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Synergistic Protective Effect of Sickle Cell Trait and Blood Group–O on the Risk of Endemic Burkitt’s Lymphoma

Sagir G. Ahmed1, Umma A. Ibrahim2, Modu B. Kagu3

1Department of Haematology, Aminu Kano Teaching Hospital, Kano State, Nigeria
2Department of Paediatrics, Aminu Kano Teaching Hospital, Kano State, Nigeria
3Department of Haematology, University of Maiduguri Teaching Hospital, Maiduguri Borno State, Nigeria

Abstract

Background: Previous research strongly suggest that malaria is an important factor in the pathogenesis of endemic Burkitt’s lymphoma (eBL). Therefore, genetic factors such as sickle cell trait (SCT) and blood group–O that offer protection against severe malaria would be expected to reduce the risks of eBL. However, previous reports on the protective roles of SCT and blood group–O against the risks of eBL were inconclusive. Hence, the need for further studies on the protective roles of SCT and blood group–O separately, and also to investigate whether or not the combined anti–severe malaria protective roles of SCT and blood group–O have synergistic effects in reducing the risks of eBL. We therefore hypothesize that SCT and blood group–O are independently associated with modest reduction in the risk of eBL. However, when SCT with blood group–O was assessed for the risk factor for eBL, we obtained an Odds ratio of 0.23, which was significantly lower than the OR values for SCT (0.52) and blood group–O (0.49) separately. These figures suggest that coinheritance of SCT and blood group–O offers greater reduction in the risk of eBL than that provided by either SCT or blood group–O separately. The greater protection against eBL provided by the coinheritance of SCT and blood group–O is interpreted to be the resultant synergistic effect of the combined anti–malarial attributes of SCT and blood group–O.

Patients and Methods: We conducted a retrospective logistic regression analysis of the frequencies of Hb phenotypes and ABO blood groups among patients with eBL in order to determine the separate and synergistic protective effects of SCT and blood group–O on the risk of eBL in Nigeria where eBL is among the most common malignant childhood cancers.

Results: The Odd Ratios (OR) for the risk of eBL were 0.52 for ‘SCT irrespective of ABO blood group’; 0.49 for ‘blood group–O irrespective of Hb phenotype’; and 0.23 for ‘SCT with blood group–O’.

Discussion: These values suggest that both SCT and blood group–O are independently associated with modest reduction in the risk of eBL. However, when SCT with blood group–O was assessed for the risk factor for eBL, we obtained an Odds ratio of 0.23, which was significantly lower than the OR values for SCT (0.52) and blood group–O (0.49) separately. These figures suggest that coinheritance of SCT and blood group–O offers greater reduction in the risk of eBL than that provided by either SCT or blood group–O separately. The greater protection against eBL provided by the coinheritance of SCT and blood group–O is interpreted to be the resultant synergistic effect of the combined anti–malarial attributes of SCT and blood group–O.

Conclusion: These findings suggest that the combined anti–malarial protective roles of SCT and blood group–O have synergistic effects in reducing the risks of eBL. This study has provided further evidence on the association between malaria–protective genetic polymorphisms and eBL, which is consistent with the aetiologic role of malaria in the pathogenesis of the tumour. Hence, the need for malaria endemic countries to intensify malaria control programs in order to curtail the incidence of eBL.

Keywords: Endemic Burkitt’s Lymphoma, Risk Factors, Sickle Cell Trait, ABO Blood Group

Introduction

The African endemic Burkitt’s lymphoma (eBL) is a clinically aggressive high grade tumor, which is associated with low altitude and high annual temperatures, rainfall and humidity1). These geographical and climatic factors favourably support reproduction and survival of the Anopheles mosquito vector and ensures high transmission rate of P falciparum malaria 1). Hence, even in malaria endemic countries the spatial distribution and risk of eBL...

was found to strongly correlate with regional intensity of malaria transmission (2) and concurrent infections with multiple P falciparum genotypes (3). Moreover, eBL is also associated with low socioeconomic status and poverty (4), both of which are common in tropical malaria endemic countries. High prevalence of Epstein–Barr virus (EBV) infection acts in concert with malaria in the pathogenesis of the tumor. Therefore, co-infection with P falciparum and EBV is a major risk factor for eBL, which is one of the most prevalent paediatric cancers in the malaria holoendemic zones of equatorial Africa (5). Recurrent and chronic immune stimulation by P falciparum malaria is thought to cause immunosuppression by depressing EBV-specific T-cell immunity (5), which causes a deregulated proliferation of EBV infected B cells (6). Furthermore, it has been demonstrated that haemoglobin, the pigment produced by the metabolic effect of P falciparum on haemoglobin, was partly responsible for inducing a deregulated expression of the DNA-mutating and double-strand-breaking enzyme referred to as ‘activation-induced cytidine deaminase (AID)’ in the infected B cells (6). Consequently, the resultant deregulated B cells develop genomic instability and have greater risks of rearrangement of the c—myc oncogene, which is subsequently activated by translocation to the proximity of a high transcription gene such as the IgH gene: t(8;14) or the kappa IgL gene: t(2;8) or the lambda IgL gene: t(8;22)(1,7). Rearrangement and activation of c—myc oncogene together with EBV—induced perturbation of apoptosis within infected B cells cause clonal malignant transformation and eventually culminate in the development of eBL (6,7,8). Epidemiologically, eBL is the predominant type of BL in Africa wherein it mainly affects children with a male to female ratio of about 2:1 (1). Nevertheless, sporadic BL, which is not associated with any specific geographic zone, and the HIV—associated BL also occur in both children and adults in Africa but at relatively lower frequencies in comparison to eBL (1). This concise review of the literature strongly suggest that malaria is an important cofactor in the pathogenesis of eBL. Therefore, genetic factors that offer protection against recurrent severe malaria would be expected to reduce the risk of eBL among children living in malaria endemic regions of the world.

Sickle cell trait (SCT) is the best—characterized genetic polymorphism known to protect against falciparum malaria (9). SCT is thought to protect against severe malaria through a number of biochemical and immune—mediated mechanisms, which include reduced red cell invasion by parasite, parasite—induced red cell sickling, low intra—erythrocytic parasite proliferation, reduced rosetting and cytoadherence of parasitized red cells, enhanced phagocytosis of parasitized red cells, as well as enhanced cellular and humoral immune response against the parasite(9). Nevertheless, contradictory findings have been reported from Africa with regards the risk of developing eBL in persons with SCT. On the one hand, some studies had shown that children with eBL had lower frequencies of SCT in comparison with controls (10,11,12), while on the other hand some studies had found that the frequencies of SCT among patients eBL did not differ from healthy controls(13,14). Hence, the literature review suggests a continuing controversy regarding the protective role of SCT against eBL.

Another genetic polymorphism that is known to significantly influence the severity of falciparum malaria is the ABO blood group. The severity of malaria infection is significantly determined by ABO blood groups with relative protection afforded by blood group—O (15) as opposed to the non—O blood groups (16) that carry higher risks of developing severe malaria. These disparities are related to reduced rosetting by group—O red cells as opposed to enhanced rosetting by non—O red cells in the course of malaria infection (15). Moreover, in comparison to non—O blood groups, blood group—O was associated higher levels of acquired anti—malarial humoral immune response (17) and greater phagocytosis of parasitized red cells (18), both of which provide further protection against severe malaria. On the basis of these variations in relative protection against severe malaria, it would be expected that blood group—O would be associated with lower risk of eBL in comparison with non—O blood groups. However, research on the relationship between ABO blood groups and the risk of eBL is very scanty and probably consists of only two studies in the literature, one of which found a protective association between blood group—O and eBL(19), while the other did not find any significant association between the risk of eBL and ABO blood groups (15). Thus, the literature regarding the effect of ABO blood groups on the risk of eBL is scanty and inconclusive.

These conflicting reports on the protective roles of SCT and blood group—O against the risk of eBL call for further research. So there is the need for further studies on the protective roles of SCT and blood group—O separately, and also to investigate whether or not the combined anti—malarial protective roles of SCT and blood group—O have synergistic effects in reducing the risk of eBL. We therefore hypothesize that SCT and blood group—O are independently associated with reduced risks of eBL, and the co—inheritance of both factors (SCT and group—O) would provide greater protection against eBL. If our hypothesis is correct, children who inherited both SCT and blood group—O would have lower risk of eBL than their counterparts who inherited SCT or blood group—O separately. To the best of our knowledge, the possible synergistic relationship between SCT and blood group—O with regards to the risk of eBL has not been previously
studied. Hence, we conducted a retrospective analysis of the frequencies of Hb phenotypes and ABO blood groups among patients with eBL in order to determine the separate and possible synergistic protective effects of SCT and blood group-O on the risk of eBL in Nigeria where eBL is among the most common malignant childhood cancers (20).

Materials and Methods

Study Description

This is a combined retrospective and prospective case–control study. The study retrospectively evaluated the Hb phenotypes and ABO blood groups of eBL patients who were diagnosed and evaluated at different time periods between 1996–2015 in four northern Nigerian tertiary hospitals, including University of Maiduguri Teaching Hospital, Maiduguri, North East Nigeria (1996–2007); State Specialist Hospital, Maiduguri, North East Nigeria (2001–2007); Federal Medical Centre Birnin Kudu, North West Nigeria (2004–2005); and Rasheed Shekoni Specialist Hospital, Dutse, North West Nigeria (2011–2015). Equal number of age and sex matched healthy control subjects were prospectively recruited from the local populations.

Patients Diagnosis and Selection

All patients studied in this report were confirmed cases of eBL that were diagnosed on the basis of the presence of classical morphological features as revealed by needle aspiration cytology (lymphoblasts with cytoplasmic basophilia and vacuolations) or tissue histology (lymphoblasts admixed with macrophages in a starry sky pattern) of clinically suspected tumors (1). However, due to local limitations of diagnostic facilities, immunophenotyping and cytogenetic analyses were not performed on these patients. Patients with clinical features of eBL but lacked cytological or histological confirmations were excluded. Patients that lacked Hb phenotypes and/or ABO blood groups in their medical records were also excluded. Moreover, patients with comorbid HIV infections were also excluded.

Ethics, Data Retrieval and Generation

This study was conducted with the approval of local institutional ethics committees. Demographic and clinical laboratory data including age, sex, haemoglobin phenotypes and ABO blood groups as determined at the time of diagnosis and laboratory investigations were retrospectively retrieved from the clinical records of patients, while similar parameters were prospectively determined in the control group with due consents of the subjects or parents/guardians.

Determination of Haemoglobin Phenotypes and ABO Blood Groups

The Hb phenotypes of subjects were determined by haemoglobin electrophoresis at a pH of 8.6 on cellulose acetate paper, sickling test and haemoglobin quantitation(21). On the basis of the electrophoretic patterns, the patients phenotypes were categorized as normal (Hb AA) or SCT (Hb AS) (21). The ABO blood groups of patients were determined manually by using monoclonal anti–A and anti–B against the subjects red cells suspended in saline tubes at room temperature and read for agglutination after 15 minutes of incubation in accordance with standard procedures (22). On the basis of the pattern of agglutination, subjects were categorized as having blood group O, A, B or AB (22).

Statistical Analysis

The data accrued from the four centers were merged and collated. Values of evaluated parameters were compared between subject categories using the X² test with a p-value of less than 0.05 was considered as significant. Risk of eBL were determined by Odds ratios (OR) for three risk categories: (a) SCT irrespective of ABO blood group, (b) blood group–O irrespective of Hb phenotype, and (c) SCT with blood group–O as follows:

(a) The OR of eBL for ‘SCT irrespective of ABO blood group’ was determined by logistic regression analysis after adjusting for differences in age, sex and frequencies of ABO blood groups between patients and controls, using the following inputs: (No. of patients with SCT irrespective of ABO blood group ÷ No. of patients with Hb AA irrespective of ABO blood group) / (No. of controls with SCT irrespective of ABO blood group ÷ No. of controls with Hb AA irrespective of ABO blood group).

(b) The OR of eBL for ‘blood group–O irrespective of Hb phenotype’ was determined by logistic regression analysis after adjusting for differences in age and sex between patients and controls, using the following inputs: (No. of patients with blood group–O irrespective of Hb phenotype ÷ No. of patients with non–O blood group irrespective of Hb Phenotype) / (No. of controls with blood group–O irrespective of Hb phenotype ÷ No. of controls with non–O blood group irrespective of Hb phenotype).

(c) The OR of eBL for ‘SCT with blood group–O’ was determined by logistic regression analysis after adjusting for differences in age and sex between patients and controls, using the following inputs: (No. of patients with blood group–O and SCT ÷ No. of patients with non–O blood group and Hb AA) / (Number of controls with blood group–O and SCT ÷ Number of controls with non–O blood group and Hb AA).
Values of OR were considered to be statistically significant for risk reduction only if the upper limit of 95% confidence interval (CI95%) was less than 1.0 with a P value of <0.05. Statistical analyses were performed using computer software SPSS version 15.0 (Chicago, Illinois, USA).

Results

A total of 279 patients with eBL were studied and the distribution of their ages and sexes are shown in Table 1. In comparison with controls, eBL patients had significantly lower frequency of SCT (20.8% vs. 33.7%; p<0.05) and lower frequency of blood group–O (35.5% vs. 52.7%; p<0.05) with a corresponding higher frequency of HbAA (79.2% vs. 66.3%; p<0.01) and higher frequency of non–O blood groups (64.5% vs. 47.3%; p<0.02) as shown in Table 2. The ORs for the risk of eBL were 0.52 for ‘SCT irrespective of ABO blood group’; 0.49 for ‘blood group–O irrespective of Hb phenotype’; and 0.23 for ‘SCT with blood group–O’ as shown in Table 3.

Discussion

Endemic BL is among the most common childhood cancers in Nigeria (20). However, the national incidence of the tumor in Nigeria appears to be gradually declining as a result of improvement in living conditions and better control of malaria (23). Moreover, our data were entirely collected from tertiary hospitals, which are virtually inaccessible to the rural dwellers who have greater exposure to poverty, malnutrition and malaria, all of which are important risk factors for eBL (2,4). The aforementioned reasons are responsible for the relatively small number of cases captured in this study despite a fairly extended period of multicentre data retrieval. However, the demographic profiles of the patients captured in this study revealed the classical pattern for eBL, which is characterized by preponderance of young children between the ages of 4 and 12 years, predominance of male sex and low proportion of adults patients(4).

The pattern of frequencies of ABO blood groups and Hb phenotypes among the control subjects in this study are comparable with the pattern previously documented in the local populations in Nigeria (24–26). However, in comparison to the normal control subjects, patients with eBL had significantly lower frequencies of SCT and blood group–O. These findings imply that eBL patients were genetically less protected from recurrent severe malaria because they had lower frequencies of SCT and blood group–O, both of which are known to confer protection against severe malaria (9,15,17). Moreover, the eBL patients have higher frequencies of Hb AA and non–O blood groups that are known to increase susceptibility to severe malaria(18). These variations in frequencies of Hb phenotypes and ABO blood groups among patients and controls gave comparatively similar Odds ratios of 0.52 and 0.49 for group–O irrespective of Hb phenotype’; and 0.23 for ‘SCT with blood group–O’ as shown in Table 3.
the risk of eBL with respect to SCT and blood group-O respectively. These values suggest that both SCT and blood group-O are independently associated with modest reduction in the risk of eBL. However, when SCT with blood group-O were jointly assessed for the risk factor for eBL, we obtained an Odds ratio of 0.23, which was significantly lower than the OR values for SCT (0.52) and blood group-O (0.49) separately. These figures suggest that coinheritance of SCT and blood group-O offers greater reduction in the risk of eBL than that provided by either SCT or blood group-O separately. The greater protection against eBL provided by the coinheritance of SCT and blood group-O is interpreted to be the resultant effect of the combined anti-malarial attributes of SCT and blood group-O [15,17]. These findings suggest that the combined anti-malarial protective roles of SCT and blood group-O have synergistic effect in reducing the risk of eBL. The results of this study have therefore substantially confirmed our research hypothesis and demonstrated that SCT and blood group-O are independently and synergistically protective against eBL, as opposed to other studies that did not find significant associations between the risk of eBL and SCT or ABO blood groups [11].

The findings of this study have provided further evidence on the association between malaria-protective genetic polymorphisms and eBL, which is consistent with the aetiologic role of malaria in the pathogenesis of the tumour, hence malaria control program can potentially control the incidence of eBL. The positive impact of malaria control on the incidence of eBL has previously been demonstrated by a short-term study in which the administration of chloroquine prophylaxis against malaria to children in Tanzania was associated with a reduction in the incidence of eBL, and a return to its previous incidence after cessation of the clinical study [27]. These facts underscore the need for malaria endemic countries to intensify efforts towards implementing the United Nation’s Sustainable Development Goals project [28], which among other goals encompasses eradication and control of poverty and malaria, both of which are epidemiologically associated with eBL [6]. However, apart from vector control, personal protection, chemotherapy and chemoprophylaxis, a truly comprehensive control strategy against malaria must include mass vaccination. A recent report of phase-III clinical trial suggest that the RTS,S/AS01 vaccine prevented a substantial number of cases of clinical malaria over a 3–4 year period in young infants and children when the vaccine was administered with or without a booster dose [29]. Nonetheless, the efficacy of the vaccine was enhanced by the administration of a booster dose in both age categories [29]. Hence, the vaccine has the potential to make a substantial contribution to malaria control when used in combination with other effective control measures in areas of high transmission [29]. It is therefore hopeful that widespread use of the vaccine in high risk areas and populations will certainly control malaria and curtail the scorch of eBL.

Conclusion

This study suggest that both SCT and blood group-O are independently associated with modest reduction in the risk of eBL. However, coinheritance of SCT and blood group-O offers greater reduction in the risk of eBL than that provided by either SCT or blood group-O separately. The greater protection against eBL provided by coinheritance of SCT and blood group-O is interpreted to be the resultant effect of the combined anti-malarial attributes of SCT and blood group-O. These findings suggest that the combined anti-malarial protective roles of SCT and blood group-O have synergistic effects in reducing the risk of eBL. This study has provided further evidence on the association between malaria-protective genetic polymorphisms and eBL, which is consistent with the aetiologic role of malaria in the pathogenesis of the tumour. Hence, the need for malaria endemic countries to intensify malaria control programs in order to curtail the incidence of eBL.

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