

Synovial Fluid Analysis for Diagnosis of Intercritical Gout

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Background: The diagnosis of gout in the intercritical phase can be difficult.

Objective: To determine whether synovial fluid analysis allows the diagnosis of intercritical gout.

Design: Cross-sectional study.

Setting: Outpatient rheumatology clinics.

Patients: 101 patients with gout.

Intervention: Arthrocentesis of 80 knees and 21 first metatarsophalangeal joints (each joint from a different patient) that had been inflamed but were currently asymptomatic.

Measurements: Frequency with which arthrocentesis yielded synovial fluid; presence of monosodium urate crystals in the synovial fluid sample; and, for synovial fluid with crystals, the number of microscope fields that had to be scanned before crystals were found.

Results: Synovial fluid was obtained from 91 of 101 joints. The fluid from all 43 patients not receiving hypouricemic agents contained monosodium urate crystals. These crystals were found in the synovial fluid of only 34 of 48 patients receiving hypouricemic agents. In 90% of the synovial fluid samples that contained crystals, crystals were seen in the first five microscope fields examined.

Conclusions: Arthrocentesis of asymptomatic knees and first metatarsophalangeal joints and synovial fluid analysis are simple procedures that facilitate the diagnosis of gout during intercritical periods.

Patients with gout tend to seek medical attention during gout attacks, at which point the standard diagnostic procedure is to search for monosodium urate crystals in synovial fluid. But patients are often seen during the intercritical periods, when, in the absence of tophi, the diagnosis is made on clinical grounds by applying the preliminary American College of Rheumatology classification criteria (1). However, classification criteria work best in the study of groups of patients, and they often fail in the evaluation of the individual patient (2, 3). A clinical approach for the diagnosis of gout may be problematic (4) and may explain why other conditions are often incorrectly diagnosed and treated as gout (5).

Monosodium urate crystals can be found in synovial fluid obtained from asymptomatic gouty joints (6–11). These crystals were found in 36 of 37 asymptomatic but previously inflamed knees from patients with gout who were not receiving hypouricemic agents (12). This finding indicates that after the crystals form, they stay in the joints if serum uric acid levels are not reduced (12). Thus, it has been suggested that identification of crystals in synovial fluid may be used to diagnose gout during intercritical periods (7, 12). We sought to determine whether aspiration of asymptomatic first metatarsophalangeal and knee joints offers a practical approach for the precise diagnosis of gout during intercritical periods.

Methods

Arthrocentesis was attempted in 101 asymptomatic joints (80 knees and 21 first metatarsophalangeal joints) from 101 patients with gout: 99 men and 2 women 30 to 83 years of age (mean age \pm SD, 55.6 ± 12.5 years). The median disease duration was 5 years (range, 2 months to 37 years; interquartile range, 2.5 to 11 years). In 78 patients, gout had previously been diagnosed by identification of monosodium urate crystals in synovial fluid obtained from inflamed joints; in the remaining 23 patients, the diagnosis was made clinically on the basis of recurrent typical attacks, including podagra and hyperuricemia. All patients fulfilled the preliminary American College of Rheumatology criteria for the classification of gout (1).

For each patient, we recorded current serum uric acid levels, time elapsed since the last gout attack, the number of previous attacks in the joint being aspirated, treatment with hypouricemic agents, and duration of this treatment. Patients also received either allopurinol or benzbromarone, but data on the type of treatment were not recorded. All studied joints had been inflamed, and at least 2 months

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must have elapsed since the resolution of the last attack. The first metatarsophalangeal joint was approached dorsally after the tip of the toe had been pulled to open the joint space; a 25-gauge needle was used for aspiration of this joint. The ethical committee of our hospital approved the study, and each patient provided informed consent.

The presence of monosodium urate crystals in synovial fluid samples was investigated immediately after extraction of the fluid by simple polarized light microscopy (magnification, $\times 400$); when crystals were detected, their negative bi-refringence was ascertained by using a first-order red compensator (13). To quantify the effort needed to find crystals, we counted the number of microscope fields that had to be examined before a crystal was found. On the basis of our previous experience with searching for crystals in synovial fluid of asymptomatic joints, we decided to count a maximum of 30 fields. When monosodium urate crystals were present in the first microscope field examined, we counted until a maximum of 5 crystals had been identified. Four rheumatologists from three separate sites participated in the study.

Statistical Analysis

Descriptive statistics are used to present the data. Comparisons were made by using the Pearson chi-square test; the Mann-Whitney U-test; or, if the two populations differed in dispersion, the Kolmogorov-Smirnov two-sample test. All reported P values are two-sided. Analyses were conducted by using SPSS Statistical Package for Windows, release 6.12 (SPSS, Inc., Chicago, Illinois).

Results

Synovial fluid samples were obtained from 91 of the 101 joints (90%): 73 of 80 knees (91%) and 18 of 21 first metatarsophalangeal joints (86%) ($P > 0.2$). The rate at which synovial fluid was obtained was similar for all participating physicians (between 80% and 93%); only two physicians aspirated more than 1 metatarsophalangeal joint.

Crystals were found in all 43 synovial fluid samples (100% [95% CI, 92% to 100%]) obtained from patients not receiving hypouricemic agents (Figure, top). All of these patients had a serum uric acid level greater than 357 $\mu\text{mol/L}$, and 41 (91%) of them had a level that exceeded 416 $\mu\text{mol/L}$.

The remaining 48 synovial fluid samples (out of 91 [53%]) were from patients receiving hypouricemic agents. These patients had lower levels of serum uric acid (treated patients: median, 351 $\mu\text{mol/L}$ [interquartile range, 280 to 422 $\mu\text{mol/L}$]; untreated patients: median, 500 $\mu\text{mol/L}$ [interquartile range,

446 to 559 $\mu\text{mol/L}$]; $P < 0.001$, Kolmogorov-Smirnov two-sample test), although 27% of them had serum uric acid levels greater than 416 $\mu\text{mol/L}$. The median time since the last gout attack in these patients was 10 months (untreated group, 9 months; $P > 0.2$, Kolmogorov-Smirnov two-sample test). In the treated group, monosodium urate crystals were found in 34 of 48 (71% [CI, 56% to 83%]) of the synovial fluid samples; the absence of crystals in synovial fluid correlated positively with more time elapsed since the last attack ($P < 0.001$) (Figure, bottom), lower levels of uric acid, and longer duration of therapy (Table).

When we considered all 91 joints from which a synovial fluid sample was obtained, monosodium urate crystals were found in similar proportions in synovial fluid obtained from knees (61 of 73 [84%]) and first metatarsophalangeal joints (16 of 18 [89%]) ($P > 0.2$).

Monosodium urate crystals were found in the first microscope field examined in 47 of 77 (61%

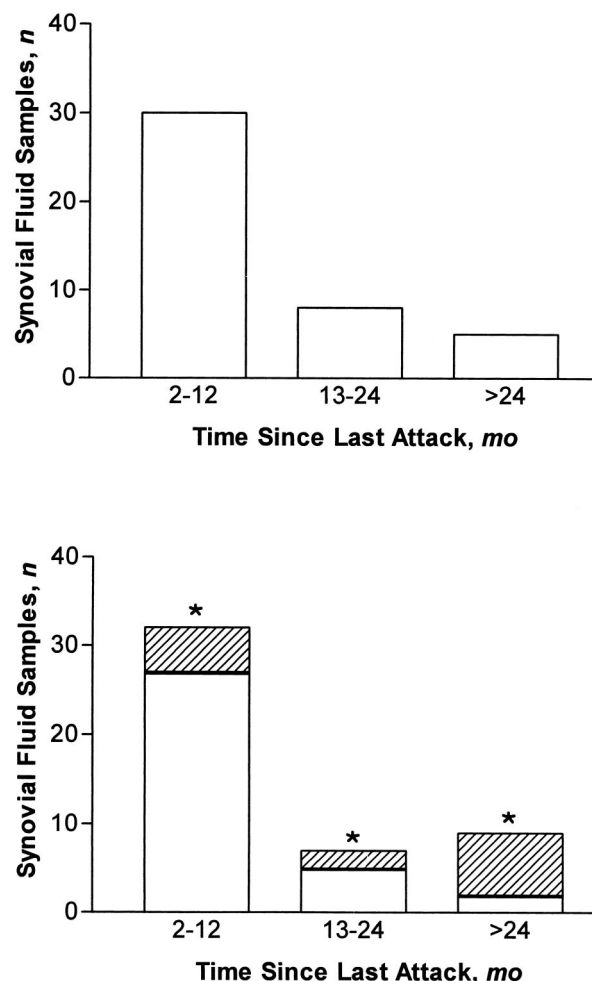


Figure. Presence (white bars) or absence (striped bars) of monosodium urate crystals in synovial fluid according to the time elapsed since the last gout attack. Top. Patients not receiving hypouricemic agents ($n = 43$). Bottom. Patients receiving hypouricemic agents ($n = 48$). $*P < 0.001$.

Table. Characteristics of 48 Patients Receiving Hypouricemic Treatment according to Presence of Crystals in Synovial Fluid Samples from Asymptomatic Joints*

Characteristic	Patients with Crystals in Synovial Fluid (n = 34)	Patients without Crystals in Synovial Fluid (n = 14)	P Value
Age, y	58.5 (46–64)	53.5 (51–61)	>0.2†
Disease duration, y	5 (1.5–10)	6 (2.5–7.0)	>0.2†
Serum uric acid level, $\mu\text{mol/L}$	363 (315–458)	280 (238–375)	0.04†
Previous attacks in the assessed joint, n	5 (2–10)	2 (1–7)	>0.2†
Duration of hypouricemic therapy, mo	6 (3–12)	26 (10–36)	0.02‡
Time since last attack, mo	6 (4–12)	26 (12–36)	0.01‡

* All data are presented as the median (interquartile range).

† Mann-Whitney U-test.

‡ Kolmogorov-Smirnov two-sample test.

[CI, 49% to 72%]) of the synovial fluid samples containing these crystals; crystals were found in 90% (CI, 81% to 95%) of joints when the first five microscope fields examined were considered. Furthermore, of the 47 synovial fluid samples in which the crystals were seen in the first field, 38 (81% [CI, 67% to 91%]) contained more than one crystal. We found no relation between synovial fluid obtained from knees or first metatarsophalangeal joints and the number of microscope fields that had to be examined to find crystals.

Discussion

Our data indicate that arthrocentesis to obtain a synovial fluid sample from asymptomatic knees and first metatarsophalangeal joints is a successful procedure in most cases; no patient had complications.

Monosodium urate crystals were found in all 43 synovial fluid samples obtained from patients who did not receive hypouricemic agents. This finding indicates a high sensitivity of this diagnostic approach in these patients; none had low uric acid levels. Similar results in untreated patients have been reported (9, 12). We found monosodium urate crystals in only 34 of the 48 synovial fluid samples from patients receiving hypouricemic agents. Length of treatment, lower uric acid levels, and longer time since the last attack were related to the absence of crystals. These data are consistent with the following events: 1) As a result of hyperuricemia, monosodium urate crystals form in the joint, remain present while hyperuricemia persists, and can be found in the synovial fluid at any time (12); and 2) when serum uric acid levels are reduced to normal, the monosodium urate crystals slowly dissolve and finally disappear from the joint, as is noted with crystals that form tophi (14). It is postulated that after crystals disappear from a joint, gout attacks no longer occur unless hyperuricemia recurs and monosodium urate crystals again form in the joint.

In a previous study (10), monosodium urate crys-

tals were found in only about half of the synovial fluid samples obtained from asymptomatic knees of patients with gout who received and those who did not receive hypouricemic treatment. However, the mean uric acid level was similar in both groups, and uric acid levels were not elevated in about 50% of both treated and untreated patients (10). Aspiration of the first metatarsophalangeal joint of 23 patients with gout allowed detection of crystals in 16 synovial fluid samples, but some of the joints had never been inflamed and most patients were being treated with allopurinol (8). The possible finding of monosodium urate crystals in never-inflamed joints of patients with gout is well documented (6, 8, 12), and crystals have been identified in the joints of patients with hyperuricemia and renal failure (8).

In the synovial fluid samples that contained crystals, crystals were generally abundant. When the first five microscope fields were examined, the crystals were seen in 90% of these samples. The duration of examination of a synovial fluid sample to determine whether it contains crystals has not been critically ascertained, but it has been considered reasonable to search for about 10 minutes before deciding that no crystals are present. We counted microscope fields in an attempt to more objectively quantify the effort needed to find the crystals.

Our data support the use of synovial fluid analysis of previously inflamed, asymptomatic knees or first metatarsophalangeal joints as a simple bedside procedure for the diagnosis of intercritical gout. Such an approach may facilitate the diagnosis of gout and help to avoid unnecessary diagnostic procedures.

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