Salmonella osteomyelitis in childhood

A report of 63 cases seen in Nigerian children of whom 57 had sickle cell anaemia

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SUMMARY A review of 63 Nigerian children with salmonella osteomyelitis showed that in all but 2 of them the disease occurred in association with HbS either in the homozygous state (57 patients) or in heterozygous combination with other haemoglobins (4 patients). Osteomyelitis was most prevalent during the first 2 years of life, and boys were more often affected than girls. In the majority, multiple sites were involved and lesions were usually bilateral and often symmetrical. Salmonella sp. was isolated from blood or pus, or both, in all patients. In some patients additional pathogens were also isolated from blood or pus. Clinical presentation was variable. In many patients the illness was slight and they were treated entirely as outpatients, but serious toxemia, severe bone lesions with pathological fractures, and chronic suppuration occurred in others. Most patients responded well to chloramphenicol and conservative management. There were 4 deaths. 17 patients recovered with sequelae.

It is suggested that the peculiar susceptibility of patients with sickle cell anaemia to salmonella osteomyelitis is due to spread of salmonella from the intestine facilitated by devitalisation of gut caused by intravascular sickling, and that infarcts in bone became infected either by transient bacteraemia or by activation of dormant foci of salmonella in bone marrow when tissues are devitalised. It is further suggested that immunological defects in sicklers may impair host response to infection, while haemolysis and hepatic dysfunction, both of which occur in sickle cell anaemia, favour propagation of salmonellae.

Salmonella infections are universally prevalent and the infection rate is considerably higher in early childhood than later in life. Clinical manifestations of infection are many and various but reports indicate that salmonella osteomyelitis is peculiarly rare. Patients with sickle cell anaemia appear to have a greater susceptibility to this complication than nonsicklers. Salmonella osteomyelitis, even among patients with sickle cell anaemia cannot, on the basis of reports published to date, be regarded as common.

The first report of the peculiar association of sickle cell anaemia with salmonella osteomyelitis was by Carrington in 1925. In 1951, Hodges and Holt in the USA, and Lambotte-Legrand in the Belgian Congo independently drew attention to the special susceptibility of patients with sickle cell anaemia to salmonella osteomyelitis. This observation has been amply confirmed by others. These reports were based on very small numbers of patients, and one of the largest series published to date is that of Hendrickse and Collard in 1960, who reported on 13 cases of salmonella osteomyelitis in Nigerian children, the majority of whom had sickle cell anaemia.

We report here experience of 63 cases of salmonella osteomyelitis, seen over an 8-year period in the Children’s Department of University College Hospital, Ibadan in only 2 of whom the condition was unassociated with HbS.

Patients

All the 63 patients were Nigerian children, mainly of Yoruba origin, living in south-western Nigeria where the hospital is situated. Table 1 shows their
sex and Hb type. It will be seen that 57 patients had sickle cell anaemia (homozygous S disease), two had Hb (AA) and the remainder had HbS in heterozygous combination with Hb A, C, or F. Findings in the S-homozygotes will be presented separately from findings in other patients.

Findings in patients with sickle cell anaemia (HbSS).

Age and sex
Table 2 shows the ages and sexes of patients: boys predominate and in the under 2-year age group there is a 2:1 male to female ratio. It will also be noted that the condition was particularly prevalent during the first 2 years of life and tended to become less so in successive age groups.

Seasonal incidence (Table 3)
Cases occur throughout the year but there is a pronounced increase in prevalence between the months of October and December at the end of the rainy season.

Sites
In most patients, osteomyelitis was present in multiple sites (Table 4). The sites affected varied according to the age of the patient. The small bones of the hands and feet were more commonly affected in the youngest patients (Table 5), while in the older ones it was more likely to be the long bones of the arms and legs. In most patients lesions were bilateral and often remarkably symmetrical.

Summary of bacteriology
The diagnosis of salmonella osteomyelitis was based on culture of Salmonella sp. from blood in 19 cases, pus in 27 cases, and blood and pus in 11 cases. Species identified included Salmonella typhi, Salmonella typhimurium, Salmonella paratyphi, Salmonella dublin, Salmonella enteritidis, Salmonella group G (probably Salmonella poona). In a number of patients specific species identification was not possible because of the lack of specific antisera.

In 31 patients the only pathogens isolated were salmonellae. A remarkable feature of many patients was the isolation of one or more other pathogens, in addition to salmonellae, from pus or blood, or both. In 18 patients one other pathogen was identified (Table 6) while in 8 patients two or more other
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pathogens were isolated (Table 7). Mixed infection was more common in the very young (less than 2 years) than in other age groups.

In 14 patients mixed infections were detected during the initial investigation. In the remainder the additional pathogens were detected when bacteriological investigations were repeated during the course of the illness in patients not responding well to treatment.

Clinical presentation
Patients with sickle cell anaemia are prone to develop periodic episodes of pain in their limbs, of variable severity and duration due to bone ischaemia, consequent on intravascular sickling and occlusion of vessels, leading to infarction. In the very young, the bones of the hands and feet are commonly affected and this leads to painful swelling of the extremities, the 'hand-foot syndrome,' which is one of the characteristic manifestations of sickle cell anaemia in Africa. In older children the long bones of the limbs tend to be more frequently affected than the hands and feet.

The onset of salmonella osteomyelitis is usually indistinguishable initially from nonseptic infarction and in many cases the diagnosis of osteomyelitis is suspected only when symptoms fail to respond to nonspecific measures—such as rest, increased fluid intake, analgesics, and alkalis. In some patients intensity of pain, evidence of local inflammatory reaction, and pronounced pyrexia and toxaemia at the time of presentation suggest osteomyelitis, but it should be noted that similar symptoms can be presented by patients with widespread noninfected infarcts.

Some of our patients were first seen some time after the onset of osteomyelitis with complaints of persistent pain and loss of function in limbs, painful swellings localised to small bones of hands and feet or other sites, or occasionally with pathological fractures or discharging sinuses. In many of the older patients who showed gross x-ray evidence of bone destruction, although local pain and tenderness were generally evident, other signs of inflammation—such as redness, increased heat, and swelling—were often not very evident.

The relatively 'slight' course of the disease in many patients is reflected by the fact that 29 patients in this series were treated entirely as outpatients with satisfactory results. Among the cases admitted for treatment there were several in whom the immediate cause for admission was not directly related to bone infection—for example measles, severe gastroenteritis with dehydration, pneumonia, and severe anaemia. The main reasons for admitting patients with salmonella osteomyelitis were: (1) extensive bone involvement requiring immobilisation; (2) special surgical procedures, such as open drainage; (3) pathological fractures of weight-bearing bones; (4) initial pronounced toxaemia, with widespread and severely painful limbs; (5) unsatisfactory response to outpatient management. In addition, some patients lived too far away for outpatient treatment.

Radiological findings
The x-ray findings in the early stages of salmonella osteomyelitis are indistinguishable from those due to aseptic infarction. Both the small and the long bones show the same pattern except that generally in the latter only the diaphysis is implicated. It is manifested by early periosteal reaction along the whole length of the shaft of the bone which gradually becomes more pronounced and invests the diaphysis almost as an involucrum, but eventually the original diaphysis becomes partially absorbed and merges with the new periosteal envelope leaving a slightly thickened shaft. The epiphysis because of its richer blood supply usually, but not always, escapes. Also of note at the initial stage of the disease is the presence of linear intracortical fissuring paralleling the shaft adjacent to the medullary involvement. Short intracortical sinus tracts seem to occur between the obvious

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. of cases</th>
<th>Source from which isolated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=18)</td>
<td>Blood</td>
</tr>
<tr>
<td>Staphylococcus pyogenes</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Coliforms</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Staphylococcus saprophyticus</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Micrococi</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Streptococcus group A</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Shigella sp.</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Organisms recovered from blood.

Table 6 Additional pathogens isolated from patients with sickle cell anaemia and salmonella osteomyelitis

Table 7 Patients with multiple pathogens in addition to salmonellae

<table>
<thead>
<tr>
<th>No. of pathogens</th>
<th>No. of cases</th>
<th>Types of organisms from pus</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2</td>
<td>Staphylococcus + coliform + streptococcus group B. Coliforms* + streptococcus + pseudomonas</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>Staphylococcus* + Streptococcus* + coliforms + diphtheroids</td>
</tr>
</tbody>
</table>

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medullary infection and cortical fissure. As the disease continues, there is progressive destruction of the bone which may lead to a 'moth-eaten' appearance extending throughout the shafts of long bones with surrounding periosteal new bone formation of variable extent and density (Fig. 1). In some patients there may be localised areas of extreme rarefaction in the shafts of bones and pathological fractures tend to occur at those sites (Fig. 2). Periarticular bone disease may lead to septic arthritis especially in the hip and shoulder region but generally septic arthritis is not a common complication of salmonella osteomyelitis. Destruction of bones around joints may lead to dislocation or to other permanent deformity of joints. Involvement of epiphyses may lead to their destruction with subsequent impairment of bone growth (Fig. 3).

The extent to which recovery can occur in bones which are grossly diseased is often remarkable and complete restitution of normal architecture (Fig. 4, a and b) can take place in bones which initially appear to be totally destroyed.

As previously noted most patients have multiple bone involvement, and lesions are commonly bilateral and often remarkably symmetrical (Fig. 5). Salmonella osteomyelitis may also occur in sites other than the limbs. Fig. 6 (a and b) shows early and late changes in a patient with spinal involvement.

**Course and prognosis**

Most patients were treated initially with chloramphenicol in a dose of 80 mg/kg per day for 3 to 4 weeks. On this regimen clinical improvement was usually evident within a week and x-ray improvement demonstrated within 2 to 4 weeks.

24 patients recovered completely without any sequelae. 12 patients defaulted before complete resolution of lesions: in 10 of them there was clear evidence of clinical improvement when last seen but 2 patients defaulted while the disease was still active.
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Fig. 3 Impaired growth proximal phalanx R-index finger after osteomyelitis.

Four patients died. Two deaths appeared to be due to overwhelming septicaemia in the acute phase of the disease. In 2 other cases the deaths were reported to us 8 to 18 weeks after the patients had been lost to follow-up. 17 patients recovered with sequelae (Table 8).

Salmonella osteomyelitis in patients without sickle cell anaemia. Table 9 summarises findings in 6 patients who did not have sickle cell anaemia (SS). One patient had sickle cell haemoglobin-C disease (SC) and was clinically indistinguishable from those with sickle cell anaemia and required blood transfusion for severe anaemia. Two patients had HbS in association with HbF. One of these was a neonate and may well have been a case of sickle cell anaemia masked by fetal Hb. This patient had overwhelming infection with Salmonella sp., coliforms, and staphylococcus, and died soon after admission. Osteomyelitis was confined to the right femur. The

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of cases (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Destruction of small bones in hands or feet with resultant shortening of fingers or toes</td>
<td>6</td>
</tr>
<tr>
<td>Shortening or deformity, or both, of long bones</td>
<td></td>
</tr>
<tr>
<td>Femur</td>
<td>3</td>
</tr>
<tr>
<td>Tibia and fibula</td>
<td>1</td>
</tr>
<tr>
<td>Radius and ulna</td>
<td>1</td>
</tr>
<tr>
<td>Flexion deformity of elbow</td>
<td>1</td>
</tr>
<tr>
<td>Other skeletal deformity</td>
<td></td>
</tr>
<tr>
<td>Spine</td>
<td>1</td>
</tr>
<tr>
<td>Sternum</td>
<td>1</td>
</tr>
<tr>
<td>Persistent discharging sinus</td>
<td>2</td>
</tr>
<tr>
<td>Cosmetic, disfiguring scar on leg and arm in a young girl</td>
<td>1</td>
</tr>
</tbody>
</table>

Fig. 4a Extensive disease of humerus, radius, and ulna, 1963.

Fig. 4b Same patient 1967 with normal bones.
Fig. 5 Osteomyelitis affecting both radii. Note bilateral and symmetrical involvement and pathological fractures.

Other patient with HbS and HbF was 18-months old and was an example of hereditary persistence of HbF in heterozygous combination with HbS. He had a septic right shoulder which required surgical drainage, but he defaulted from follow-up before full recovery.

One patient, a 3-year-old girl with sickle cell trait, had osteomyelitis in multiple sites. Salmonella sp. and coliforms were isolated from pus and Staphylococcus pyogenes from blood. She showed a good response to chloramphenicol but required surgical drainage of pus, and recovered completely. Her clinical behaviour was similar to that of our patients with sickle cell anaemia and salmonell osteomyelitis.

One of the patients with entirely normal Hb who...
developed salmonella osteomyelitis was a 10-year-old boy who was initially regarded as a case of sickle cell anaemia both on clinical and x-ray criteria. He had osteomyelitis in multiple sites and the lesions in the legs were bilateral and symmetrical. He ran a chronic course and was slow to respond to treatment, but ultimately he made a complete recovery. Fig. 7 shows x-ray appearances on admission. The remarkable similarity between his bone lesions and those seen in salmonella osteomyelitis in sickle cell anaemia is worthy of note. This patient’s Hb was repeatedly examined and confirmed as HbAA.

The other patient with normal Hb was a girl under one year of age who presented with purulent meningitis (no organism recovered from CSF) and bilateral osteomyelitis of the humeri from which Salmonella sp. was isolated from aspirated pus. She recovered from her meningitis on chloramphenicol and other antibiotics but defaulted before she had recovered fully from the osteomyelitis.

Discussion

A wide variety of salmonellae are endemic in Ibadan17–18 and are a frequent cause of morbidity in childhood. The finding of only 2 patients with normal Hb among 63 patients who had salmonella osteomyelitis, of whom 57 had sickle cell anaemia, reinforces previous observations5 7 8 10 of the peculiar susceptibility of sicklers to this combination, and its rarity in the normal population.

The diagnosis of osteomyelitis in patients with sickle cell anaemia presents peculiar difficulties as bone lesions secondary to infarction present clinical and x-ray features which may be indistinguishable from bone infection.9 10–21 Experience shows that salmonella osteomyelitis should be considered whenever the course of a patient with sickle cell anaemia suggests bone infection. Because of the rarity of salmonella osteomyelitis7 9 it is equally true to assume that its occurrence suggests haemoglobinopathy until the contrary is proved.

Multiple sites of bone involvement reported to be characteristic of salmonella osteomyelitis in patients with sickle cell anaemia11 15–16 occurred with remarkable frequency in this series as well. Also of note is the bilateral and symmetrical nature of the lesions in many cases.

Our findings confirm earlier reports15–16 22 that the disease is particularly common in infancy and early childhood and becomes less so with advancing age. A contrary view is that the age prevalence is more apparent than real because of the poor survival of patients with sickle cell anaemia in the population studied.11 Survival of patients with sickle cell anaemia has improved considerably in our population during the last decade and it can be confirmed that salmonella osteomyelitis is rare after adolescence.

Response to treatment with chloramphenicol was satisfactory in most patients but the drug had to be given for long periods as therapeutic response is generally slow. Notwithstanding prolonged and sometimes repeated use of chloramphenicol, aplastic anaemia or other blood dyscrasias was not observed in any patient.

The reasons for the peculiar susceptibility of patients with sickle cell anaemia to salmonella infections and the mechanisms responsible for

### Table 9 Salmonella osteomyelitis in patients without sickle cell anaemia

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Hb type</th>
<th>Source of salmonella</th>
<th>Other organisms isolated and source</th>
<th>Sites of osteomyelitis</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-10</td>
<td>M</td>
<td>AA</td>
<td>Pus</td>
<td>Nil</td>
<td>Right hand and right radius and ulna both tibiae and fibulae, Both humeri also had purulent meningitis</td>
<td>Chloramphenicol and other antibiotics</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>2-3</td>
<td>F</td>
<td>AA</td>
<td>Pus</td>
<td>Nil</td>
<td>Right humerus and forearm with pathological fractures in 2 sites</td>
<td>Chloramphenicol and other antibiotics</td>
<td>Default before complete recovery</td>
</tr>
<tr>
<td>4-1/12</td>
<td>F</td>
<td>SF</td>
<td>Pus and stool</td>
<td>Staphylococcus from blood; coliforms from pus</td>
<td>Right femur</td>
<td>Chloramphenicol and other antibiotics, IV therapy, aspiration of pus</td>
<td>Died: dehydration, acidosis and septicemia</td>
</tr>
<tr>
<td>5-11/2</td>
<td>M</td>
<td>SF</td>
<td>Pus</td>
<td>Nil</td>
<td>Right shoulder</td>
<td>Chloramphenicol. Surgical drainage</td>
<td>Defaulted</td>
</tr>
<tr>
<td>6-10</td>
<td>M</td>
<td>SC</td>
<td>Pus</td>
<td>Nil</td>
<td>Both hands, left forearm, both femora</td>
<td>Chloramphenicol. Blood transfusions</td>
<td>Recovery with shortening of left femur. Sinus discharge</td>
</tr>
</tbody>
</table>
salmonella osteomyelitis to susceptibility but our (HbAA), note similarity osteomyelitis in sickle cell anaemia.

In young patients with splenomegaly a form of functional asplenia, which is transfusion reversible, may occur with depression of splenic phagocytic function which is permanently lost when auto-splenectomy occurs at a later age.\textsuperscript{23-24} Clearance of infecting organisms from the circulation will be impaired in these circumstances. There is evidence also that sera from patients with sickle cell anaemia may be deficient in opsonising ability for pneumococci\textsuperscript{11 37} and this has been shown to be related to a reduced ability to fix the third component of complement to the bacterial cell surface owing to an abnormality in the alternate pathway of complement activity.\textsuperscript{25} Notwithstanding these subtle cellular immune abnormalities, studies on host reaction to intramuscular salmonella vaccine in sickle cell anaemia have shown normal antibody responses.\textsuperscript{26-27} The immunological deficiencies which have been noted in sickle cell anaemia appear to be age related, with older subjects tending to show more persistent abnormalities. The greater susceptibility of younger rather than older patients to salmonella osteomyelitis suggests that while immunological derangements may contribute to the pathogenesis of the lesions they are unlikely to be a major determinant of the pathology.

Gastrointestinal defences against exogenous enteric pathogens like salmonellae include the level of gastric acidity, integrity of mucosal surfaces, and normal liver function.\textsuperscript{28-29} Gastric acid secretion appears to be normal in sickle cell anaemia\textsuperscript{30} and direct evidence that disease secondary to sickling in the gastrointestinal tract enhances susceptibility to bacteraemia is largely lacking.\textsuperscript{7 38} But, liver function is often impaired in sickle cell anaemia in childhood\textsuperscript{31} and structural damage leading to hepatic fibrosis occurs with increasing age.\textsuperscript{29 32} There is also experimental evidence in animals that morbidity from salmonella infection is enhanced by haemolysis with or without anaemia.\textsuperscript{33}

Taking all available evidence into account the occurrence of salmonella osteomyelitis in sickle cell anaemia seems to reflect both the peculiarities of the lesion in sickle cell anaemia and peculiarities of the \textit{Salmonella} sp.

We suggest that the pathogenesis is as follows:

1. In areas like Ibadan, where sanitation is poor, the population is exposed to frequent gastrointestinal infection with \textit{Salmonella} sp. to which infants and young children are especially susceptible.
2. In sicklers, haemotogenous spread is probably facilitated by devitalisation of gut caused by intravascular sickling. Abdominal 'crises' are common in sickle cell anaemia and presumably involve the same basic mechanism responsible for crises in other anatomical sites. Lack of direct proof of blood spread from devitalised gut is not surprising considering the technical constraints on such investigation and does not invalidate the concept which is consistent with the basic pathology in sickle cell anaemia.

3. The expanded marrow in sickle cell anaemia with its increased metabolic activity, high oxygen demands, and sluggish circulation is especially vulnerable to infarction. The characteristic x-ray changes in bone are consistent with interruption of medullary blood supply with persistence of intact periosteal vascular bed. In infancy and early childhood the collateral circulation to medulla via periosteal vessels is poorly developed and this observation is consistent with the increased susceptibility of the very young to osteomyelitis.

4. Salmonellae characteristically tend to linger in bone marrow long after other sites are sterile, and dormant medullary foci proliferate if tissues are devitalised by infarction or other causes.

5. In sicklers, hepatic dysfunction and persistent haemolysis provide favourable conditions for propagation of Salmonella sp., while immunological derangements may diminish the effectiveness of the host's response to infection.

References


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