TITLE

Can C-reactive protein be used to predict acute septic arthritis in the adult population?

ABSTRACT

**Objectives:** The primary objective of this study was to establish whether C-reactive protein (CRP) can be used to predict native joint septic arthritis (SA) in the adult population.

**Method**: All patients who underwent native joint aspiration in A&E between April 2012 and September 2016 were identified from lab microbiology records. Patients were divided into three groups for analysis: patients with SA, those with crystal arthropathy and those with normal or osteo/inflammatory arthritic joints.

**Results**: 15 patients (7.9%) were deemed to have SA, 18 patients had a crystal arthopathy (9.5%) and 157 patients (82.6%) were deemed to have normal or osteo/inflammatory arthritic joints. All patients with CRP > 200 mg/L had SA. Patients with CRP 90-200 mg/L had a mix of crystal arthropathy and SA and patients with CRP < 90 mg/L had either normal or osteo/inflammatory arthritic joints or crystal arthropathy. Mean CRP in patients with a normal or osteo/inflammatory arthritic joint was 25 mg/L. This was compared with 100 mg/L (p=<0.001) in crystal arthropathy and 308 mg/L (p=<0.001) in patients with SA.

**Conclusion**: We have demonstrated CRP to be a reliable independent marker to help differentiate between SA, crystal arthopathy and normal/arthritic joint in an adult population. No patients with CRP < 90 mg/L had SA.

KEYWORDS

CRP, orthopaedics, septic arthritis

INTRODUCTION

The hot swollen native joint is a common presentation to both primary and secondary care in the United Kingdom (UK). A wide range of potential differential diagnoses exist, the most serious being septic arthritis (SA). In the UK, SA is most common in children and the elderly. The incidence of SA increased from approximately 6/100,000 in 1998 to 8/100,000 in 2013. This increase was more apparent in the elderly population, which may be associated with an increasing level of co-morbidity1.

Since the introduction of childhood immunisation, Staphylococcal and Streptococcal species are consistently the most frequently reported causative organisms1. Patients at greater risk of infection include those with type II diabetes or HIV; patients taking regular steroids; intravenous drug users and previously damaged joints, especially those affected by rheumatoid arthritis2. Haematogenous spread, local spread from adjacent osteomyelitis and direct joint inoculation via penetrating injury are all potential causes of infection. Whilst any joint can be affected by these processes, the hip and knee joint are the most commonly affected3.

Clinical features of SA include an acutely hot swollen joint with movement limitation and pyrexia9. Patients may also present unwell, with signs of systemic sepsis fulfilling the systemic inflammatory response syndrome (SIRS) criteria. It is important to note that children may present atypically, however several studies have demonstrated that the presence of non-weight-bearing and pyrexia greater than 38.5 degrees can reliably differentiate between SA and transient synovitis4-5.

In the Accident and Emergency (A&E) setting, bloods including full blood count (FBC), urea and electrolytes (U&Es), C-reactive protein (CRP) and peripheral blood cultures should be taken. X-rays often demonstrate joint effusion and may also show osteomyelitis10. Urgent joint aspiration should be performed, preferably before commencing antibiotic treatment; aspirates should be sent for urgent gram stain, cell count and crystal analysis10.

Early orthopaedic opinion should be sought in all patients with suspected native joint SA. Treatment with intravenous (IV) antibiotics and urgent removal of the infective focus should be performed. Most patients, especially those with infection of larger joints such as the hip or knee, require this in the form of washout of the affected joint in theatre11-14.

There is an increasing evidence base to support the role of CRP as a strong independent predictor of SA in children6-8. The primary aim of this study was to establish whether CRP can also be used to predict SA in the adult population.

MATERIALS AND METHODS

All patients who underwent native joint aspiration in A&E between April 2012 and September 2016 were identified from lab microbiology records. This was particularly appropriate for our institution as all aspirations required in A&E on presentation are done by the orthopaedic team. Exclusion criteria were patients with recent surgery or joint injections; prosthetic joints; paediatric patients; concomitant demonstrable infection and overlying cellulitis. For each patient the following variables were recorded: age; gender; joint aspirated; gram stain; aspirate white cell count (WCC); crystal analysis; extended culture; peripheral WCC, CRP and definitive treatment.

Patients were subsequently divided into three groups depending on their diagnosis to allow for statistical analysis. The three groups were: patients with SA, those with crystal arthropathy and those with normal or osteo/inflammatory arthritic joints.

As in clinical practice, there was no absolute value or criteria used to diagnose septic arthritis. The diagnosis was based on the consultant clinician’s overall interpretation of the above investigations and the clinical presentation of each individual case.

Our null hypothesis for our primary outcome measure, was that ‘there is no significant difference in CRP values in patients with acute SA, when compared to patients with crystal arthropathy and patients with normal or osteo/inflammatory arthritic joints’. Analysis of variance (ANOVA) of the three groups was performed in order to calculate an F statistic and P-value.

Two receiver operating characteristic (ROC) curves were produced, with the first comparing septic joints to crystalline joints and the second comparing septic joints to arthritic joints. The ROC curves display the trade-off between the sensitivity (true positive rate) and (1- specificity) (false positive rate) across a series of cut-off points. Area under the ROC curve is considered as an effective measure of inherent validity of a diagnostic test. The optimal cut-off point was determined by the minimum distance between the point (0, 1) and any point on the ROC curve.

Statistical analysis was performed using Statistical Package for the Social Sciences (IBM) and XLSTAT (Addinsoft).

Ethical approval was deemed unnecessary for this study.

RESULTS

A total of 190 patients underwent joint aspiration in A&E by the orthopaedic team, of which 128 (67.4%) patients were male and 62 (32.6%) were female with a median age of 63. 140 knees, 12 shoulders, 11 ankles and 9 wrists were aspirated; the remainder were fingers and toes or not recorded. 15 patients (7.9%) were deemed to have SA. Multiple causative organisms were seen, but most commonly Staphylococcal and Streptococcal species accounting for 5 and 4 cases, respectively.

Of those with SA, 1 patient died in A&E; 2 were treated with prolonged IV antibiotics and 12 were treated with surgical washout. 18 patients (9.5%) had a crystal arthropathy, with 12 having gout and 6 having pseudogout on crystal analysis. The remaining 157 patients (82.6%) were deemed to have normal or osteo/inflammatory arthritic joints and were treated symptomatically and discharged, with no readmissions or subsequent infective diagnosis.

Comparing the mean CRP values between the 3 groups showed a statistically significant difference. All patients with CRP > 200 mg/L had SA. We found that patients with CRP 90-200 mg/L had a mix of crystal arthropathy and SA and patients with CRP < 90 mg/L had either normal or osteo/inflammatory arthritic joints or crystal arthropathy.

**Figure 1: CRP by Group**

We performed an analysis of variance to test for difference between the groups. We found that the mean CRP in patients with a normal or osteo/inflammatory arthritic joint was 25 mg/L [15-37]. This was compared with 100 mg/L (p=<0.001) in crystal arthropathy [71-125] and 308 mg/L [265-362] (p=<0.001) in patients with SA (Figure 1). There was also a statistically significant difference when comparing the mean CRP in crystal arthropathy with those with SA.

Receiver operative curves (ROC) produced for CRP demonstrated an AUC of 0.88 (95% CI: 0.77, 0.99) with an optimal cut off of >=65 mg/L to differentiate between patients with normal or osteo/inflammatory arthritic joints (Figure 3) and crystal arthropathy (sensitivity 77.8%; specificity 92.3%) (Figure 4). An AUC of 0.99 (95% CI: 0.99, 1.00) with an optimal cut off of >=90mg/L was found to differentiate between patients with normal or osteo/inflammatory arthritic joints and SA (sensitivity 100%; specificity of 96.2%).

Mean peripheral WCC was 11x109/L [10-12] in those with normal or osteo/inflammatory arthritic joints, 12x109/L [10-13] in crystal arthropathy and 13x109/L [10-16] in patients with SA. There was no significant difference between WCC when comparing the three groups (p=0.111).

**Figure 2: Peripheral WCC by Group**

Mean aspiration WCC was 8215/mm3 in those with normal or osteo/inflammatory arthritic joints, 25,964/mm3 in crystal arthropathy and 48,554/mm3 in patients with SA. Aspiration WCC differentiated between SA and a normal or osteo/inflammatory arthritic joint (p=0.001), but we found no significant difference between SA and crystal arthropathy (p=0.059).

4 (2%) patients had a positive gram stain and 23 (12%) had a positive extended culture. Only 13 (7%) of these patients were treated as septic, with the rest labelled as contaminants. 2 patients had clinically septic joints with no growth. The reliability of gram stain and extended culture are shown in Table 1.

DISCUSSION

We have demonstrated that CRP is a useful test in aiding the diagnosis of a patient presenting with hot swollen joints. We have found it to be reliable independent positive predictor of SA and that it can be used to differentiate between the normal or osteo/inflammatory arthritic joints (p=<0.001), SA and crystal arthropathy (p=<0.001) in an adult population. Mean CRP was 25 mg/L in those with normal or osteo/inflammatory arthritic joints, 100 mg/L in crystal arthropathy and 308 mg/L in patients with SA. No patients with CRP < 90 mg/L had SA. ROC analysis demonstrated a cut of 90 mg/L to differentiate between normal or osteo/inflammatory arthritic joints and SA, with a highly favourable sensitivity of 100% and specificity of 96.2%.

This is in keeping with a prospective study by Jain *et al.* who reported CRP values of more than or equal to 96 mg/L in 84% of patients presenting with SA in their series7. In a similar study, Earnst *et al.* reported mean CRP values in patients presenting with hot swollen joints of 124 mg/L in SA, 81 mg/L in inflammatory arthritis and 57 mg/L in the normal knee8.

We have found that peripheral WCC is an unreliable predictive marker. Aspiration WCC was reliable as a predictive marker between SA and normal or osteo/inflammatory arthritic joints (p=0.001), but not between SA and crystal arthropathy (p=0.059). It is also important to note that mean aspiration WCC was 48,554/mm3 in patients with SA, which is less than the gold standard value of 50,000/mm3. Therefore, in practice, aspiration WCC may not be as useful as other parameters, such as CRP, and the gold standard value of 50,000/mm3 should perhaps be used with caution. We propose a value of 20,000/mm3 as a value to help exclude SA, but ensure that it is not missed.

In children, Bruce *et al.* demonstrated CRP and weight-bearing status to independently differentiate between SA and transient synovitis and used them in a two-variable algorithm as an excellent negative predictor6. Our results suggest that CRP could also be used in a similar adult model to differentiate between normal or osteo/inflammatory arthritic joints, crystal arthropathy and SA.

CONCLUSIONS

We have demonstrated CRP to be a reliable independent marker to help differentiate between SA, crystal arthopathy and normal/arthritic joint in an adult population. No patients with CRP < 90 mg/L had SA. Future studies should focus on the development of a reliable criteria to diagnose septic arthritis in adults, similar to the Kocher criteria in children16.

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None to declare.

REFERENCES

1. Rutherford A, Subesinghe S, Bharucha T, Ibrahim F, Kleymann A, Galloway J. A population study of the reported incidence of native joint septic arthritis in the United Kingdom between 1998 and 2013. Rheumatology. 2016;55(12):2176-2180.

2. Al-Ahaideb A. Septic arthritis in patients with rheumatoid arthritis. Journal of Orthopaedic Surgery and Research. 2008;3(1):33.

3. Jagodzinski N, Kanwar R, Graham K, Bache C. Prospective Evaluation of a Shortened Regimen of Treatment for Acute Osteomyelitis and Septic Arthritis in Children. Journal of Pediatric Orthopaedics. 2009;29(5):518-525.

4. CAIRD M, FLYNN J, LEUNG Y, MILLMAN J, DʼITALIA J, DORMANS J. FACTORS DISTINGUISHING SEPTIC ARTHRITIS FROM TRANSIENT SYNOVITIS OF THE HIP IN CHILDREN. The Journal of Bone and Joint Surgery-American Volume. 2006;88(6):1251-1257.

5. Sultan J, Hughes P. Septic arthritis or transient synovitis of the hip in children: THE VALUE OF CLINICAL PREDICTION ALGORITHMS. Journal of Bone and Joint Surgery - British Volume. 2010;92-B(9):1289-1293.

6. Singhal R, Perry D, Khan F, Cohen D, Stevenson H, James L et al. The use of CRP within a clinical prediction algorithm for the differentiation of septic arthritis and transient synovitis in children. The Bone & Joint Journal. 2011;93-B(11):1556-1561.

7. Jain S, Tittal P, Rohilla N, Sud A, Yadav C, Kanojia R et al. Acute septic arthritis revisited: a prospective study in 93 patients correlating C-reactive protein levels with duration of intravenous antibiotic therapy, clinical and radiological outcomes. European Journal of Orthopaedic Surgery & Traumatology. 2009;19(7):447-455.

8. Ernst A, Weiss S, Tracy L, Weiss N. Usefulness of CRP and ESR in Predicting Septic Joints. Southern Medical Journal. 2010;103(6):522-526.

9. Gupta M. A prospective 2-year study of 75 patients with adult-onset septic arthritis. Rheumatology. 2001;40(1):24-30.

10. Coakley G. BSR & BHPR, BOA, RCGP and BSAC guidelines for management of the hot swollen joint in adults. Rheumatology. 2006;45(8):1039-1041.

11. Banzet P. Acute septic arthritis of the fingers. A clinical study of 87 cases. Plastic and Reconstructive Surgery. 1983;72(2):275.

12. Wirtz D, Marth M, Miltner O, Schneider U, Zilkens K. Septic arthritis of the knee in adults: treatment by arthroscopy or arthrotomy. International Orthopaedics. 2001;25(4):239-241.

13. Stutz G, Kuster M, Kleinstück F, Gächter A. Arthroscopic management of septic arthritis: stages of infection and results. Knee Surgery, Sports Traumatology, Arthroscopy. 2000;8(5):270-274.

14. Goldenburg L, Brandt D, Cohen S, Cathcart S. Treatment of septic arthritis: comparison of needle aspiration and surgery as initial modes of joint drainage. Arthritis and Rheumatology. 1975;18(1):83-90.

15. Office for National Statistics. Wirral population estimate (mid 2013). Retrieved 26 June 2014.

16. Kocher MS, Zurakowski D, Kasser JR. Differentiating between septic arthritis and transient synovitis of the hip in children: an evidence-based clinical prediction algorithm. J Bone Joint Surg Am. 1999;81(12):1662-70.

FIGURE AND TABLE LEGENDS

Figure 1 – CRP by Group

Figure 2 – Peripheral WCC by Group

Table 1 – Gram stain and extended culture reliability

ARTICLE SUMMARY

Why is this topic important? Native joint septic arthritis is associated with significant morbidity and mortality and is often difficult to diagnose.

What does this study attempt to show? The primary objective of this study was to establish whether C-reactive protein (CRP) can be used to predict native joint septic arthritis (SA) in the adult population.

What are the key findings? We have demonstrated CRP to be a reliable independent marker to help differentiate between SA, crystal arthopathy and normal/arthritic joint in an adult population.

How is patient care impacted? The findings of this study will be used locally to implement a pathway in Accident and Emergency (A&E). Externally, we would advise that all patients presenting with hot, swollen joints have CRP measured to reduce the likelihood of missing this potentially highly significant diagnosis.