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Repeat Examination of Synovial Fluid for Crystals: Is It Useful?

To the Editor:
The crystal arthropathies, gout and calcium pyrophosphate dihydrate deposition disease, are caused by deposition of monosodium urate (MSU) or calcium pyrophosphate dihydrate (CPPD) crystals, respectively. A diagnosis of urate gout or calcium pyrophosphate dihydrate deposition disease is based on characteristic clinical findings and the microscopic identification of intracellular crystals in synovial fluid.

Several studies have shown the lack of sensitivity of microscopic examination of synovial fluid for MSU or CPPD crystals [sensitivity, 78% (1) and 79% (2) for MSU and 12% (1) and 67% (2) for CPPD]. Not surprisingly, this leads to a lack of reproducibility of synovial fluid analyses (1, 2). The suboptimal sensitivity, frequently attributed to the low concentrations or the small sizes of the crystals, has been difficult to im-prove without resorting to clinically impractical methods such as crystal extraction from synovial fluid (3) or electron microscopy (4). Problems with sensitivity have led experts to caution that a negative examination by polarized light microscopy does not exclude the presence of small numbers of crystals (5).

We have occasionally encountered synovial fluids from patients with gout that were negative for urate crystals by microscopic examination on initial viewing of a fresh specimen and then were found to be positive when the microscopic examination was repeated on the same specimen a day later. Similar cases have been reported by others (6–8). In the case we observed and the cases reported in the literature, the patients had clinical features of gout, and the positive results on repeat examination were considered true positives.

Prompted by these cases, we investigated whether repeat examination of the same synovial fluid 24 h later could improve the sensitivity of crystal detection. During a 6-month period, microscopic examinations for crystals with ordinary and compensated polarized light microscopy were performed with wet-mount slides on 130 consecutive synovial fluid specimens in which a crystal examination was ordered at three hospitals. Eighteen [14%; 95% confidence interval (CI), 8–21%] of these were positive for MSU crystals, and 5 were positive for CPPD (4%; 95% CI, 1–9%) crystals on initial examination. These 23 (18%; 95% CI, 12–25%) crystal-positive specimens were excluded from further study. A repeat examination was performed on the 107 specimens that were initially negative. For these 107 specimens, a fresh wet-mount was prepared and examined after the specimen was stored for 24 h at 4°C. The repeat examinations were performed by a different observer in most cases. In 23 of these patients, gout or pseudogout was the main clinical differential diagnosis.

The major findings of the study are presented in Table 1. Of the 107 initially negative cases we examined, 7 showed crystals on reexamination at 24 h. Of these seven new cases, at least five cases (four MSU-positive cases and one of the three CPPD-positive cases) were clinically significant because they were considered by the clinicians to be true positives. In one case, the synovial fluid was aspirated from a middle-aged man with a history of gout, who presented with a 1-day history of knee swelling and pain similar to his previous gouty attacks. The initial examination of the aspirated synovial fluid with compensated light microscopy did not show crystals. However, a second synovial fluid specimen aspirated the next day showed abundant urate crystals. Similarly, reexamination of the fluid from the first day, performed after 24 h of storage at 4°C, revealed abundant crystals. In two of the delayed CPPD-positive cases, the patients had septic arthritis, and the clinical significance of the CPPD crystals was unclear in this setting. This diagnostic challenge has been noted by others (9). Of the total number of crystal-positive cases identified in our study, 24% (7 of 30; 95% CI, 10–42%) were detected only with the repeat examination. The overall yield of crystal detection on repeat examination was 6% (7 of 107; 95% CI, 3–13%). However, for the 23 cases in which gout or pseudogout was listed as the leading diagnostic possibility and the initial examina-

| Table 1. Summary of the findings on 130 consecutive specimens submitted for microscopic examination of synovial fluid for the presence of crystals a |
|---------------------------------|-----------------|-----------------|
| Initial exam negative | Repeat exam positive | Repeat exam negative |
| [total = 107 (82%)] | [total = 95 (79%)] | [total = 75 (77%)] |
| Result n (%) | Result n (%) | Result n (%) |
| MSU | 18 (14) | MSU | 4 (3) |
| CPPD | 5 (4) | CPPD | 3 (2) |

a In 23 of the 107 initially negative specimens, gout or pseudogout was the main clinical differential diagnosis. Repeat examination at 24 h produced seven (6%) additional positives. At least five of these seven additional positives were clinically significant.
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References

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Plasma N-Terminal Pro-B-Type Natriuretic Peptide Concentrations in a Control Population of Infants and Children

To the Editor:
Recent studies suggest that the B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) may be useful diagnostic tools in children with congenital heart disease or cardiomyopathy (1–3). Reference data, however, are rare, especially for children. The aim of this study was to measure plasma concentrations in a control population of infants and children, using the Elecsys NT-proBNP assay (Roche Diagnostics).

EDTA plasma (centrifuged at 3000g for 5 min and frozen at −20 °C until analysis; stable for 12 months as provided by the manufacturer) was obtained from 13 neonates (<1 month of age) and from 78 children (37 girls and 41 boys; median age, 6.1 years; range, 4 months to 18 years). Patients with cardiac, renal, and hepatic diseases as well as water and electrolyte disturbances were retrospectively excluded from the study according to their diagnoses.

Concentration limits were calculated by regression analysis based on formulas derived from Virtanen et al. (4), which makes it unnecessary to partition the reference data into subgroups. A relatively small sample size is sufficient. This is of great advantage considering the costs and difficulties in collecting samples from large reference groups, especially pediatric samples. Because the variability of NT-proBNP increased with its mean concentration, we used natural log transformations in the regression analyses. After transforming the data back to the original scale, we established nomograms using the 2.5th, 50th, and 97.5th percentiles with 95% confidence intervals (Fig. 1).

The NT-proBNP concentration was highest during the first days of life (range, 1121–7740 ng/L) with a rapid decrease (Fig. 1, inset) similar to that described for BNP because of assumed perinatal circulating changes (5, 6). We observed no significant difference between plasma concentrations in male and female children (median, 62.3 ng/L; mean, 83.4 ng/L; range, 11–379 ng/L; Mann–Whitney test, P = 0.74). The lack of significance may be attributable to the small sizes of the groups. A negative correlation between age and concentration was evident for individuals >1 month (r = −0.45; P <0.001). On the basis of the 97.5th percentile curve, the maximum value of 299 ng/L (age, 1 year) decreased to 48 ng/L (age, 16 years). For adults, increased reference limits according to age are provided by the supplier (97.5th percentiles for age <50 years, 153 ng/L for females and 88 ng/L for males; for adults 50–65 years of age, 334 ng/L for females and 227 ng/L for males).

Very few studies have been pub-