AFRICAN JOURNAL OF MEDICINE and medical sciences

VOLUME 31, NO. 4 DECEMBER, 2002

ISSN 1116—4077

Afr. J. Med. med. Sci. (2002) 31, 341-343

Certain red cell genetic factors and prevalence of chloroquine – induced pruritus

OG Ademowo[1] and O Sodeinde[2]
[1]Postgraduate Institute for Medical and Research and Training and [2]Department of Paediatrics, College of Medicine, University of Ibadan, Ibadan, Nigeria.

Summary
The hypothesis that chloroquine-induced pruritus (CIP) may be determined by certain genetic factors was tested by investigating the epidemiology of CIP with respect to certain genetic red cell markers namely, haemoglobin genotype , glucose-6-phosphate dehydrogenase (G6PD) deficiency and the ABO blood groups. Three hundred consecutive patients treated for malaria with chloroquine at the University College Hospital, Ibadan, Nigeria were recruited into the study. They were observed over 3 days for presence of CIP. ABO blood groups, G6PD and Hb genotypes were determined appropriately for each patient. One hundred and twenty four (41.3%) of the patients responded positively to CIP. There was a reduced frequency of the sickle cell trait (HbAS) among itchers relative to non-itchers. This suggests that the trait may be protective against CIP. G6PD deficiency was also found to be relatively more common among itchers than non-itchers. This indicates that G6PD deficiency may increase susceptibility to CIP. There was however no difference in the distribution of itchers among the different ABO blood groups. It was concluded that CIP may be associated with certain genetic red cell markers particularly Hb and G6PD types which are known malaria markers but not ABO blood groups.

Keywords: *Haemoglobin, G6PD, ABO blood groups, chloroquine pruritus*

Résumé
L'hypothése que les prurites indiute par la chloroquine (PIC) pent être determiner par certains facteurs genètiques etaient examinés en investigant l'épidemiologie de la PIC par rapport a certains markeurs genetiques de globule rouge qui sont les suivants; le genotype d'hèmoglobine, la déficience du glucose -6-phosphate déhydrogenase (DCI6P) et les group sanguins A.B.O. Trois cent patient paludiens consécutivement recruites etaient traités du paludisme a la chloroquine an center Hospitalier universitaire (UCH), Ibadan, Nigeria. Le genotype, le group sangrin, la DG6P,et les genotype d'Hb evaient ete determines chez cheque patient I/S etaient suivi pendant plus de trios jours pour la PIC. Cest Kingt quatre patients (41.3%) avaient des demangesons (PIC positive). La frequence des drepanosit (HbAS) etait reduite chez ceux qui avaient des demangeaisons par rapport au ceux qui bi en avaient pas. Ceci suggere que le trait pent etre protecteur contre les demangeaisons induite par le chloroquine. La carence en DG6P etait relativement commun chez ceux qui avaient des démangeaisons par rapport a ceux qui avaient par; indiquant que la corence du DG6P peut augmenter la susceptibilite aux demageaisons induite par la chloroquine. Il n'y avait cependant aucune difference dans la distribution des demangeaisons parmi les differents groupe sanguins. Il avait ete conclu que la PIC peut etre associé avec certain markeurs genétiques des globules rouges partculierement L'Hb et les types de DG6P qui sont les markeurs connus du paludisme mais pas les groupe sanguins.

Correspondence: Dr. O.G. Ademowo, Postgraduate Institute for Medical Research and Training, College of Medicine, University of Ibadan, Ibadan, Nigeria.

Introduction

Chloroquine inspite of resistance by *Plasmodium falciparum* remains the first line drug for the treatment of malaria in most endemic areas. Chloroquine-induced pruritus (CIP) constitutes a major problem to the use of chloroquine for malaria chemotherapy [1,2].

It has been suspected for long that genetic factors may determine the population distribution of CIP. The fact that it occurs mainly in blacks and seems to run through families lend credence to this [1,2].

Certain genes particularly haemoglobin S (Hb S) and glucose-6-phosphate dehydrogenase (G6PD) deficiency are polymorphic genes which are recognised host genetic red cell markers specific for both malaria and blacks [3,4]. These genes are known to influence not only host-parasite interactions [4,5,6] but also drug-parasite interation [7].

It was therefore thought necessary to investigate the influence of these genetic markers on host-drug interactions which CIP represents. However, ABO blood groups which are also genetic red cell markers but are not peculiar to blacks nor reliably proven to be specific for malaria were used as internal control for the survey.

Patients and methods

Patients who received chloroquine phosphate for clinically suspected or microscopically proven malaria at the University College Hospital (UCH) were recruited into the study. Informed consent was obtained from the patients, or parents/guardians in the case of children after explaining the purpose of the study to them. Each patient was administered the WHO recommended dose of 25mg/kg body weight of chloroquine spread over 3 days during which they were observed for presence or absence of CIP. Demographic and clinical information of the patients were obtained by administering a questionnaire . Pruritus when present was scored according to its intensity as mild, slightly incapacitating or severe to cause insomnia. They were also asked to report the time course of the itching. Children below 1 year and those with other diseases that can cause pruritus were excluded from the study. For the purpose of genetic analysis, only one index patient per family was recruited.

Blood (2ml) was withdrawn from each patient into sequestrene bottle for ABO, haemoglobin and G6PD type determination. ABO blood group was determined using the tile method. Haemoglobin type was determined by electrophoresis on cellulose acetate membrane strips at pH 8.6 [8]. G6PD status was determined by both the fluorescent spot test of Beutler and Mitchel [9] and electrophoresis on cellulose acetate gel in Tris-EDTA-Borate buffer at pH 8.6.

Results

Three hundred patients (196 males and 104 females) with age range of 1-33years (mean ± standard deviation of 10 ± 12.1

years) were recruited into the study. 124 (41.3%) comprising 68 males and 36 females responded positively to CIP. Pruritus started between 6 and 24 (13±15) hr after chloroquine administration and increased in intensity until it got to a peak between 12 and 36 (22 ± 9) hr It subsided between 36 and 96 (58±18) hr depending on the individual.

Table 1 shows the distribution of itching and Hb types. It indicates a lower percentage of itchers among sickle cell trait carriers (HbAS) when compared with other haemoglobin genotypes. The frequency of HbAS was also markedly lower among itchers than in non-itchers. ($P < 0.05$).

Table 1. Distribution of itchers and non-itchers with haemoglobin types

Hb	Itchers	Non-itchers	Total	% Itchers
AA	65	78	143	45.6
AS	12	28	40	30.0
AC	5	7	12	41.7
SS	40	60	100	40.0
SC	2	3	5	40.0
Total	124	176	300	41.3
%AS	9.7	15.9	13.3	

Table 2 shows the distribution of G6PD types and itching in males. For epidemiological studies with G6PD, males were used for analysis as G6PD deficiency is fully expressed in males unlike in females where there could be heterozygous G6PD deficiency since the gene is X-linked. One hundred and eighty-six males were used for the analysis. There was a higher percentage of itchers among G6PD deficient (A^-) subjects than in normals (types A or B). There was also a significantly higher frequency of G6PD deficiency among itchers when compared with non-itchers ($P<0.05$).

Table 2: Distribution of itchers and non itchers with G6PD variants in males.

G6PD type	Itchers	Non-itchers	Total	% Itchers
A	7	15	22	31.8
B	58	77	137	43.0
A^-	17	12	29	38.6
Total	82	104	186	44.1
% A^-	20.7	11.5	15.6	

The distribution of ABO blood groups and itching is shown on table 3. It showed that there was no significant difference ($P > 0.05$) in the percentage of itchers among the different blood groups.

Table 3: Distribution of itchers and non-itchers with ABO blood groups.

Blood group	Itchers	Non-itchers	Total	% Itchers
A	27	32	59	45.8
B	38	47	85	44.7
AB	4	5	9	44.4
O	59	86	145	40.7
Total	128	170	298	43.0

Discussion

Chloroquine-induced pruritus (CIP) is a major an side effect of chloroquine therapy. It limits the tole drug and therefore threatens the compliance to the first line drug for malaria treatment. Reports have CIP may be determined by certain genetic factors here the epidemiology of CIP with respect to some laria resistant genes namely, G6PD deficiency and H as ABO blood groups.

The distribution of the Hb genotype, G6PD type blood groups in the study are as expected in the gene tion. It should however be noted that sickle cell pat recruited and studied separately, hence its high prc the study. The lower frequency of itchers observed am individuals when compared with other Hb types or th frequency of HbAS among itchers relative to non-i suggestive that the sickle cell trait may confer some p against CIP. One explanation for this could be that H viduals suffer less intense malaria attacks when comp other Hb types. That is the sickle cell trait is protecti malaria [4,10]. Therefore Hb AS individuals may be p to be less exposed cumulatively to chloroquine as c with those with other Hb types and hence develop CIP quently. This theory is reinforced by the fact that it observed that there is an association between CIP and tive intake of chloroquine [11] Another possible hy could be that sickle cell trait carriers are know hypostenuric i.e. there is reduced ability to concentrate HbAS when compared with HbAA individuals [12]. T result to faster elimination of the drug or its metabolite f body than in HbAA individuals [13].

The result also showed that there was signi higher frequency of G6PD deficiency (A^-) among itche tive to non-itchers in males. There was also more itche G6PD deficiency than were non-itchers. This is suggesti subjects with G6PD deficiency are more prone to CIP mechanism for this observation is not clear. Howeve G6PD deficient red cells have been reported to accu higher concentration of chloroquine than normal cell [1 also that G6PD deficiency has been demonstrated in th [15] which is the main site of chloroquine metabolism [16 offer a lead.

As ABO blood groups had been used as interna trol. It was interesting to note that there was no differen the frequency of itchers among the different blood groups. showed that in contrast to G6PD and Hb types, there wa association between CIP and ABO blood groups. It can concluded that CIP may be associated with certain genetic cell markers particularly, Hb and G6PD status.

Reference

1. Osifo NG. Mechanisms of enhanced pruritogeni of chloroquine among patients with malaria: a rev Afr. J. Med. Sci. 1989: 18: 121 – 129
2. Ademowo OG Walker O and Sodeinde O Chlo quine-induced pruritus: Evidence for heredo-fam ial factors. Malaria Inf. Dis. Afr. 1998; 8: 14-18
3. Sodeinde O Glucose-6-phosphate dehydrogenase d ficiency. Clin. Haem. 1982: 5 (2) 367 – 382.
4. Luzzatto L. Genetics of red cells and susceptibili to malaria. Blood 1979; 54: 961 – 976.
5. Martin SK Malaria G6PD deficiency hypothesi Postgraduate Doctor 1982; 11 – 15.

Fleming AF, Akintunde A, Attai EDE, Bradley-Moore AM Greenwood BM, Bradley AK, Kirkwood BR and Gilles HM. Malaria and haemoglobin genotype in young Northern Nigerian Children. Ann. Trop. Med. Parasitol. 1985; 79: (1) 1 – 5.

Nguyen-Dinh P. and Parvin RM. Haemoglobin S and in-vitro chloroquine susceptibility to *Plasmodium falciparum*. Lancet 1986; 2: 1278.

Dacie JV. and Lewis SM. Practical Haematology. Churchill livingstone. 7th edition 1991..

Beutler E and Mitchel M Special modification of the fluorescent screening method for glucose-6-phosphate dehydrogenase deficiency Blood: 1968; 32: 816 – 818.

Hendrickse RG, Hossen AH, Olumide LO, Akinkunmi A. Malaria in early childhood. Ann. Trop. Med. Parasitol. 1971; 65: 1 - 20.

Ademowo OG. Walker O. and Sodeinde O The disposition of chloroquine and its main metabolite desethylchloroquine in volunteers with and without chloroquine induced pruritus: Evidence for decreased chloroquine metabolism in volunteers with pruritus. Clin. Pharmacol. Ther. 2000; 67: 237-241

12 Taylor OG, Oyediran ABOO, Saliu I. Effects of haemoglobin electrophoretic pattern and seasonal changes on urine concentration in young adult Nigerian males. Afr. J. Med. Sci. 1978; 7: 201 – 205.

13. Ademowo OG. Walker O and Sodeinde O The disposition of chloroquine in volunteers heterozygons for the sickling gene are similar to normals. Malaria Inf. Dis. 1998; Afr. 8: 55 – 59.

14. Orjih A.U. Increased accumulation of chloroquine and desethylchoroquine in homozygous sickle cells. Bull. W.H.O. 1987; 65 (1) 51 – 55.

15. Oluboyede O.A., Esan G.J.F., Francis T.I. and Luzzatto L. Genetically determined deficiency of glucose-6-phosphate type A- is expressed in the liver. J. Lab. Clin. Med. 1979; 93 (5) 783 – 789.

16. Gandette LE. and Coatney GR. A possible mechanism of prolonged antimalarial activity. 1961; A.M. J. Trop. Med. Hyg. 10, 321 – 326.