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Eosinopenia as a marker of infection in patients with sickle cell anaemia: A preliminary report

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ABSTRACT: Neutrophilia is a useful marker of infection in many clinical settings but it is of limited value in SCA patients in whom neutrophilia with left shift is common even in steady state in the absence of infection. We hypothesize that eosinopenia may be a more reliable marker of infection in SCA patients. Retrospective analysis of the neutrophil and eosinophil counts of SCA patients in steady state with microbiologically confirmed infections in comparison to that of SCA patients without infection was conducted. The sensitivity and specificity of neutrophilia and eosinopenia as markers of infection in SCA patients were determined and compared. Neutrophilia and eosinopenia had similar sensitivity values of 100%. However, eosinopenia had a specificity of 93.3% that was significantly higher than the specificity of 80% for neutrophilia ($p<0.05$). Therefore, eosinopenia has the potential of being a more reliable marker of infection in SCA. However, there is the need to establish the significance of this preliminary report by larger multi-centre studies.

Keywords: Sickle cell anaemia; Eosinopenia; Neutrophilia.

Introduction

Sickle cell anaemia (SCA) is the homozygous state for the sickle cell gene. The clinical manifestations of SCA are caused by vascular occlusions resulting from polymerization of deoxygenated Hb S and sickling of erythrocytes[1]. The clinical course of SCA is characterized by periods of the steady state interspersed by painful periods of vaso-occlusive crisis[2]. Patients with SCA are susceptible to bacterial infections due to splenic atrophy, impaired phagocytosis and defect in the alternate complement pathway[3]. Infection is an important trigger of vaso-occlusive crisis in patients with SCA[2]. Hence, early identification and treatment of infections in SCA patients is essential in order to prevent progression to vaso-occlusive crisis[2]. Neutrophilia is a useful marker of infection in many clinical settings but it is of limited value in SCA patients in whom neutrophilia with left shift is common even in steady state in the absence of infection[4]. Therefore, the finding of neutrophilia in SCA patients does not necessarily indicate the presence of infection.

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Recent studies have rekindled the usefulness of eosinopenia as a reliable marker of acute infection[5,6]. Eosinopenia was found to be a more sensitive diagnostic marker than C-reactive protein in patients with acute infections[5,6]. Despite the limitations of neutrophilia as a marker of infection in SCA patients, we are not aware of any studies that evaluated the potential usefulness of eosinopenia as a more reliable marker of infection in such patients. We hypothesize that eosinopenia would be a more reliable marker of infection than neutrophilia in patients with SCA. In this paper we compared the levels of specificity and sensitivity of neutrophilia and eosinopenia as markers of infection in patients with SCA in Kano, northwest Nigeria.

Materials and Methods

This is a retrospective study conducted by a review of case notes of patients seen between January and December 2008 in the adult Haematology clinic of Aminu Kano Teaching Hospital, Kano, Nigeria. All patients studied were within the ages of 18-35 years and the diagnoses of SCA were established by positive sickling test and haemoglobin electrophoresis at a pH of 8.6 on cellulose acetate paper[7].

In accordance with routine departmental procedures, all SCA patients seen at the clinic or emergency room were investigated for infections if they present with vaso-occlusive crisis or if they present in steady state but had clinical features suggestive of infection.

In a retrospective analysis, the neutrophil and eosinophil counts of 30 randomly selected SCA patients in steady state with microbiologically confirmed infections were evaluated and compared with that of equal number (30) of age and sex matched SCA patients in steady state without infection to serve as controls. The pattern of clinical presentations and microbiological agents responsible for infections in the infected patients studied were documented. Celltac Alpha (MEK 6400) blood analyzer was used to determine the blood cell parameters including total leucocyte count and differentials for the patients studied, and the number of cases with neutrophilia and eosinopenia were identified and enumerated. Neutrophilia and eosinopenia were taken as neutrophil count greater than $4.5x10^9$/l and eosinophil count less than $0.03x10^9$/l respectively[8]. The level of sensitivity and specificity of neutrophilia and eosinopenia as markers of infection were calculated based on standard statistical formulae: Sensitivity = [True Positives / (True Positives + False Negatives)] x100 and Specificity = [True Negatives / (False Positives + True Negatives)] x100.

Statistical calculations for mean and standard deviation were carried out using computer soft ware SPSS version 11.0. Student's t test was used compare mean values while the χ^2 test was used to compare test specificity and sensitivity, and a p-value of less than 0.05 was taken as significant.

Results

The infective agents and clinical presentations among the infected SCA patients are shown on Tables 1 and 2. The predominant causative agents of infection were Streptococcus pneumoniae, Salmonella species, Plasmodium falciparum and Escherichia coli and the common forms of clinical presentation were respiratory and gastro-intestinal tract infections, malaria and sepsis.

The variations in neutrophil and eosinophil counts among SCA patients with and without infection are shown on Table 3, which revealed statistically significant higher mean neutrophil and lower mean eosinophil counts among patients with infection in comparison to those without infection. The pattern of neutrophilia and eosinopenia among SCA with and without infection is show on Table 4. Patients with infections had neutrophilia in 30 cases (true positives) and no neutrophilia in 0 cases (false negatives). However, patients without infection had neutrophilia in 6 cases (false positives) and no neutrophilia in 24 cases (true negatives). Hence, neutrophilia as a marker of infection among SCA patients had sensitivity and specificity levels of 100% and 80% respectively. Considering the eosinophil count, patients with infections had eosinopenia in 30 cases (true positives) and no eosinopenia in 0 cases (false negatives). However, patients without infection had eosinopenia in 2 cases (false positives) and no eosinopenia in 28 cases (true negatives). Therefore, eosinopenia as a marker of infection among SCA patients had sensitivity and

specificity of 100 and 93.3% respectively. This data showed neutrophilia and eosinopenia had similar sensitivity values of 100%. However, eosinopenia had a specificity of 93.3% that was significantly higher the specificity of 80% for neutrophilia ($p<0.05$).

Table 1: Infective Agents in SCA Patients with Infections

INFECTIVE AGENTS	NUMBER OF PATIENTS INFECTED (%)
Streptococcus pneumoniae	8 (26.4)
Salmonella species	8 (26.4)
Plasmodium falciparum	6 (20)
Escherichia coli	4 (13.3)
Staphylococcus aureus	3 (10)
Haemophilus influenzae	2 (6.7)
Shigella species	2 (6.7)

Table 2: Clinical Pattern of Infections among SCA Patients

CLINICAL SETTING	NUMBER OF PATIENTS AFFECTED (%)
Chest Infection	8 (26.4)
Enteritis/colitis	8 (26.4)
Malaria	6 (20)
Pharyngitis/Tonsilitis	5 (16.7)
Septicemia	5 (16.7)
Urinary Tract Infection	3 (10)
Infected Leg Ulcer/Osteomyelitis	2 (2.6)
Subcutaneous Abscess/Cellulitis	1 (1.3)

Table 3: Neutrophil and Eosinophil Counts of SCA Patients with and without Infection

PATIENT GROUP	NEUTROPHIL COUNT ($x10^9$/l) Mean± SD	EOSINOPHIL COUNT ($x10^9$/l) Mean± SD
Patients in steady state with Infection (N=30)	11.3 ± 3	0.025 ± 0.01
Patients in steady state without Infection (N=30)	9.4 ± 2.3	0.2 ± 0.08
P value	$p<0.05$	$p<0.05$

Table 4: Neutrophilia and Eosinopenia among SCA Patients with and without Infection

PATIENT GROUP	No. OF PATIENTS WITH NEUTRPHILIA	No. OF PATIENTS WITHOUT NEUTROPHILIA	No. OF PATIENTS WITH EOSINOPENIA	No. OF PATIENTS WITHOUT EOSINOPENIA
Patients with Infection (N=30)	30	0	30	0
Patients without Infection (N=30)	6	24	2	28

Discussion

The pattern of infections among our patients revealed the predominance of encapsulated bacteria and plasmodium falciparum while the main clinical presentations included respiratory and gastro-intestinal infections, septicemias and malaria. This pattern is in keeping with defective splenic function resulting from infarctive atrophy, which makes patients with SCA to be particularly at risk of infection from encapsulated bacteria and malaria parasites[3,9].

The finding of a high mean neutrophil count in SCA patients with infection was consistent with appropriate neutrophilic response to infections[10]. However, the finding of a high mean neutrophil count in SCA patients without infection was interpreted to be due to redistribution of neutrophils from marginal to circulating pool as part of the impaired neutrophil kinetics in patients with SCA[4]. Other factors that could contribute to neutrophilia in the absence of infection in patients with SCA include asplenia, haemolysis and inflammatory response to tissue infarcts[10]. These factors could also explain occurrence of neutrophilia in all infected cases including those due to salmonella and malaria species, which are infections that are not regularly associated with neutrophilia[11,12]. The finding of a significantly lower mean eosinophil count in SCA patients with infection as compared to those without infection was consistent with the systemic inflammatory response associated with acute infections[5,6]. Eosinopenia of acute infection was thought to

be mediated by adrenal corticosteroids, epinephrine and chemotactic factors that caused rapid peripheral sequestration of eosinophils and migration of eosinophils into inflammatory sites[5,6].

This study revealed that both neutrophilia and eosinopenia had comparable and excellent sensitivity values as markers of infection in patients with SCA. However, eosinopenia had a significantly superior specificity over neutrophilia as a marker of infection among patients with SCA. The relatively low level of specificity of neutrophilia as a marker of infection could be attributed to impaired neutrophil kinetics associated with SCA[4]. Consequently, many patients presented with neutrophilia in the absence of infection, resulting in high number of false positive neutrophilia and a significant reduction in the level of specificity. On the other hand, eosinopenia was associated with relatively few false positives with a resultant high specificity that was significantly higher than that of neutrophilia.

Conclusion

In comparison to neutrophilia, eosinopenia had similar sensitivity and higher specificity as a marker of infection in patients with SCA. Therefore, eosinopenia has the potential of being a more reliable marker of infection in SCA. However, there is the need to establish the significance of this preliminary report by larger multi-centre studies.

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