

Sickle Cell Disease in Children

Differentiating Osteomyelitis From Vaso-occlusive Crisis

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Objective: To identify clinical and laboratory features predictive of osteomyelitis in children with sickle cell disease and bony pain.

Design: Patients in the case group and participants in the control group were randomized in a 1:3 ratio.

Setting: The Hospital for Sick Children, Toronto, Ontario, Canada.

Participants: Patients with sickle cell disease and osteomyelitis (case patients) and patients with sickle cell disease and bony, vaso-occlusive crisis (control patients), 18 years or younger.

Main Outcome Measures: Five characteristics (number of painful sites, white blood cell count, swelling of the affected limb[s], and duration of pain and fever before presentation) at the time of presentation to hospital.

Results: Data were analyzed for 31 cases and 93 controls. Compared with controls, cases had more days of

pain (5 vs 2 days; odds ratio [OR], 1.2; 95% confidence interval [CI], 1.1-1.4 days) and fever (1 vs 0 day; 1.7; 1.2-2.4 days) before presentation. Cases were also more likely to have swelling of the affected limb(s) (71% vs 17%; OR, 11.8; 95% CI, 4.6%-30.0%) and fewer painful sites (1 vs 2; 0.7; 0.5-1.0). On laboratory evaluation, cases had higher white blood cell counts (18.6 vs 15.6/ μ L; OR, 1.1; 95% CI, 1.0-1.1/ μ L). Multivariate logistic regression showed that the significant predictors of osteomyelitis were duration of fever (OR, 1.8; 95% CI, 1.2-2.6) and pain (1.2; 1.0-1.4) before presentation and swelling of the affected limb (8.4; 3.5-20.0). The risk of osteomyelitis was decreased if more than 1 painful site was present (OR, 0.7; 95% CI, 0.5-1.0).

Conclusion: In the clinical scenario of a child with sickle cell disease presenting with bony pain and swelling affecting a single site, with prolonged fever and pain, the physician should consider closer monitoring and investigations to exclude a diagnosis of osteomyelitis.

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SICKLE CELL DISEASE (SCD) IS the most common single gene disorder in African Americans, affecting approximately 1 of 375 persons of African ancestry. Major complications of the disease in childhood include acute splenic sequestration crisis, aplastic crisis, acute chest syndrome, stroke, cholelithiasis, renal disease, infection, and pain.¹ A vaso-occlusive crisis (VOC) can manifest as pain in the chest, abdomen, back, or limbs, occurring when the red blood cells sickle and cause localized ischemia. Vaso-occlusive crisis affecting the bone is the most common acute clinical manifestation of SCD in children.

Severe infections occur frequently as a result of impaired immune function and functional asplenia, increasing the risk of bacterial sepsis and infection of the bone.² Osteomyelitis can be an acute or a chronic

inflammatory process of the bone caused by infection with pyogenic organisms. In children with SCD, the most common organism responsible for osteomyelitis is non-*Salmonella typhi*, which has been reported to occur 2.2 times more often than *Staphylococcus aureus*.³ Diagnosing osteomyelitis in children with SCD can be extremely difficult. Children with osteomyelitis often present with fever and a painful, swollen, tender limb with limited range of motion, signs and symptoms that are similar to those found in patients with a VOC.

There is no definitive feature on history, physical examination, laboratory test, or radiological study that can reliably differentiate between osteomyelitis and VOC, with the possible exception of a positive bacterial culture from the bone. However, a bone biopsy or aspiration is often not performed because it is an invasive procedure and should be done before start-

ing antibiotics to maximize the chance of obtaining a positive culture result. Furthermore, bone cultures are reported to be positive in only 30% to 86% of cases,⁴ implying that there is still a high false-negative rate. Cultures from the peripheral blood are even less specific in supporting a diagnosis of osteomyelitis, and they are reported to demonstrate an organism in 30% to 76% of cases.⁴ Thus, there are many cases in which no definitive diagnosis can be made.

Many patients with SCD, in tandem with pain in the bone and fever, are initially treated empirically for possible osteoarticular infection or sepsis with broad-spectrum antibiotics. The antibiotics are discontinued at 48 hours if the blood culture remains negative. However, in cases in which the patient's fever and pain are persistent despite negative blood, clinicians are often faced with the dilemma of whether to treat for osteomyelitis. Failure to treat an unconfirmed case of osteomyelitis can have serious consequences, including chronic bone damage, limb deformity, and sepsis.¹ However, unnecessary treatment for what is mistakenly thought to be osteomyelitis can have significant psychosocial, financial, and health care resource implications and can contribute to antibiotic resistance. Patients may also unnecessarily experience adverse effects of the antibiotics and are at risk of complications from central intravenous lines that may be inserted to facilitate administration of antibiotics.

In a review of osteoarticular infections in children with SCD, 14 cases were identified during a 22-year period.⁵ The predominant symptoms on presentation were pain, swelling, fever, and tenderness. The vast majority of patients had an elevated white blood cell (WBC) count and erythrocyte sedimentation rate. However, this was a descriptive study with a small sample size and there was no comparison with patients with SCD having bony VOC.

Our goal in this study was to identify features on presentation that were predictive of osteomyelitis in children with SCD. Based on a review of the literature, our clinical experience, and discussions with experts in this field, our hypothesis was that patients with SCD and osteomyelitis would be more likely to present with a longer history of pain and fever than would patients with VOC. In addition, we anticipated that patients with a single painful site, a higher WBC count, and swelling of the affected limb(s) would be more likely to have osteomyelitis than to have VOC.

METHODS

STUDY SAMPLE AND DESIGN

We performed a case-control study of patients with SCD, 18 years and younger, who were admitted to The Hospital for Sick Children between January 1, 1988, and December 31, 2005. All participants were identified through use of the hospital's health records database. The study was approved by the Research Ethics Board at The Hospital for Sick Children.

Cases were defined as patients with SCD who had a discharge diagnosis of osteomyelitis and 1 or more of the following criteria: (a) positive blood culture, (b) positive culture of a bone or joint aspirate, and/or (c) typical radiographic findings of osteomyelitis, as reported by a staff radiologist. Radio-

graphic data included the findings from radiograph, bone scan, ultrasound, magnetic resonance imaging, and gallium scan examinations. Patients with any imaging findings that were reported by the radiologist as being "possible osteomyelitis" or "osteomyelitis vs vaso-occlusive crisis," and were therefore inconclusive, were not included as cases of osteomyelitis. Only patients with radiographic imaging that was reported as "consistent with osteomyelitis" or "typical of osteomyelitis" were coded as true cases. For instance, a patient with a radiographic report of "subperiosteal collection consistent with osteomyelitis" would have been included as a case.

Cases were excluded from the study if the patient was treated with antibiotics for less than 2 consecutive weeks, because this would indicate that the responsible physician did not treat the patient as a true case of osteomyelitis. Cases were also excluded if the patient had chronic osteomyelitis, rather than an acute presentation.

Control participants were patients with SCD who were admitted with a discharge diagnosis of VOC in the same year as the case. Each potential control participant was assigned a code, which was entered into a random number generator (www.randomizer.org/form.htm). For each case included in the study, 3 randomly selected control participants were matched by year of admission.

For each case and control, we recorded the age of the patient on admission, the patient's sex, and the genotype of SCD. We collected data regarding the duration of pain and fever before presentation and the number of painful sites for each patient. The presence and duration of fever and the duration of pain before presentation were based on the history given by the parent or patient and documented in the emergency department record or the admission note. If there was a discrepancy between the admission note and the emergency department note, in that one documented fever or pain and the other did not, we used the record that documented the data. We assumed that if this information was not documented, it was likely that the question was not asked by the physician. If there was a discrepancy in the information, we looked for corroborating evidence elsewhere in the patient's medical chart to clarify the issue. We also recorded whether the physician found swelling of the affected limb on physical examination in the emergency department or at the time of admission. If there was no documentation regarding the presence or absence of swelling, then this was coded as no swelling. The WBC count on the day of admission was recorded directly from the laboratory records.

STATISTICAL ANALYSIS

Data for cases and matched controls were compared using the χ^2 test or Fisher exact test for categorical variables and *t* test or the Mann-Whitney test for quantitative variables, as appropriate. Statistical analyses were conducted using SAS (version 9.1; SAS Institute Inc, Cary, North Carolina). Univariate analysis was performed on candidate variables: duration of fever before presentation, duration of pain before presentation, number of painful sites, presence of swelling, and WBC count. Variables with a value of $P < .10$ in the univariate analysis were entered into the multivariate analysis so as to identify which factors were independently significant after controlling for other variables. Variables were deemed to be significant prognostic factors when $P < .05$ in the multivariate analysis using stepwise selection.

RESULTS

There were a total of 70 case patients with SCD who had a discharge diagnosis of osteomyelitis (**Figure**). Nine-

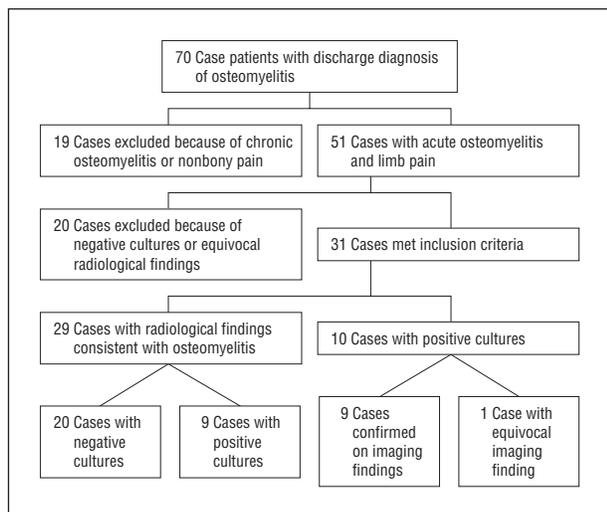


Figure. Study participants who meet inclusion criteria for cases of osteomyelitis.

teen of these cases were excluded for having nonbony pain or chronic osteomyelitis. Of the remaining 51 cases, 20 were excluded for not having a positive blood culture result, positive bone aspirate culture, or typical radiographic imaging consistent with osteomyelitis. Thirty-one cases met inclusion criteria. Data were analyzed for these cases and 93 matched controls with SCD and acute, bony VOC.

Of the total 31 cases, 29 had findings on radiographic imaging that were recorded by the radiologist as being consistent with osteomyelitis. Two had abnormalities on imaging and neither had a bone biopsy performed, but they both had positive blood culture. Many of the cases had more than 1 imaging modality confirming their diagnosis. Nine cases were confirmed on magnetic resonance imaging, 13 on radiography, 8 on ultrasound, 1 on technetium bone scan, and 7 on gallium scan. Of the 29 cases with typical imaging for osteomyelitis, 9 also had positive blood or bone aspirate culture, while the remaining 20 had negative culture.

CLINICAL AND LABORATORY CHARACTERISTICS

There were no significant differences between cases and controls in terms of age, sex, and genotype of SCD (**Table 1**). Cases had a median of 5 days of pain before presentation, excluding the day of presentation (range, 0-22 days), whereas controls had a median of only 2 days of pain (range, 1-18 days; odds ratio [OR], 1.2; 95% confidence interval [CI], 1.1-1.4 days). Cases had a median of 1 day of fever (range, 0-20 days), whereas controls reported no fever before the day of presentation (range, 0-4 days; OR, 1.7; 95% CI, 1.2-2.4 days). Seventy-one percent of cases compared with only 17% of controls presented with documented swelling of the affected limb (OR, 11.8; 95% CI, 4.6%-30.0%). Cases had a median of only 1 painful site (range, 0-6) compared with 2 sites of pain in controls (range, 1-6; OR, 0.7; 95% CI, 0.5-1.0). On laboratory evaluation, participants had a 10% increase in the likelihood of having osteomyelitis for every 1-U

Table 1. Baseline Characteristics

Characteristic	Cases ^a (n=31)	Controls ^b (n=93)	P Value
Age, y, mean (SD)	8.9 (5.7)	8.5 (5.3)	.78
Female, No. (%)	17 (55)	57 (61)	.53
SCD genotype, No. (%)			
HbSS	25 (81)	66 (71)	.57
HbSC	5 (16)	18 (19)	.57
HbS/β-thalassemia	1 (3)	9 (10)	.57

Abbreviations: Hb, hemoglobin; SCD, sickle cell disease.

^aParticipants 18 years or younger with SCD and osteomyelitis.

^bParticipants 18 years or younger with SCD and bony, vaso-occlusive crisis.

(1/μL) increase in the WBC count (95% CI, 1.0-1.1/μL) (**Table 2**).

Ten of the 31 cases had either a positive blood culture or a positive bone aspirate culture. All 31 cases had a blood culture sent to the laboratory and 6 (19%) were positive for bacteria. Of these 6 cultures, 3 were positive for *Salmonella* species, 1 for *Haemophilus influenzae*, 1 for *S aureus*, and 1 for *Acinetobacter*. Fourteen cases had a bone aspirate performed; 5 (36%) were positive for bacteria. All 5 were identified as *Salmonella* species. One case had both positive blood and bone aspirate culture results.

MULTIVARIATE LOGISTIC REGRESSION ANALYSIS

After adjustment for all variables entered into the model, the multivariate logistic regression analysis showed that the number of days of fever and pain before admission, swelling of the affected limb, and the number of painful sites remained significant independent predictors of osteomyelitis (**Table 3**).

The probability of osteomyelitis increased by 80% for each day a child had fever before presentation (95% CI, 1.2-2.6) and by 20% for each day a child had pain before presentation (95% CI, 1.0-1.4). Patients were 8.4 times more likely to have osteomyelitis if they presented with documented swelling of the affected limb (95% CI, 3.5-20.0). The risk of osteomyelitis was decreased by 30% for each additional painful site if more than 1 painful site was present (95% CI, 0.5-1.0). A high WBC count was not found to be a significant prognostic factor for osteomyelitis in the multivariate analysis.

COMMENT

Multivariate logistic regression analysis showed that the probability of osteomyelitis in a child with SCD and bony pain was increased if there was swelling affecting a single site, as well as prolonged fever and/or pain.

Studies to date that have reviewed cases of osteomyelitis in pediatric patients with SCD have had very small sample sizes,⁵⁻⁹ and, to our knowledge, none have used a case-control method to compare the presentation of osteomyelitis with that of VOC, which is the most common cause of bony pain in these children. Other studies

Table 2. Clinical and Laboratory Characteristics^a

Characteristic	Cases ^b (n=31)	Controls ^c (n=93)	Crude OR (95% CI)	P Value
No. of days of pain before presentation	5 (0-22)	2 (1-18)	1.2 (1.1-1.4)	.003
No. of days of fever before presentation	1 (0-20)	0 (0-4)	1.7 (1.2-2.4)	.001
Swelling of the affected limb, No. (%)	22 (71.0)	16 (17.2)	11.8 (4.6-30.0)	<.001
No. of painful sites	1 (0-6)	2 (1-6)	0.7 (0.5-1.0)	.06
WBCs μ L count, per microliter	18.6 (5.8-58.7)	15.6 (1.7-36.2)	1.1 (1.0-1.1)	.03

Abbreviations: CI, confidence interval; OR, odds ratio; WBCs, white blood cells.

SI conversion factor: To convert WBCs to $\times 10^9/L$, multiply by 0.001.

^aData are given as median (range) unless otherwise indicated.

^bParticipants with sickle cell disease and osteomyelitis, 18 years or younger.

^cParticipants with sickle cell disease and bony, vaso-occlusive crisis, 18 years or younger.

Table 3. Multivariate Logistic Regression Analysis

Variable	OR (95% CI)	P Value
No. of days of fever before admission	1.8 (1.2-2.6)	.004
No. of days of pain before admission	1.2 (1-1.4)	.02
Swelling of affected limb on presentation	8.4 (3.5-20.0)	<.001
No. of painful sites	0.7 (0.5-1.0)	.03

Abbreviations: CI, confidence interval; OR, odds ratio.

have included adult patients,^{10,11} whose findings may not hold true in children. Older studies may not reflect the more recent introduction of prophylactic therapies, including penicillin and hydroxyurea.^{6,9,11}

It is important to note that *Salmonella* was the most common organism identified on both blood and bone aspirate cultures in our study. There has been some controversy in the literature as to whether *Salmonella* or *S aureus* is more prevalent in patients with SCD.⁵ However, in most of the North American literature, *Salmonella* is the most common organism found in osteomyelitis in patients with SCD. In 2 separate review articles, Wong et al¹² reported that *Salmonella* accounts for 70% of bone infection in children with hemoglobinopathies, and Burnett et al³ found that the ratio of cases caused by *Salmonella* vs *S aureus* was 2.2:1. In a retrospective review of 14 cases of osteomyelitis in pediatric patients with SCD, Chambers et al⁵ found that *Salmonella* occurred in 8 cases. Therefore, it is imperative that patients with SCD who present with features suspicious for sepsis, osteomyelitis, or septic arthritis receive appropriate antibiotic therapy, which includes coverage of *Salmonella* species.

Our study has a number of strengths. It is the first to compare children with SCD and osteomyelitis with a control group of patients with SCD and VOC. By adopting a case-control method, we were able to identify risk factors for osteomyelitis in children with SCD who present with bony pain. In addition, we present the largest review in either the pediatric or adult medical literature of patients with SCD who were diagnosed as having osteomyelitis. Our ability to collect a large study sample was in part due to the fact that Toronto is a multicultural Canadian city with a large African and Caribbean population, in whom SCD is common. Our hospital is the referral center for children with SCD in Toronto. The sickle cell clinic at The Hospital for Sick Children provides out-

patient care for approximately 700 children, and there are more than 150 admissions annually for the management of VOC.

There are some limitations to this study. There is no criterion standard for the diagnosis of osteomyelitis in SCD. However, our case definition included only children with a positive blood or bone aspirate culture or radiographic findings consistent with osteomyelitis. It is known that not all cases of osteomyelitis will have a positive blood or bone culture,⁴ so we believe that it was important to include the cases with typical radiographic findings of osteomyelitis. Of note, we did exclude 20 children with SCD during this period who had a discharge diagnosis of osteomyelitis and were treated as such but had negative culture and lacked definitive radiographic findings.

An additional limitation is that, as with all retrospective medical record reviews, data collection can be affected by the quality and quantity of documentation, which would have affected both cases and controls. Specifically, we were unable to assess how patients defined fever and why they did not seek medical attention at the onset of fever, as they are instructed to do by their health care providers at the sickle cell clinic. We could hypothesize that in patients with VOC, their fever may be low grade and spontaneously resolve as the crisis improves, whereas patients with osteomyelitis have a more persistent fever, which ultimately results in their coming to the emergency department.

There were no specific criteria to define pain aside from the subjective reporting of the patient or the parent reporting pain on behalf of the child. We could not collect historical data on the quality or severity of the pain, which may have influenced the decision about when to seek medical attention. Patients with SCD who have pain from osteomyelitis may have delayed their visit to the hospital due to a difference in the quality or severity of the pain compared with their normal vaso-occlusive pain but ultimately presented to the emergency department because their pain did not improve with time. In future studies, researchers examining this problem should consider measuring the quality and severity of pain associated with bone infarction and infection to determine whether there are differences.

Finally, one should interpret the WBC counts in the 2 groups with caution. In retrospect, it may have been more prudent to look at the change in WBC count from

the baseline steady state to the time of acute presentation in each patient, rather than the absolute WBC count, because there is significant variation in baseline WBC counts in children with SCD.

It is important to highlight that osteomyelitis is much less common than VOC. Studies suggest that VOC is 50 times more common than osteomyelitis in a patient with SCD.^{6,13} Therefore, even if a patient with SCD presents with fever and bony pain and has many of the risk factors for osteomyelitis identified in this study, this should be considered in the context of the rarity of osteomyelitis compared with that of VOC. The presence of some or all of these risk factors should nevertheless increase the index of suspicion for osteomyelitis and make the physician more inclined to request imaging or a definitive bone aspirate for culture.

In conclusion, this case-control study of pediatric patients with SCD has identified factors that are predictive of an increased risk of osteomyelitis. Multivariate logistic regression analysis showed that the number of days of fever and pain before admission, swelling of the affected limb, and number of painful sites remained significant independent predictors of osteomyelitis.

By identifying whether a patient has the aforementioned risk factors, physicians can make a more informed choice in deciding whether to proceed with radiological investigations and bone aspirate for culture and when to initiate a prolonged course of antibiotics as treatment for osteomyelitis.

A prospective multicenter study would be helpful to review a larger sample size and potentially provide sufficient data for the development of a clinical decision rule.

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Author Contributions: Drs Berger, Saunders, and Friedman had full access to all of the data in the study

and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Berger and Friedman. *Acquisition of data:* Berger and Saunders. *Analysis and interpretation of data:* Berger, Saunders, Wang, and Friedman. *Drafting of the manuscript:* Berger, Wang, and Friedman. *Critical revision of the manuscript for important intellectual content:* Berger, Saunders, and Friedman. *Statistical analysis:* Wang. *Obtained funding:* Friedman. *Administrative, technical, and material support:* Berger and Friedman. *Study supervision:* Friedman.

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Because all the sick do not recover does not
prove that there is no art of medicine.
—Cicero, 106-43 BC