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Analysis of synovial inflammatory markers to differ infectious from gouty arthritis

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ABSTRACT

Objectives: Septic and gouty arthritis show the same clinical symptoms, but septic arthritis is an orthopedic emergency and needs immediate surgical intervention, whereas a systemic drug therapy is needed in acute gouty arthritis. The aim of this study was to investigate which inflammatory markers allow an accurate differentiation of septic and gouty arthritis.

Design and methods: This was a retrospective examination of serum markers (peripheral white blood cells, C-reactive Protein and uric acid) and inflammatory markers in the synovial fluid (lactate, glucose, uric acid, lactate dehydrogenase, synovial fluid white blood cell count, total protein, and interleukin-6) in 53 patients with culture-verified septic arthritis and 29 with gouty arthritis. Receiver-Operating-Characteristic-curves with corresponding Area under the curve (AUC), sensitivity, specificity, likelihood-ratio and interval likelihood-ratios were calculated to define the diagnostic potential of the inflammatory markers.

Results: Synovial lactate showed the greatest diagnostic potential (AUC = 0.901, sensitivity = 89.5%, specificity = 77.3%, negative likelihood-ratio = 0.14) followed by synovial glucose (AUC = 0.853) and synovial uric acid (AUC = 0.841).

Conclusions: Lactate in the synovial fluid has excellent diagnostic potential to differ septic arthritis from gouty arthritis. Synovial lactate levels above 10 mmol/L almost proofed septic arthritis, lactate levels lower than 4.3 mmol/L make it very unlikely.

Introduction

Patients suffering from both, septic and aseptic inflammatory arthritis, present the classic clinical infection signs such as heat, swelling, redness, pain or reduced range of motion [1–4]. Septic arthritis is an orthopedic emergency and needs immediate surgical intervention, whereas the correct treatment in acute gouty arthritis consists of systemic drug therapy. Underdiagnosed bacterial arthritis, delayed antibiotic treatment and surgical intervention may result in irreversible joint destructions and increased mortality rate [1,5,6].

Otherwise patients with gouty arthritis show high complication rates after surgical interventions [7]. The most common complications are wound healing disorders, infections, skin necrosis and the need of skin grafts [8,9].

In order to minimize morbidity, physicians have to distinguish both pathologic conditions from the beginning. The routine laboratory markers CRP and peripheral WBC count may be increased in both types of inflammatory arthritis resulting in low specificities, however [10].

The purpose of this study was to determine, which inflammatory markers in the blood or in the synovial fluid were the most accurate to differ septic arthritis from gouty arthritis.

Design and methods

This was a retrospective clinical study of all patients suffering from culture-verified septic arthritis (n = 53) and gouty arthritis (n = 29), who presented at the Emergency Department of the Hospital of Dachau, Germany, from March 2008 to November 2012. The standard operating procedure in suspected infectious arthritis was already established and the inflammatory parameters in the blood (peripheral white blood cells (pWBC), C-reactive Protein (CRP), uric acid (UA_s)) and in the synovial fluid (lactate, glucose, uric acid (UA_{syn}), lactate dehydrogenase (LDH_{syn}), total protein (TP_{syn}), synovial fluid white blood cell count (SFWBC) and interleukin-6 (IL-6)) were determined during admission.

No consult of the ethics Review Committee of the Technical University of Munich, Germany, was requested, as this was a retrospective clinical study without personal data. This study was conducted in accordance to the Declaration of Helsinki. Neither joint aspiration nor test of the blood was done for the sole purpose of this study, diagnostic and

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therapeutic procedures were not directly influenced. Patients underwent arthrocentesis, if they showed at least three of five classic symptoms of infection in a joint and infectious arthritis could not be ruled out. The quantification of biomarker levels in the blood (CRP, uric acid) and in the synovial fluid (lactate, total protein, LDH, uric acid, glucose) was ascertained in a clinical laboratory by the AU 640/2700 Beckman Coulter, following the manufacturer's protocol. Synovial IL-6 was determined by using an IL-6 immunoassay (IMMUNOLITE 1000® Immunoassay System, SIEMENS Healthcare, Germany). The pWBC and the SFWBC were detected by the ADVIA 120/1120® (SIEMENS Healthcare, Germany). All blood and synovial fluid tests are accepted by the manufacturer's instructions for use, except IL-6.

The SFWBC was determined before the synovial fluid samples were optimized for the assay. Synovial fluid samples with streaks or particles were centrifuged. Afterwards every synovial fluid sample was charged with hyaluronidase until it became liquid and workable. The IL-6 assay was not validated for interference from hyaluronidase. The levels of each sample were analyzed and compared with levels of standard positive and negative controls. Several dilution steps were necessary to account for the extremely elevated synovial IL-6 levels compared to serum levels. Microscopic synovial fluid analysis was performed by a microbiologist. Patients were included in this study if they suffered from culture-verified septic arthritis or gouty arthritis with positive synovial fluid crystal analysis.

53 patients suffered from culture-verified septic arthritis, gouty arthritis was diagnosed 29 times. Cultural verification of septic arthritis and synovial fluid crystal analysis are known as gold standards for diagnosing their corresponding pathologic conditions [11,12]. The mean age ± standard deviation was 70.4 ± 11.0 years in patients with culture-verified septic arthritis (median 73 years; range 43 to 96 years) and thus lower than in patients with gouty arthritis, who were 76.0 ± 13.6 years old (median 82 years; range 30 to 91 years). The gender was equally distributed in patients with culture-verified septic arthritis (25 females, 28 males), but not in patients with gout (10 females, 19 males).

The most common isolated pathogens were staphylococci (61%), Gram negative bacteria (23%) and streptococci (15%), causing 99% of all cases of culture-verified septic arthritis. A culture-verified septic arthritis was detected in 34 knees, 13 hips, 3 shoulders and 1 elbow. Gout was most frequently detected in the knee (n = 27), followed by the shoulder (n = 2).

SPSS 17.0 for Windows (SPSS, Inc., Chicago, IL, USA) was used to perform statistical analysis. The main outcomes of this study were primarily the positive likelihood ratio (LR+), the negative likelihood ratio (LR−), the interval likelihood ratios (iLR), sensitivities (SE) and specificities (SP). The diagnostic potential of each biomarker was determined by calculating the Receiver Operating Characteristic (ROC) curve and the Area under the curve (AUC). Statistical significant difference of the arithmetical means of biomarker levels in infectious arthritis and gouty arthritis was determined using the *T*-test for a difference in mean for independent samples. Mean values were considered to differ statistically significantly at $p < 0.05$. Cutoff-values were determined by maximizing sensitivity and specificity (Youden J statistic) or used as proposed in the literature.

The introduction of likelihood ratios in studies about inflammatory markers in septic arthritis was requested [1], because likelihood ratios show a greater diagnostic utility in bedside application than sensitivity, specificity and ROCs [13].

Likelihood ratio values from 0 to 1 decrease the post-test probability of a disease: for a LR of 0.5 the post-test probability decreases 15%, for a LR of 0.1 it decreases 45% [14]. Values greater than 1 increase the post-test probability of a disease: for a LR of 2 the post-test disease probability increases 15%, for a LR of 10 it increases 45% [14].

The introduction of several cutoff-values of biomarkers and the investigation of their significance for diagnosing septic arthritis have led to difficulties in the interpretation of biomarker levels in the synovial fluid. As a result Carpenter et al. requested that interval likelihood ratios (iLRs) should be introduced for the evaluation of biomarker concentrations in infectious arthritis [1]. The use of iLR allows physicians to estimate the likelihood of septic arthritis for the examined biomarker level. iLR estimates the disease probability for every biomarker level without thresholds that lead to false positive or false negative results. Thus iLRs exemplify more of the information in collected data [15].

Results

Scatter plots that show the distribution of biomarker levels in septic arthritis and gouty arthritis are illustrated in Fig. 1. The mean values of inflammatory marker levels on admission in infectious and gouty arthritis are shown in Table 1. The ROC curves of inflammatory markers with valuable diagnostic potential are shown in Fig. 2. Table 2 indicates the diagnostic potential of all investigated biomarkers and Table 3 shows the iLR of lactate, glucose, UA_{syn}, UA_S, LDH_{syn}, SFWBC and TP_{syn}.

Mean values of lactate levels in the synovial fluid were significantly higher ($p = 0.00003$) in septic arthritis with 11.7 mmol/L (range 0.2–48.0) than in gouty arthritis with 3.5 mmol/L (range 1.5–7.9). The AUC of $lactate_{syn}$ was 0.901, the optimal threshold was calculated by maximizing sensitivity and specificity and was 4.3 mmol/L (SE = 89.5%, SP = 77.3%, LR+ = 3.94, LR− = 0.14). The determination of the iLR showed that septic arthritis was highly unlikely at $lactate_{syn}$ levels <4.3 mmol/L (iLR = 0.14), $lactate_{syn}$ levels >10 mmol/L were only found in patients with septic arthritis. In 21 of 38 patients suffering from septic arthritis and examined lactate level, the $lactate_{syn}$ level was above 10 mmol/L.

A significant difference ($p = 0.000003$) of mean $glucose_{syn}$ concentrations was found between septic arthritis with 41 mg/dL (range 1.0–203) and gout with 100 mg/dL (range 47–262). Glucose levels in the synovial fluid had an AUC of 0.853, a beneficial cutoff-value was 51.5 mg/dL [= 2.9 mmol/L] (SE = 65.9%, SP = 92.0%, LR+ = 8.24, LR− = 0.37). When using the iLR, septic arthritis was unlikely at $glucose_{syn}$ levels >51.5 mg/dL (iLR = 0.37), patients with $glucose_{syn}$ levels of 27 mg/dL or lower always belonged to the septic arthritis-group.

The arithmetical mean of uric acid levels in the synovial fluid was lower ($p = 0.00003$) in septic arthritis with 5.31 mg/dL (range 0.5–19.2) than in gout with 8.33 mg/dL (range 3.0–11.5). The AUC for UA_{syn} was 0.841, the introduced optimal threshold was 7.0 mg/dL (SE = 78.1%, SP = 82.8%, LR+ = 4.53, LR− = 0.27). A joint infection was likely at UA_{syn} levels < 6.0 mg/dL (iLR = 6.37) and unlikely at levels > 7.0 mg/dL (iLR = 0.27).

During septic arthritis the mean value of uric acid in serum was 6.0 mg/dL (range 2.6–12.6) and significantly lower ($p = 0.00004$) than during gouty arthritis 8.7 mg/dL (3.4–12.5). As cutoff-value 7.2 mg/dL (SE = 70.0%, SP = 85.2%, LR+ = 4.73, LR− = 0.35%) was selected. The post-test disease probability for septic arthritis increased for UA_S levels of ≤6.0 mg/dL (iLR = 4.50) and for the range 6.0 and 7.2 mg/dL (iLR = 5.40), whereas a decrease was found for levels >7.2 mg/dL (iLR = 0.35).

The LDH concentration in the synovial fluid during septic arthritis showed the mean value 4623 U/L (range 213–19,796) and was significantly higher ($p = 0.004$) than 1161 U/L (range 124–5794) during gouty arthritis. LDH_{syn} showed an AUC of 0.811. The optimal cutoff-value was 1900 U/L (SE = 68.9%, SP = 88.9%, LR+ = 6.2, LR− = 0.35). While septic arthritis was likely at LDH_{syn} levels of ≥1900 U/L (iLR = 6.20), this diagnosis was unlikely at levels of 400–1900 U/L (iLR = 0.38) and <400 U/L (iLR = 0.30).

The mean SFWBC during septic arthritis was 78.75×10^3/μL (range 0.17×10^3–500×10^3) and thus significantly elevated ($p = 0.0004$) compared to 19.41×10^3/μL during gout (range 0.30×10^3–65.7×10^3). The SFWBC had an AUC of 0.700 and the optimal threshold was 38.0×10^3/μL (SE = 58.1%, SP = 86.2%, LR+ = 4.22, LR− = 0.49). The post-test likelihood of septic arthritis was little decreased for counts lower than 25×10^3/μL (iLR = 0.48) and 25×10^3/μL to 50×10^3/μL (iLR = 0.81) and increased for SFWBCs of 50×10^3/μL or higher (iLR = 4.95).