Ultrasonography in gout: a case-control study

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Abstract

Objectives

To determine the sensitivity and specificity of ultrasonography for gout, and to investigate the relationship with severity of gout.

Methods

In this case-control study, we prospectively enrolled 53 patients with crystal-proven gout and 50 controls. Ultrasonography was performed on 10 joints for each patient (metatarsophalangeal [MTP] joints 1–2, knees, metacarpophalangeal [MCP] joints 2–3) to determine the prevalence of the double contour (DC) sign and tophi in each site.

Results

We assessed 530 joints in gouty patients and 500 in controls. Gouty patients had a mean disease duration 9.2±10.7 years and a mean of 14.7±19.8 acute attacks. Clinical exam revealed tophi in 44% of patients. Mean urate level was 656.7±145.3 µM. Inter-reader agreement between the 2 sonographers was excellent for both DC sign and tophi. The frequency of the DC sign in MTPs, knees and MCPs for gouty patients and controls was 67% vs. 2%, 57% vs. 0%, and 21% vs. 0%, respectively (all p<0.001), whereas that of tophi, only found in gouty patients, was 74%, 42% and 22%, respectively (p<0.001). The sensitivity of the DC sign was 67% for MTPs, 57% for knees and 21% for MCPs, and specificity was high (all >98%). The sensitivity of tophi was 74%, 42% and 22%, respectively, and specificity 100% for all sites. For MTPs, the DC sign, but not tophi, was significantly associated with uricemia (p<0.05) and disease duration (p=0.01).

Conclusions

Ultrasonography has good sensitivity and specificity to diagnose gout. Sensitivity depends on disease duration, joint site and severity of the disease.

Key words

gout, ultrasonography, urate, ultrasound

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Introduction

Gout is a common arthritis caused by deposition of monosodium urate (MSU) crystals within joints secondary to chronic hyperuricemia. It affects 1%–2% of adults in developed countries and may be increasing in prevalence (1). The presence of MSU crystals in synovial fluid is the gold standard test to diagnose gout (2). However, synovial fluid is sometimes difficult to obtain in some articular sites such as metatarsophalangeal (MTPs) and tarsal joints. Moreover, in some patients, the clinical presentation is atypical, with acute tendinitis or polyarthritis. Thus, in the absence of synovial fluid or clinical evidence of tophi, the diagnosis of gout remains uncertain.

Ultrasonography (US), which has recently been evaluated for crystal diseases, notably gout, might help the clinician with diagnosis. US could help the clinicians to allow detection of urate deposits in inflamed joints, but also in never inflamed sites. Several patterns seen on US have been reported in patients with gout (3). Two sonographic features are considered characteristic of gout: the double contour (DC) sign and hyperechoic cloudy areas, which represent urate deposits within the joints and tendons or soft tissues (4-7). The presence of bright dotted foci and hyperechoic stippled aggregates with a "snowstorm" appearance of synovial fluid have also been described with high specificity (96%) in gouty patients (8). US reveals tophi as hypoechoic to hyperechoic non-homogenous material surrounded by a small anechoic rim (5). Finally, a useful revealing lesion is the double-contour (DC) sign, corresponding to a hyperechoic irregular band over the superficial margin of the cartilage (Fig. 1). This aspect is secondary to the deposition of MSU crystals on the surface of the hyaline cartilage, anechoic in US, and the presence of a physiological hyperechoic band under the cartilage corresponding to the subchondral bone. This feature seems to be highly specific but has variable sensitivity depending on the study and US assessment (4-6). However, only a few studies with a moderate number of patients have evaluated the sensitivity and specificity of the main US features of gout (DC sign and tophi) (4-6). Moreover, little is known about the presence of these features and the duration and clinical presentation of gout.

We aimed to assess the diagnostic value of US for gout by detecting 2 features, the double-contour (DC) sign and intra-articular tophi, in patients with crystal-proven gout and controls with other rheumatic diseases. We also aimed to investigate the relationship between US features and severity of gout.

Materials and methods

Ethics statement

The Institutional Review Board (IRB no. 00006477) of Paris North Hospitals reviewed and approved this study. All patients gave their written informed consent to participate.

Subjects and study design

To be included in this single-centre, case-control study, gouty patients had to have gout proven by demonstration of MSU crystals in synovial fluid between November 2008 and October 2010. All individuals underwent a detailed clinical evaluation, including disease history, clinical examination, laboratory testing and radiological assessment. Patients were asked to recall the number of acute attacks they had experienced, and past acute arthritis was diagnosed according to recent criteria (9).

For all patients, synovial fluid was obtained from inflamed or asymptomatic joints (knees, elbows, ankles or MTP joints) and then analysed by trained rheumatologists (TB, SO, PR) who used a compensated polarising microscope equipped with a rotating stage to demonstrate the presence of negatively bi-refringent MSU crystals. Urate arthropathy was defined by the presence on x-rays of at least 2 of the following: intra- or peri-articular opacity (tophus defined radiographically), joint space narrowing, erosions or cystic bone lesion with bridging osteophytes.

We enrolled control patients, matched for age and sex, who had a diagnosis of a rheumatic disease other than gout, without evidence of MSU crystals on synovial fluid testing.

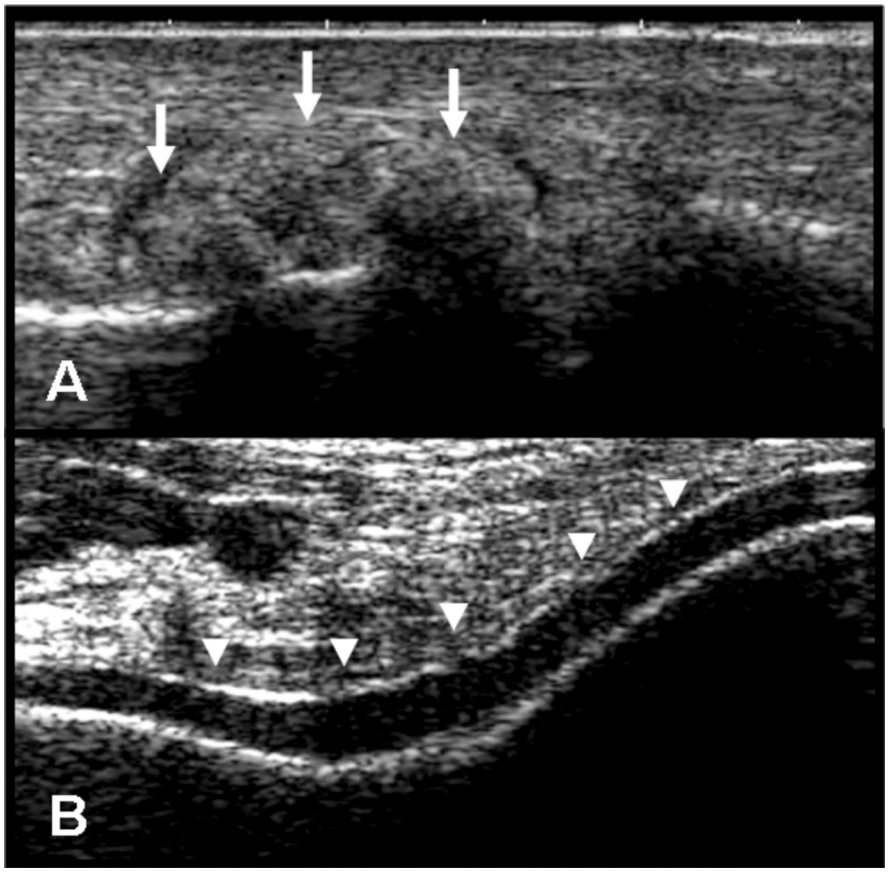

Fig. 1. US features: tophi (panel A) and the DC sign (panel B).
Panel **A**. 1st MTP: isoechoic cloudy area with anechoic rim corresponding to intraarticular tophus (white arrows).
Panel **B**. Femoral cartilage of the knee in suprapatellar plan: hyperechoic band over the superficial margin of cartilage corresponding to the "double contour" sign (white arrowheads).

Ultrasonography assessment

US analysis was performed by 2 rheumatologists trained in musculoskeletal US (SO and AA). All procedures involved the use of an Esaote Technos MP machine (Esaote Italy) with a multilinear probe (7–15 MHz).

The first and second MTP joints, both knees and the second and third metacarpophalangeal (MCP) joints were assessed in each patient, which corresponded to 10 screened joints per patient. All joints were scanned in the longitudinal plane and dorsal side. To analyse MTPs and MCPs, fingers and toes were flexed to visualise wider portion of the hyaline cartilage. Knees were explored on the transversal suprapatellar plane in maximal flexion according to guidelines for musculoskeletal US (10).

For each joint, 2 features of urate deposits were recorded as present or absent: 1) the DC sign, which corresponds to a hyperechoic, irregular band over the superficial margin of the articular cartilage; and 2) tophi within the joint, which appear as hypo- to hyperechoic nodular deposits (4, 6).

An ultrasonographer (SO) acquired and read the set of US images for each patient. The second ultrasonographer (AA), who was blinded to clinical details and US results of the first observer, read the recorded images. Any discrepancies were resolved by consensus. Inter-reader agreement was assessed by computing the Kappa coefficient (κ) for the DC sign and presence of tophi for each joint site.

Statistical analysis

Data are mean±SD or number (%). We estimated the sensitivity and specificity for each single US sign, as well as for the positive predictive value and the negative predictive value. Non-parametric or Fisher's exact test was used to compare quantitative or categorical data, respectively. We arbitrarily defined the severity of uricemia as a urate level ≥600 μmol/l (10 mg/dl). Uricemia above this cut-off has been associated with a high risk of recurrence of acute gout attacks (>80%) (11, 12). A two-tailed $p<0.05$ was considered statistically significant. All tests involved use of StatView v5.0 (SAS Inst., Gary, NC, USA).

Results

Demographic characteristics of patients

We screened 148 patients with rheumatic diseases diagnosed between November 2008 and October 2010 in our department: 78 were found to have gout and 70 other rheumatic diseases. Of the 78 patients with gout, 25 did not have MSU crystals in synovial fluid (n=23) or refused to participate (n=2**).** Among the 70 patients with other rheumatic diseases, 20 did not have synovial fluid results (n=18) or refused to participate (n=2). We prospectively enrolled 53 patients with crystal-proven gout and 50 controls.

Gouty patients and controls did not differ in mean age (59.7±15.8 *vs*. 59.5±15.3 years) or body mass index (25.7±2.4 *vs*. 24.8±2.5 kg/m^2); 92% and 80% were males, respectively (Table I). Psoriatic arthritis was diagnosed in 25 control patients, rheumatoid arthritis in 13, calcium pyrophosphate deposition disease in 7 and osteoarthritis in 5. For gouty patients, the delay between the first acute attack and the US assessment was 9.2±10.7 years, and the mean number of acute attacks before inclusion was 14.7±19.8. Tophi were found in 44% of gouty patients. Urate levels and creatinine clearance were 656.7±145.3 μmol/l and 69.7±29.7 ml/min, respectively. Urate arthropathy was found in 46% of gouty patients. Only 25% received urate-lowering therapy (ULT; allopurinol in all cases) at the time of US investigation and none of the patients had attempted a level of uricemia allowing dissolution (<360 μmol/l).

US findings

A total of 530 joints were assessed in gouty patients and 500 in controls (10

images per patient). The inter-reader agreement between the 2 sonographers for the DC sign at MTPs, knees and MCPs was κ=0.91, κ=0.92 and κ=0.96, respectively, and for presence of tophi κ=0.94, κ=0.95 and κ=0.96, for excellent agreement for all articular sites.

The frequency of the DC sign in MTPs, knees and MCPs for gouty patients and controls was 67% and 2%, 56% and 0%, and 21% and 0%, respectively (all $p<0.001$). A DC sign was found in at least one articular site in 77% of gouty patients. The frequency of US tophi in MTPs, knees, and MCPs for gouty patients and controls was 42% and 0%, 74% and 0%, and 23% and 0%, respectively (all $p<0.001$). Tophi were found by US in at least one articular site in 79% of gouty patients.

The sensitivity of US for the DC sign in MTPs, knees and MCPs was 67%, 57% and 21%, respectively, and the specificity 98%, 100% and 100%. The sensitivity of US for tophi in the same sites was 74%, 42% and 23, respectively, and the specificity 100% for all sites. The positive predictive value of the DC sign in MTPs, knees and MCPs was 97.2%, 100%, and 100%, respectively, and the negative predictive value 73.1%, 68.5% and 54.3%. The positive predictive value of tophi was 100% in all sites and the negative predictive value 78.1%, 61.7% and 54.9%.

Association of DC sign and tophi and uric acid level

The prevalence of the DC sign on US was significantly higher in MTPs, knees and MCPs (all $p<0.05$) for patients with high (uricemia ≥600 μmol/l) than low uricemia (Table II). In contrast, the presence of tophi on US in each site was not associated with level of uricemia.

Conversely, patients with a DC sign in MTPs and knees had significantly high levels of uricemia (686.5±141.4 *vs*. 594.4±133.2 μmol/l, $p=0.005$, and 710.7±150.2 *vs*. 582.9±98.1 μmol/l, $p=0.001$, respectively) but significance was not reached for MCPs ($p=0.08$). The presence of the DC sign was associated with urate arthropathy ($p<0.001$) and tophi on both clinical ($p=0.005$) and US examination ($p<0.001$). Patients with a DC sign in MTPs but not knees or MCPs had significantly longer disease duration than those without a DC sign (140.0±139.1 *vs*. 49.5±68.5 months, $p=0.01$).

Table I. Demographic characteristics of gouty patients and control patients with other rheumatic diseases.

	Gouty patients n=53	Control group n=50
Age, years	59.7±15.8	59.5±15.3
Sex (% male)	92	80
Body mass index, kg/m^2	25.7±2.4	24.8± 2.5
n. of acute attacks	14.7±19.8	NA
Symptom duration, years	9.2±10.7	NA
Tophi (% of patients)	44	NA
Uricemia (μmol/l)	656.7±145.3	ND
Creatinine clearance (ml/min)	69.7±29.7	ND
Uratic arthropathy (% of patients)	46	NA

Data are mean±SD unless indicated; NA: not applicable; ND: not done.

Table II. Clinical and ultrasonography findings in gouty patients according to uric acid levels.

	Serum uric acid		
	<600 μmol/l	≥600 μmol/l	*p*-value
Clinical findings			
Age, years (mean±SD)	64.9±13.0	55.9±16.8	ns
Body mass index, kg/m^2 (mean±SD)	26.3±2.0	25.3±2.5	ns
n. of acute attacks (mean±SD)	6.4±6.9	18.9±22.9	ns
Symptom duration, years (mean±SD)	84.8±126.4	123.6±126.9	ns
Tophi	26.3	52.9	ns
Creatinine clearance, ml/min (mean±SD)	66.2±28.5	73.1±31.2	ns
Uratic arthropathy	26.3	55.9	0.04
Urate-lowering therapy	10.5	32.4	ns
Ultrasonography findings			
DC MTPs	36.8	82.4	0.001
DC Knees	36.8	67.6	0.03
DC MCPs	5.3	29.4	0.04
T MTPs	57.9	82.4	ns
T Knees	26.3	50.0	ns
T MCPs	10.5	29.4	ns

Data are mean±SD or percentage.
DC: double contour sign; T: tophi; MCP: metacarpophalangeal joints; MTP: metatarsophalangeal joints; ns: not significant.

Discussion

This prospective case-control study is the largest reported to investigate the presence of US joint features in patients with and without crystal-proven gout. Nearly 80% of our gouty patients exhibited a DC sign and/or tophi by US, whereas clinical exam revealed tophus in only 44% of cases.

The specificity of US for gout was very good, in accordance with previous results (Table III) (4-6); however, the reported US sensitivities varied from 22% to 92% (Table III). This finding could be explained in part by differences in the apparatuses, the examination procedure used across studies and stage of the disease. In our study, the first MTP joint was assessed only on the dorsal plane, whereas in other studies, US examination involved dorsal and volar planes (4, 5). We did not examine MTP joints in the volar plane due to the risk of false positive. Indeed, the normal hyperechoic aspect of the synovium in this plane could be mistaken as a DC sign and we made the choice to promote specificity to sensitivity. Other studies examined various joints. We examined MCP and MTP joints and knees and found that the investigation of MCP joints did not reveal important

Table III. Prevalence of DC sign and tophi revealed by US in the literature and this study.

Reference	n. of gouty patients (joints)	Clinical tophi (% of patients)	Mean level of uricemia (μmol/l)	Echograph	Joint site	US assessment	Sensitivity of DC sign	Specificity of DC sign	Prevalence of US tophi
Filippucci *et al*. 2009	32 (64)	–	–	Esaote MyLab 70XVG	Knees	Dorsal, suprapatellar	44% of patients	99%	–
Wright *et al*. 2007	39 (78)	–	410	Siemens Sonoline	1st MTP	Dorsal and medial	22% of joints	100%	48% of joints
Thiele *et al*. 2007	23 (37)	39	672	GE Logic 3	Elbows 1st MTP MCP 2/3 Knees	Volar Dorsal/volar Dorsal/volar Suprapatellar	92 % of joints	100%	–
Present study	53 (530)	44	657	Esaote Technos MP	MTP 1/2 MCP 2/3 Knees	Dorsal Dorsal Suprapatellar	77% of patients	98%	79% of patients

DC: double contour sign; MCP: metacarpophalangeal joints; MTP: metatarsophalangeal joints.

information. The low prevalence of US features in MCPs could be explained in part by the absence of anterior cartilage US assessment. Moreover, we have only screened MCP 2 and 3 and not all MCPs. US assessment of MTP joints and knees, the most frequently involved joints in gout, can be performed in less than 15 min and screening of these joints alone can be recommended in clinical practice.

Logically, we found the DC sign more frequently in MTP than knees joints, the 1st MTs being more frequently affected by gout (1). The only misclassification we made with crystal-proven calcium pyrophosphate deposition (which involves the mid-zone of the cartilage [6]) was probably explained by the finding of an equivocal DC sign in a thin MTP cartilage. The DC sign is probably easier to see in the knee because its cartilage is thicker than in MTP joint, so the contrast between the 2 hyperechoic bands and the anechoic cartilage is more easily discernable. For the same reason, the search for the DC sign seemed difficult in patients with severe arthropathy and destruction of cartilage.

Another explanation for discrepancies across studies could be differences in gout severity of the studied populations. The amount of MSU crystal deposits is indeed likely to influence the US ability to detect deposits. Our patients had longstanding gout, high level of uricemia and thus high amount of urate deposits. These particular selected patients could have introduced a selection bias in this work, which might partly explain our findings. In our study, we found the presence of the DC sign in MTPs more frequent in diseases of longer duration and the DC sign in knees and MTP joints associated with a high level of uricemia, urate arthropathy and clinical and US detection of tophi. These results suggest that US is more likely to detect urate deposits in severe gout. US might therefore be used to assess the severity of urate deposits and help clinicians decide on ULT at the onset of the disease: evidence of a significant crystal load could shift the risk/benefit ratio toward treatment in a patient who experienced only 1 or 2 gout attacks (13). However, our results should be cautiously interpreted. First, the sonographer was not blinded to the diagnosis representing an important bias but the second reader was blinded and inter-reader agreement was excellent in our study and in the literature (5, 6). This high inter-reader agreement could be explained by clearest echographic signs in longstanding and untreated gout. However, in a previous study, we found US features of gout in about 50% of patients at the early stage of the disease (13). Moreover, our patients are poorly treated with ULT and with high level of uricemia representing a bias of recruitment. However, more than half of the patients were recruited after emergency visit without previous diagnosis of gout.

US may have other uses in the diagnosis and management of gout. This study focused on joints, but in our experience, the value of US in gout may be increased by the examination of tendons (14, 15), in particular patellar, quadricipital and Achilles' tendon and bursae and soft tissue. Tendon deposits may be an early feature of gout because they have been found in the patellar tendon of 7 of 35 patients with asymptomatic hyperuricemia (16). Another study of 50 patients with asymptomatic hyperuricemia found a DC sign of the first MTP joint and tophi in 25% and 6% of subjects respectively, which suggests that intra-articular deposits can also be found before the occurrence of acute attacks (17). US can also detect effusions and help with synovial fluid aspiration in joints difficult to aspirate, thus allowing MSU crystal identification, which remains the gold standard of gout diagnosis (18). Moreover, US could be used to assess the efficacy of ULT, because evidence of urate deposition has been shown to disappear under efficient ULT (19) and to monitor the decrease in tophus size (20). These measurements might improve adherence to treatment by patients and help clinicians to decide when to stop treatment (*i.e*. when deposits are no longer discernable).

In conclusion, US appears a fairly inexpensive tool with good diagnosis value in gout. DC sign and tophi seen by US are highly specific to gout. The

sensitivity of US may depend on the amount of deposited urate, the joint site and disease duration. US could help clinicians decide on ULT in early gout and when ULT is no longer necessary. Thus, US may be useful for both diagnosis and management of gout.

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