Original Article

The Bone Pain Crisis of Sickle Cell Disease and Malaria: Observations from Gujarat, India

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Abstract

Background: Sickle cell disease is a common problem across central India, but its clinical features may differ from that in African populations. There is a need to define the features of sickle cell disease in India, and the current study addresses some features of the bone pain crisis. **Objectives:** The objective of the study was to describe the epidemiology of the bone pain crisis of sickle cell disease in Gujarat and explore the relationship with infection by *Plasmodium vivax*. **Materials and Methods:** This was a prospective review of all admissions in patients with sickle cell disease to a private pediatric institution in Bardoli, Gujarat, in the year 2015. Hemoglobin electrophoresis of all patients was consistent with homozygous sickle cell disease, but family studies indicated that at least seven cases had the severe sickle cell-beta+ thalassemia presumed to be the common IVS1-5G>C mutation. Clinical, hematological, and parasitological features were recorded. **Results:** There were 914 admissions among 654 patients who had between one and seven admissions. The bone pain crisis accounted for 763 (83%) of admissions and increased between July and October coinciding with the monsoon period. Blood smears were examined for malarial parasites in 811 admissions and were positive for *P. vivax* in 73% patients. There was no evidence that *P. vivax* infections varied with the cause of admission or increased during the monsoon period. **Conclusions:** There was a high prevalence of *P. vivax* infection in hospital admissions of sickle cell patients, but the data did not support an etiological role in the bone pain crisis. A trial of malarial prophylaxis might determine its effect on the clinical features and outcome of sickle cell disease.

Keywords: Bone pain crisis, monsoon, *Plasmodium vivax* infection, sickle cell disease

Introduction

The sickle cell (HbS) gene is widespread in central India affecting peoples in eastern Gujarat, Madhya Pradesh, Maharashtra, Chhattisgarh, and Western Odisha with a smaller focus in the north of Tamil Nadu and Kerala.[1,2] The mutation in HbS affects the beta globin gene, but the DNA sequence flanking this gene differs from that in populations of African ancestry, and it is believed to represent a separate occurrence of the HbS mutation, known as the Asian haplotype.[3] The distribution of the HbS gene in India coincides with that of the scheduled tribes, but it is also widespread among the "other backward classes" and the scheduled castes occurring throughout Hindu caste society.[4] Inheritance of the HbS gene from both parents results in homozygous sickle cell (SS) disease which, in Indian peoples, is often associated with alpha thalassemia and high levels of fetal hemoglobin. Both factors inhibit sickling, and there may be important differences in clinical features between Indian patients and those of African ancestry.[5] Splenomegaly persists for longer in Indian patients and persistence of splenic function is suggested by the lack of reports of pneumococcal septicemia in contrast to African forms of the disease. Leg ulceration and priapism appear much less frequent in Indian patients, but the bone pain crisis persists as a major clinical feature in both Indian and African forms of the disease. There is a need for better clinical documentation of the features of Indian disease,[6] and the current paper addresses the bone pain crisis and explores the relationship with infection by *Plasmodium Vivax*.

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Materials and Methods

This was a prospective study of all cases with sickle cell disease will acute illness deemed to be of sufficient severity to warrant hospital admission in 2015. The study was sited in a private pediatric institution with a long history of interest in sickle cell disease located in Bardoli, central Gujarat.

Laboratory methods

The genotype diagnosis was based on a single heavy band in the position of HbS on alkali hemoglobin electrophoresis supported by a positive solubility test. Family studies were not routinely performed, but in 7 (1.2%), a parent had an AA phenotype consistent with sickle cell-beta + thalassemia and the remaining 647 patients were assumed to have SS disease. Although not confirmed by structural studies, the cases of sickle cell-beta + thalassemia were likely to have the IVS1-5G>C mutation common in this population[7] and associated with very low levels of HbA; the genotypes have been combined for the present report. A venipuncture sample was collected in ethylenediaminetetraacetic acid (EDTA) for daily complete blood counts or more often if a fall in hemoglobin is suspected. Red cell indices were measured electronically (KX 21 hematology analyzer, Sysmex, Japan). Thin and thick blood smears were made directly from a blood drop from the syringe before the rest of the sample was collected into EDTA, stained by Giemsa stain and examined for malaria parasites under a high power oil immersion lens by the same observer (B.P.).

Clinical definitions

The bone pain crisis was based on the typical distribution and characteristics of bone pain without any history of trauma or other pathology. The clinical diagnosis of malaria was based on fever, rigors, and nonspecific symptoms and was easily overlooked in conjunction with the bone pain crisis. The acute chest syndrome was based on clinical signs in the chest and was not always confirmed radiologically.

Results

There were 914 admissions in 654 patients (single admissions in 490, two admissions in 116, three in 34, four in 13, five in 5, six in 1, and seven admissions in one). Ages ranged from 1 to 59 years (mean 18 years and median 17 years), and among the 490 single admissions, there were 297 (60.6%) males. All patients except three were of the scheduled castes and admissions were seen by a single physician who allocated the clinical diagnosis. Mean and median duration of admission was 4.3 days (range 0–37 days). Hemoglobin levels were available in 772 admissions and did not differ between those negative for vivax (n = 208, mean 8.38, median 8.70, and range 2.4–12.4) and those with positive films (n = 564, mean 8.43, median 8.70, and range 2.1–13.5 g/dl).

Admission diagnosis

Bone pain crises accounted for 763 (83%) admissions (bone pain alone, 644 and bone pain associated with other features, 119) and diagnoses are summarized in Table 1.

Secular changes in admissions

Admissions peaked from July to October, most of this excess being attributed to bone pain crisis alone or with associated clinical features [Figure 1].

Secular changes in malarial parasite detection

Of the 914 admissions, blood films were examined in 811 (89%) admissions, were negative in 218 admissions and positive in 593 (73%) admissions. Parasite detection by month varied from 56% to 88% but did not differ during the 4 months at the peak of the monsoon (72%, positive) from the other 8 months (73%, positive). Furthermore, the proportion

Table 1: Clinical diagnoses in admitted patients

Diagnosis	Number
Bone pain alone	644
Bone pain with other features	119
Malaria	79
ACS	8
Fever	7
Pregnancy	3
UTI	3
Gastroenteritis	3
Bronchitis	3
Others	13
Diagnoses without bone pain	151
ACS, bronchitis	24
Gastroenteritis	13
Anemia	5
ASS	15
Fever	11
Hepatitis	4
Malaria	55
Septicemia	2
URTI	11
UTI	4
Others	7
Total	914

UTI: Urinary tract infection, ACS: Acute chest syndrome, URTI: Upper respiratory tract infection, ASS: Acute splenic sequestration

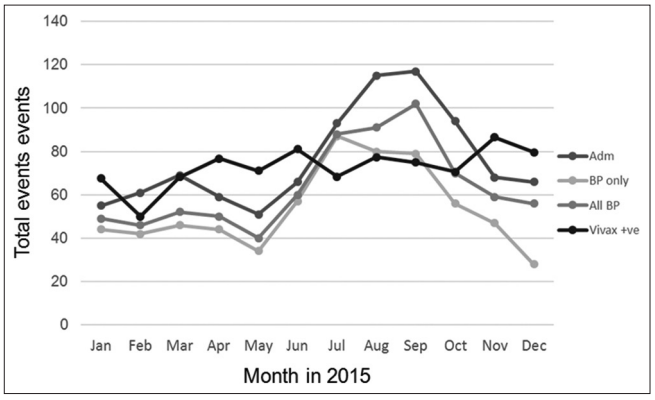

Figure 1: Monthly distribution of admissions (Adm) for bone pain only (BP only), bone pain with other features (All BP) and percentage positive for *Plasmodium Vivax* (Vivax + ve)

of positive samples for *P. vivax* did not differ between causes of admission and were not more common in bone pain crises. All parasites had the characteristics of *P. vivax* and no cases of *P* falciparum were detected.

Discussion

P. vivax is the dominant malarial species throughout India[8,9] although *Plasmodium falciparum* occurs in some forested areas of Odisha, this pattern may be changing.[10] Diagnosis of infection may be performed by rapid diagnosis tests detecting antigen or polymerase chain reaction detecting plasmodial DNA, but the gold standard is still microscopic examination by a skilled observer. Data in the current study are based on microscopy with the same experienced observer who found parasites in 73% of blood films. Interpretation of this finding is hampered by the lack of suitable control data in the general population or in steady state patients with SS disease. Attempts to use admission data in patients without bone pain crises were limited by the very small number of patients who did not have either bone pain crises or a clinical diagnosis of malaria.

The bone pain crisis of sickle cell disease is usually attributable to bone marrow necrosis which is most prominent in the juxta-articular areas of the long bones, spine, ribs, and sternum. It is episodic in nature, and most events have clear precipitating factors such as skin cooling, infection, dehydration, and stress. The relationship with skin cooling although well recognized[11,12] is not yet clearly understood.[13] The striking increase in bone pain crisis between July and October in the current study coinciding with the monsoon is consistent with these observations. In the current study, there was no evidence that *P. vivax* infection contributed to the increased bone pain crisis during the monsoon period from July to October. Furthermore, although control figures are not available, the presence of *P. vivax* parasites in 73% admissions draws attention to the potential importance of this infection in patients with sickle cell disease.

Sickle cell disease in India is a major public health problem with its dominance in rural areas with limited medical resources. Although much is known about the clinical features and management of sickle cell disease in peoples of African origin, Indian sickle cell disease remains to be properly documented, and with this lack of knowledge, physicians in India may have to use models of care derived for African disease which may be inappropriate and wasteful of scarce resources. Although some clinical differences are clear, the bone pain crisis remains a major feature of both African and Indian disease, and the current study is consistent with skin cooling being an important precipitating factor. Patient education on the importance of avoiding skin cooling and dressing warmly, especially, during the monsoon period may prevent bone pain crises. Since both *P. vivax* infection and sickle cell disease are common in central India, it would be interesting to study the effect of malarial prophylaxis in this population.

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Conflicts of interest

There are no conflicts of interest.

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