 128-slice dual source CT system (Definition Flash; Siemens Healthcare, Forchheim, Germany) with two X-ray tubes operating at 80 kV and 140 kV. Syngo Dual Energy software (CT Workplace VA44, identical prototype, Siemens Healthcare, Forchheim, Germany) was used to process these data applying a parameter ratio of 1.25 for the depiction of the images. DECT images were assessed by three different readers of the Radiology and Rheumatology Departments of the University of Erlangen-Nuremberg, who were blinded to each other's results. All readers were formally trained in DECT imaging prior to the beginning of the study. The reading was performed by two radiologists whose readings were computed as one reader, and by one rheumatologist. The agreement between the radiologists' and the rheumatologist's readings is represented by Cohen's Kappa. CT scans were scored positive or negative with respect to the presence of MSU deposits. Such deposits are visualized in DECT scans by green color coded voxels located in joints, tendons, and periarticular tissue [16]. Artefacts, which are typically located at toenails and hyperkeratotic footpads, were excluded (Fig. 1A). For the assessment of the exact amount of MSU deposits, Syngo Software (prototype, identical to CT workplace, VA44, Siemens, Forchheim, Germany) allowed for a computerized volume measurement, which was applied to positive scans.

Statistical analysis

The study patient cohort and the subgroups of patients with positive and negative findings were statistically analyzed. The inter-rater reliability was determined by calculation of Cohen's kappa. In order to determine the parameters, which significantly correlated with the presence of urate deposits in patients with RA, a logistic regression using a forced entry method with respect to characteristics of interest was conducted. Predictors for logistic regression were chosen after careful consideration of clinical as well as demographic characteristics that were either known or, from an expert point of view, likely to be related to a positive DECT result with respect to MSU crystal deposits. Furthermore, factors associated with the volume of MSU deposits were assessed by calculation of the Spearman correlation for current age, DAS 28, serum urate and creatinine, Mann–Whitney-*U* tests for serostatus, gender, presence of metabolic syndrome and use of serum urate lowering drugs, as well as the Kruskal–Wallis test for the number of used urate elevating drugs. Descriptive results are represented by arithmetic mean ± standard deviation for continuous characteristics and frequencies for categorical characteristics, respectively, if not stated otherwise. All analyses were performed using IBM SPSS software (version 21). $p \leq 0.05$ was considered statistically significant. Missing data were not imputed at any time in order to maintain the original information available from the raw data.