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CLINICAL RESEARCH

Septic Arthritis in Adults with Sickle Cell Disease Often is Associated with Osteomyelitis or Osteonecrosis

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Abstract

Background Septic arthritis is a known complication of sickle cell disease (SCD) in children, and the association with osteomyelitis and osteonecrosis has been described. However, it is unclear whether this association applies to adults.

Questions/Purposes We therefore asked whether septic arthritis is a frequent complication in adults with SCD and whether it also is associated with osteomyelitis or osteonecrosis.

Methods We retrospectively reviewed the charts of 2000 consecutive adult patients diagnosed with SCD and recorded symptoms, select findings during physical examination, laboratory data, and select radiographic CT, and MRI observations.

Results Fifty-nine of the 2000 patients (3%) had septic arthritis, 56 of the 59 patients had hemoglobin SS. Thirty-six of the 59 infections (61%) were in the hip. The most frequent findings were pain, swelling, fever greater than 38.2°C (71% of cases), a leukocyte count exceeding 15,000/mm^3 (range, 7900–32,300/mm^3), a Westergren sedimentation rate greater than 24 mm/hour, and C-reactive protein exceeding 20 mg/L. Cultures were positive in 96% of the joint aspirates. Staphylococcus and Gram-negative infection predominated; no patients had Salmonella joint infections. Preexisting factors of bacterial arthritis included osteonecrosis (29 patients) and osteomyelitis (37 cases) in childhood. Diabetes, rheumatoid arthritis, glucocorticoids, and immunoparesis related to medical treatment by hydroxyurea were associated comorbidities. CT and MRI confirmed the diagnosis of associated osteonecrosis or osteomyelitis and allowed joint aspiration and detection of soft tissue abscess.

Conclusions The incidence of septic arthritis in adults with SCD is low, but often is associated with osteomyelitis or osteonecrosis.

Level of Evidence Level II, prognostic study. See Guidelines for Authors for a complete description of levels of evidence.

Introduction

SCD is an autosomal-recessive disorder that produces hemolytic anemia related to abnormal hemoglobin and erythrocytes. Children who are homozygous for the sickle cell gene (hemoglobin SS) have a high risk of infection [2]

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Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.
This work was performed at Hôpital Henri Mondor, Creteil, France, and at the Hospital Edgar Santos, Salvador, Brazil.

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resulting from the association of recurrent episodes of sloughing of the intestinal mucosa resulting in enteric bacteremia. Additionally, these children have a high risk of osteonecrosis caused by microvascular occlusion [3]. This incidence also is high in children with hemoglobin SC (compound heterozygotes for HbS- and HbC-producing alleles: SC) and in those with various types of the sickle-beta-thalassemia (SThal). Since Barrett-Conner reported his findings in 1971 [2], several studies [3, 13, 26] have reported a frequency of septic arthritis in children with SCD of 0.2% to 5.4% and an association with osteomyelitis, osteonecrosis, and septic arthritis. However, it is unclear whether septic arthritis is a frequent complication in adults with SCD and whether it also is associated with osteomyelitis or osteonecrosis. Bulmer [5] and Kelly et al. [21] presented the two largest series of patients with adult septic arthritis in the 1960s, but no case was reported for patients with SCD.

We therefore reviewed a large number of adult patients with SCD to establish (1) the incidence of infection in the various types of SCD; (2) the nature of the presenting history; (3) the description of presenting signs and laboratory findings; (4) the source of infection and the association of septic arthritis with osteomyelitis or osteonecrosis; (5) the organisms involved in the infections; and (6) the imaging findings.

Patients and Methods

We retrospectively reviewed the medical records at our institutions (Table 1) of 2000 consecutive patients with SCD who were older than 18 years between 1979 and 2009 (we arbitrarily stopped our review at 2000 patients). The initial diagnosis of SCD was made by serum electrophoresis in all patients. We found septic arthritis in 56 patients who were homozygous for the sickle cell gene (hemoglobin SS), two who had hemoglobin S/hemoglobin C, and one who had hemoglobin S associated with beta-thalassemia (Table 1). We suspected joint infection when patients had pain associated with fever, decreased ROM of the joint, and abnormal laboratory values (leukocyte count, differential, C-reactive protein, and erythrocyte sedimentation rate). Joint aspiration was performed in 126 patients and all 59 with septic arthritis were confirmed by a pathogen in the joint or by histologic analysis. We excluded patients who had previous surgery at the site of infection. We diagnosed osteomyelitis in 137 of the 2000 patients (7%) and osteonecrosis in 634 patients (32%) (Table 1). Osteomyelitis (contiguous or distant to septic arthritis) and osteonecrosis were present in 96 of the 2000 patients (5%). Among these 96 patients, 59 had septic arthritis: 24 had septic arthritis at the site of osteonecrosis, 13 had septic arthritis with osteomyelitis but without osteonecrosis at the site of arthritis, five had septic arthritis with osteonecrosis at the site of arthritis but without osteomyelitis, and 17 had septic arthritis without osteomyelitis or osteonecrosis. There were 39 male patients and 20 female patients. The average age at onset of the acute septic arthritis was 25 years (range, 18–43 years).

Table 1. Patient demographics and incidence of infection

Patient demographic variable	Total number of cases (n = 2000)	Patients with septic arthritis (n = 59)
Gender		
Male	1023 (51%)	39 (66%)
Female	977 (49%)	20 (34%)
Genotype		
S/S (number, %)	1514 (76%)	56 (95%)
S/C (number, %)	389 (19%)	2 (3%)
S/B (number, %)	97 (5%)	1 (2%)
Osteomyelitis (number, %)	137 (7%)	37 (62%)
Osteonecrosis (number, %)	634 (32%)	29 (49%)
Osteonecrosis and osteomyelitis	96 (5%)	24 (41%)

$p \leq 0.01$ for all variables.

We reviewed patients' charts to identify clinical features at the time of admission including pertinent medical history, risk factors, physical examinations, and radiographic and laboratory findings; no patients were recalled specifically for this study. All charts were reviewed for information regarding the symptoms (Table 2) at the time of admission (ie, pain, fever, swelling, inability to walk, or limited joint motion). The presence or absence of specific findings in the physical examination was noted, including fever, location(s) of soreness, and location of swelling, ROM of the joint, heat, erythema, and gait. Pertinent laboratory data at admission were leukocyte count, differential, C-reactive protein, and erythrocyte sedimentation rate.

The numbers and types of other cultures varied for our patient population, blood culture, or tissue biopsy. Of the 59 patients 54 had blood cultures, 50 had joint aspiration, and 43 had tissue cultures. Blood cultures were positive in 63% (34 of 54 patients), tissue biopsy cultures were positive in 60% (30 of 50 patients), and aspiration was positive in 96% (48 of 50 patients). The joint fluid was grossly turbid in 16 patients, purulent in 14, and serosanguinous in eight.

Three of us (PH, GD, AP) independently reviewed the radiographs of all 59 patients and recorded any abnormal findings (AP and lateral views of the joint, and a pelvis film for patients with involvement of the hip) (Table 3). We recorded narrowing of joint space, evident avascular necrosis, lytic changes, erosion of bone, osteomyelitis, soft tissue gas in the joint, recognizing that radiographs can be normal at the beginning of the disease [3, 13, 22].

Table 2. Presenting history for 59 patients

Variable	Value
Delay between beginning of symptoms and diagnosis	
< 10 days	21
11 days << 30 days	26
> 30 days	12
54 patients with unifocal infections	
Hip	36
Knee	12
Shoulder	3
Spine	3
5 patients with multifocal infections	
Pain and decreased motion	59 (100%)
Soreness over affected area	54 (91%)
Temperature ≥ 38.2°C	53 (89%)
Leukocyte count ≥ 15,000/mm^3	54 (91%)
Polymorphonuclear leukocytes	77% ± 4%
Anemia	
Hematocrit ≤ 20%	23 (39%)
Hematocrit < 16%	15 (25%)
Westergren sedimentation rate (mm/hour)	52 (range, 24–87)
C-reactive protein (mg/L)	48 (range, 22–126)

We obtained CT scans for all 36 patients with suspected infection during the early part of the study (before MRI was available). We specifically looked for erosion of the subchondral bone, narrowed joint space, the presence of fluid and/or gas in the joint, adjacent osteonecrosis, and contiguous or distant osteomyelitis. After it became available, we obtained MR images in 35 of the 59 patients with a 1.5-T unit. The following imaging parameters were used: T1-weighted spin-echo imaging, T2-weighted fast spin-echo imaging, and gadolinium-enhanced T1-weighted spin-echo imaging. A fat-suppression technique based on frequency-selective excitation was used in T2-weighted fast spin-echo imaging and gadolinium-enhanced T1-weighted spin-echo imaging. Axial and coronal images were obtained with each pulse sequence. We evaluated coronal and axial contrast-enhanced T1-weighted spin-echo images for alterations in signal intensity in the soft tissue and the bone marrow of the affected joint. Osteonecrosis was diagnosed when we observed abnormal band-like signals and hypointense band-like zones on T1-weighted images and matching hyperintense zones on short tau inversion. The specific images reviewed for diagnosing infection using the MR images included a thick synovial membrane, signal intensity alterations in the soft tissues around the joint, abnormal signal intensity in the bone marrow, and coexistent contiguous or distant osteomyelitis.

Proportions of patients with infection in the different groups with SCD (S/S;S/C; S/β; male and female) and proportions of patients with and without osteomyelitis or osteonecrosis were compared using the chi square test or Fisher's exact test as appropriate. Continuous data as leukocyte counts are reported as mean ± SDs or mean and range values.

Table 3. Imaging findings in patients with septic arthritis

Type of imaging	Number of patients (%)
Radiographs (total)	59
Abnormal finding	29 (49%)
Narrowed joint space	19 (32%)
Evident avascular necrosis	14 (24%)
Lytic changes	4 (7%)
Erosion of the bone	12 (20%)
Osteomyelitis	18 (31%)
Soft tissue gas in the joint	2 (3%)
CT (total)	36
Abnormal finding	36 (100%)
Fluid	36 (100%)
Cortical erosion of the subchondral bone	23 (64%)
Gas in the joint	12 (33%)
Osteomyelitis	3 (8%)
Osteonecrosis	8 (22%)
MRI (total)	35
Abnormal finding	35 (100%)
Osteonecrosis	21 (60%)
Osteomyelitis	4 (11%)
Thick synovial membrane	17 (49%)
Signal intensity alterations in the soft tissues around the joint	17 (49%)
Abnormal signal intensity in the bone marrow	9 (26%)
Soft tissue abscess	2 (6%)

Results

The incidence of articular infection was 0.3% (59 among 2000) patients. Infection was more frequent (Table 1) in male patients ($p = 0.01$), in patients homozygous (hemoglobin SS) for the sickle cell gene ($p = 0.004$), in patients with osteomyelitis ($p = 0.002$), and in patients with associated osteomyelitis and osteonecrosis (24 among 96; $p = 0.001$).

Presentation history varied: the duration of symptoms before diagnosis ranged from 1 day to more than 1 month (Table 2). Septic arthritis was diagnosed during the first 10 days in 29 patients who presented with sudden pain and temperature after a long history of osteonecrosis. By contrast, the diagnosis of arthritis was delayed to 1 month in another 12 patients with systemic infections. Fifty-four

Table 4. Associated conditions in the 59 patients with sickle cell disease and septic arthritis

Disease	Number	Percentage
Osteonecrosis	29	(49%)
Osteomyelitis	37	(62%)
Diabetes mellitus	4	(7%)
Immunosuppression therapy	3	(5%)
Corticosteroids treatment	2	(3%)
Septicaemia	2	(3%)
Vascular	1	(1%)
Dental abscess	1	(1%)

patients had unifocal infections (Table 2); the sites were the hips in 36, the knees in 12, the shoulders in three, and three had spondylodiscitis. Five patients had multifocal joint infections; all the patients with multifocal infections had associated spondylodiscitis.

At the time of admission, the findings of the patients varied, although some common themes emerged (Table 2). Patients experienced pain and decreased motion of the affected area, temperature greater than 38.2°C, leukocyte count exceeding 15,000/mm^3, Westergren sedimentation rate greater than 24 mm/hour, C-reactive protein greater than 20 mg/L, and anemia related to the disease.

The septic arthritis appeared to have been blood-borne in 52 of the 59 patients (88%), as only seven patients had contiguous osteomyelitis to septic arthritis (Tables 4, 5). In 37 patients, septic arthritis was associated with a primary focus of bone infection (osteomyelitis) at a distance from (30 patients) or contiguous (seven patients; five hips, two knees) to the infected joint. Comorbid conditions were present in 13 of these 59 patients with articular infections. All five patients with multifocal infections had associated comorbidities, three of them with immunosuppressive therapy.

A pathogen (Table 6) was identified in the joints of 57 of the 59 patients (97%). In two patients who were receiving antibiotic therapy at the time cultures were obtained, the pathogen could not be identified but the infection was confirmed by histologic analysis. Staphylococcus aureus was the most common isolate (35 cases), but cultures from only two patients grew isolates of methicillin-resistant S. aureus. None of the 22 patients without osteomyelitis had Salmonella joint infections, and none of the 37 patients had Salmonella joint infections although it was the pathogen for osteomyelitis in 12 of these 37 patients. Furthermore, even in the three patients with Salmonella in a contiguous focus of osteomyelitis to the septic joint, the pathogen in the joint was not Salmonella (Table 5).

Table 5. Pathogens in the 37 patients with associated osteomyelitis (known = 26; unknown = 11)

Pathogen	Osteomyelitis contiguous to septic arthritis (n = 7)	Osteomyelitis distant to septic arthritis (n = 19)
Salmonella (n = 12)	3	9
Staphylococcus (n = 10)	4	6
Escherichia coli (n = 4)		4

Table 6. Pathogens found in septic arthritis

Pathogen	Number
Staphylococcus aureus	33
Methicillin-resistant S. aureus	2
Escherichia coli/Enterococcus	12
Hemophilus influenzae	6
Streptococcus pneumoniae	4

Radiographs were abnormal in 29 patients and normal in 30 at the time of diagnosis. None of the patients on whom CT or MRI was performed had normal findings (Table 3). CT also was useful for joint aspiration and to evaluate the recurrence of fluid in the joint.

Discussion

Septic arthritis is a known complication of SCD in children, and the association with osteomyelitis and osteonecrosis has been described. However, it is unclear whether the association applies to adults. We therefore asked whether septic arthritis is a frequent complication in adults with SCD and whether it also is associated with osteomyelitis or osteonecrosis.

We note several limitations. First, we performed only a chart review and did not determine the overall prevalence of osteomyelitis or osteonecrosis in patients with or without septic arthritis, because MRI or CT was performed only for patients with symptoms. Because this study is a chart review, we do not know the exact frequency of comorbidities [19] in patients with SCD and without septic arthritis. Although some patients had missing data in at least one of the selected variables (eg, we did not know the pathogen for all cases of septic arthritis or osteomyelitis; all the patients did not have CT or MRI), we included all patients admitted during a long period to the musculoskeletal departments of the two institutions of the senior authors (PH, GD). We presume these missing data did not influence the data on infections per se and that our data

may give some indications for the diagnosis and pathogens of this rare disease.

The incidence of articular infections in our series (0.3%) appears low as compared with the incidence of osteomyelitis (7%). Our data are consistent with a published observation regarding how rarely osteoarticular infection occurs in patients with SCD [20]. Investigators from Saudi Arabia [30] and Nigeria [15] documented incidences of arthritis and osteomyelitis in children with SCD who had extremity disorders. Estimates of the prevalence of osteoarticular infection in children with sickle cell anemia have ranged from 0.2% [11] to 5.4% [2].

Because the presenting history is not typical and diagnosis can be delayed, it is important to have a high index of suspicion in patients with SCD who have joint pain and fever. Patients with SCD and septic arthritis superimposed on osteonecrosis were particularly difficult to diagnose unless there was a high index of suspicion. A study by Keeley and Buchanan [20] suggested that acute long-bone infarction occurred at least 50 times more commonly than bacterial osteomyelitis or arthritis in patients with SCD. Patients with SCD frequently have systemic illnesses [22, 26], and their symptoms of sepsis may be attributed to sites other than their joints. The value of laboratory studies in the differential diagnosis of osteoarticular infections and bone infarction in children with SCD is controversial [4, 10–12, 22, 30]. Ninety-two percent of our adult patients with documented articular infections had leukocyte counts exceeding 15,000 mm^3 (range, 7900–32,300/mm^3). Westergren sedimentation rates exceeded normal values in 100% of patients in the articular infection group. However, in the presence of bone infarction related to SCD, the Westergren sedimentation rates are variable during a long period and reportedly exceed normal values in 75% [6]. In our experience, the C-reactive protein is normal in osteonecrosis without associated infection. It exceeded normal values in 100% of patients in our infection group.

Distant osteomyelitis was more frequently the source of joint infection than contiguous osteomyelitis in our patients. Few studies in adults without SCD suggest an association between septic arthritis and osteomyelitis. However one of these reports [36] suggests the presence of a septic arthritis in an adult should raise the suspicion of an adjacent hematogenously-induced osteomyelitis as commonly observed in children [25, 28]. The phenomenon in children relates to the presence of transphyseal vessels in children younger than 18 months, and the intraarticular location of the metaphysis in joints such as the hip. Hematogenous seeding of the joint from the site of a distant or adjacent osteomyelitis may be the explanation for the association of septic arthritis and osteomyelitis in our adult patients. Although the association between osteonecrosis and septic arthritis has been described [14, 27, 29] in adults, the paucity of documented cases in patients without SCD suggests this association may be rare. In this series of patients with SCD, this association was frequent and clearly more frequent than in other causes of osteonecrosis. It is known that devitalized tissue [3, 8, 9, 24, 31] enhances the development of sepsis, and it is likely that the presence of osteonecrotic tissue provides favorable conditions for localization of the infective organisms. Furthermore, sickle cell and infection are etiologic agents for osteonecrosis.

The most common organism found in osteomyelitis in patients with SCD is Salmonella [1, 33], especially the nontypical serotypes S. typhimurium, S. enteritidis, S. choleraesuis, and S. paratyphi B followed by S. aureus [12, 15, 17, 32]. Less often the causative organism is a Gram-negative enteric bacilli [23]. Several authors suggest tiny infarctions in the gastrointestinal tract lead to Salmonella (and other enteric Gram-negative) bacteremia and ultimately to infection [18, 22]. Other authors suggest bone infarction, a common sequelae of SCD, combined with sluggish microcirculation and impaired opsonization [18], causes Salmonella bacteremia to "almost invariably localize to bone" with resulting osteomyelitis. However, the incidence of septic arthritis in SCD with salmonella is more poorly defined. In our series, salmonella was never found as a pathogen in the joint, even when it was found in contiguous osteomyelitis. Even after arthroplasties, salmonella has not been reported as a pathogen in joint infection in adult patients with SCD [16].

Routine radiographs generally are not useful in identifying early septic arthritis. CT depicts abscesses and fluid collections but is less specific than MRI for osteomyelitis and osteonecrosis [34]. In one report of 35 patients without SCD, MRI was 92% sensitive and 96% specific for the diagnosis of acute osteomyelitis [35]. However, other studies of patients with SCD concluded the distinction among acute infarction, septic arthritis, and osteomyelitis is difficult [3, 6, 7, 32].

If the diagnosis of infection is suspected or made, the patient should be subjected to articular aspiration to obtain the pathogen, CT or MRI should be performed to research osteomyelitis or osteonecrosis which frequently is associated with septic arthritis in SCD.

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