African Journal of Biomedical Research, Vol. 7 (2004); 97 - 101
ISSN 1119 – 5096 © Ibadan Biomedical Communications Group
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Full Length Research Article

PROFILE OF CHLOROQUINE – INDUCED PRURITUS IN NIGERIAN CHILDREN RESIDENT IN IBADAN, NIGERIA

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Chloroquine is still the first-line drug in the treatment of malaria in Nigeria and West-Africa sub-region. A major drawback to the use of chloroquine is pruritus. We studied a total of 175 children aged 1–15 years with a view to assessing some factors that may influence chloroquine induced pruritus and the possible impact on therapy with this drug. The mean age was 5.2±4.0 and there were 87 females and 88 males. Chloroquine-induced pruritus was found in 43/175 (24.6%). All the subjects experienced the itching within 24 hours of ingestion of the drug and median duration of the itching was 2 days. Majority of those who itched still used chloroquine to treat malaria for various reasons. There was positive family history in 34/43 (79%) of those who itched and 57/132 (43%) of those who did not itch to chloroquine. Those who had chloroquine-induced pruritus were relatively older (mean age 6.90±3.68 years versus 4.64±4.00; p< 0.05) and mean age onset of chloroquine-induced pruritus was positively associated with mean age of the children r = 0.91; 95% confidence limits: 0.71< r < 0.91. We concluded that chloroquine-induced pruritus in this group of children evolved with increasing age and was associated with positive family history.

***Keywords**: Children, Chloroquine, Pruritus, Malaria, Antimalarial drugs*

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INTRODUCTION

Malaria causes considerable morbidity and mortality in the sub Saharan Africa (WHO, 1991). In Nigeria, an estimated 300,000 deaths per annum are attributable to malaria[2]. Children under the age of 5 years, pregnant women and non-immune visitors are especially at risk (Nigeria Fed. Min. Health, 1989; WHO, 1990). Prompt treatment of an acute infection remains a very important aspect of malaria control programmes. Of the available drugs, chloroquine has been the most widely used and perhaps the safest in all populations of patients. Pruritus is a common and disturbing side effect of Chloroquine, which usually affects compliance to therapy (Mayinka & Kihamia, 1991; Sowunmi et al, 2000). Systematic assessment of chloroquine-induced pruritus in children is still largely lacking, the possible contribution of poor drug compliance to the development and spread of chloroquine resistant strains of *Plasmodium falciparum* also remain to be fully elucidated. Nigerian children carry disproportionate burden of malaria and the need for assessment of this nature cannot be over-emphasized. It is of utmost importance to define the profile of and some confounding factors of chloroquine-induced pruritus in order that appropriate pro-active measures may be taken to alleviate or prevent any unintended undesirable effects of malaria therapy. The foregoing issues were considered and an attempt made to address some of them.

MATERIALS AND METHODS

This cross sectional study was carried out among 175 children attending the General outpatient clinic of the University College Hospital, Ibadan, Nigeria between the months of September 2001 and January 2002. A structured questionnaire (Appendix 1) was the instrument employed.

The study was explained to the parent or guardian thereafter, verbal consent was obtained: 1) to administer the questionnaire, and 2) to obtain blood sample (2 millilitres) for haemoglobin genotype and blood group. Where blood sample was refused or phlebotomy impossible, the questionnaire was administered all the same.

Information was obtained from the accompanying parent or guardian and where possible the child. The questionnaire addressed the social demographic data, frequency of malaria (mostly on clinical suspicion) and choice of drug for the treatment, the occurrence and severity of pruritus, continued use or not of chloroquine in spite of itching and methods employed to reduce or prevent itching (see appendix). The haemoglobin genotype and blood group were determined respectively, by electrophoresis on cellulose acetate membrane strips and tile methods.

The data were analysed using EPI-INFO version 6.04. Chi Square was calculated for discrete variables and normally distributed data, for example, age were compared by Student's t test. Level of statistical significance was set at $p<0.05$.

RESULTS

Sociobiological characteristics of patients studied

One hundred and seventy-five children agreed (by proxy) to answer the questionnaire but only 81 consented to collection of blood sample for haemoglobin genotype and blood group; 7 results were not retrieved from the laboratory. Of the 175 respondents, 87 were females and 88 were males. The mean age was 5.2 $\pm$ 4.0 years with a range of 1 to 15 years. More than 61% of all respondents have had at least one episode of malaria in the 3 months preceding presentation and 85% of them used chloroquine for treatment. Forty-three (24.6%) of these children itched to chloroquine, and their mean age was 6.90$\pm$3.68 years (Table 1). Of the 132 who did not itch to chloroquine, 57(43.2%) had positive family history. Children with chloroquine-induced pruritus were relatively older than those without (6.90$\pm$3.68 versus 4.64+3.997, $p<0.05$). Seventy nine percent of those who itched to chloroquine have positive family history and in 31/34 (76%) and 19/34 (56%); chi square 10.88; $p<0.05$ of cases mother and father were, respectively involved. None of our respondents itched as a result of malaria or to other antimalarial drugs. The distribution of the blood groups and haemoglobin genotypes were similar between those who had chloroquine-induced pruritus and those who did not (table 2).

Table 1: Sociobiological characteristics of 175 children evaluated for chloroquine-induced pruritus.

	Positive history of chloroquine-induced pruritus	Negative history of chloroquine-induced pruritus
Number	43	132
Sex ratio female:male	19:24	68:64
Mean age	6.90±3.68	4.64±4.00
Number treated for malaria in previous 3 months	34 (79%)	74 (56%)
Use chloroquine for malaria	28 (65.1%)	121 (91.7%)
Number with positive family history of Chloroquine-induced pruritus	34 (79.1%)	57 (43.2%)

Table 2: Distribution of blood groups and haemoglobin genotype amongst the respondents

	Children with positive history of pruritus	**Children with negative history of pruritus**
Haemoglobin genotype		
AA	16	36
AC	0	2
AS	9	9
S	0	1
SC	0	1
Total	**25**	**49**
Blood group		
AB positive	1	2
A negative	0	1
A positive	5	12
B positive	3	9
O negative	0	3
O positive	11	20
AB negative	0	1
Total	**20**	**48**

Profile of chloroquine-induced pruritus

Forty-three (24.6%) of these children itched to chloroquine (Table 3). The mean age of

onset of chloroquine-induced pruritus was 5.21±3.10 years.
In all, only 3 were aged 2 years and below and the mean age of the children who itched to chloroquine was 6.90±3.68 years.
In five (11.6%) of those who itched only hands were involved, 4 (9.3%) involved both hands and feet and it was generalised in 11/43 (26.6%).

Table 3:
Indices of severity of pruritus among 43 Nigerian children with chloroquine-induced pruritus

Onset of itching following ingestion	**Number of patients (%)**
<6hours	4(9.3%)
6-12 hours	34(79.1%)
13-24 hours	5(11.6%)
Total	**43 (100%)**
Duration of itching after last dose	Number of patients (%)
13-24 hours	3(7%)
25-47 hours	16(37.2%)
≥48 hours	24(55.8%)
Total	**43 (100%)**
Severity of itching	Number of patients (%)
Hands only	5(11.6%)
Hands and feet only	4(9.3%)
Generalised, no insomnia	11(25.6%)
Generalised and insomnia	23(53.5%)
Total	**43 (100%)**

In 23/43 (53.5%) of the children with chloroquine-induced pruritus, it was associated with insomnia. In all but one case the object used for scratching was the hand. The period of onset of itching was between 6 and 12 hours in most cases (79.1%) and the median duration of itching was 2 days. Thirteen of 93 children aged less than 5 years had chloroquine-induced induced pruritus as compared to 30 of 82 aged 5 years and above (X^2: 12.02; p< 0.05). The 9 children who had chloroquine-induced pruritus with no family history were otherwise similar to those with positive family history. The means age were 6.95±3.94 versus 6.89±2.67 (p>0.05), respectively in those with positive family history and those without. The 2 groups were also similar with respect to severity, for example 20/34 and 3/9 of those with positive family history and negative family history respectively, had generalised pruritus with insomnia (Table 4).

Use of Chloroquine in spite of itching
Sixty-five percent (28/43) of our respondents who itched to chloroquine continued the use of the drug for various reasons. The reasons stated include: the use of antihistamine receptor-1 (H-1 receptor blocker) to prevent and/or reduce itching (12/28), availability (1/28) and efficacy (15/28). Some of the respondents combined chlorpheniramine with vitamin B complex. Five of 13 children aged less than 5 years still use chloroquine for reasons of effectiveness and alleviation by the use of chlorpheniramine. None of the children has ever used steroid to prevent or reduce itching.

Table 4:
Characterisation of children with chloroquine-induced pruritus with respect to family history

	Positive family history	Negative family history
Number	34	9
Sex ratio female: male	14:20	5:4
Mean age	6.95 ±3.94	6.89 ±2.67*
Mean age of onset	5.12 ±3.24	5.56 ±2.60*
Number still use chloroquine (number)	22	6*
Number treated for malaria in 3/12	27	7
Severity: number involved		
Hands only	3	2
Hands and feet	4	-*
Generalised but no insomnia	7	4
Generalised and insomnia	20	3

**P < 0.05*

Table 5:
Drugs that were used by the respondents to reduce or prevent chloroquine-induced pruritus

Drugs	**Number of patients**
Chlorpheniramine	34
Promethazine	4
Multivitamins	6
Herbal remedies	0
None	3
Total	47*

**Some patients selected more than one option.*

Table 6:
Reasons for use of chloroquine inspite of pruritus**.**

Reasons	**Number of patients (%)**
Effectiveness	15(53.4%)
Itching reduced with use of other drugs	12(42.9%)
Availability	1(3.6%)
Total	28

DISCUSSION

In the present study of 175 children aged between 1 and 15 years, we observed an incidence of 24.7% of chloroquine-induced pruritus. A similar incidence of 19% had earlier been reported in children recruited into controlled trial of chloroquine versus cotrimoxazole in the same area of study (Fehintola *et al*, 2002). Ademowo and Sodeinde (2002) recorded a higher incidence of 41.3% but with age range of 1-33 years. Similar studies in adults have recorded even higher incidence of chloroquine-induced pruritus (Ajayi *et al*, 1998).

We observed that the mean age of children with chloroquine-induced pruritus was higher than those without pruritus and the age of onset of chloroquine-induced pruritus was positively associated with age of respondents. It was also observed that children with chloroquine-induced pruritus were more likely to have positive family history than those without: with the mother being more commonly involved than the father. No immediate explanation could be proffered for this though, such observation may support familial basis for the chloroquine-induced pruritus. In all the 43 children with chloroquine-induced pruritus onset was 12 hours or less following drug ingestion. The itching was generalised in 34/43 (79.1%) of cases and associated with insomnia in 23 (53.5%). In this study the antihistamine drugs were the most popular choice in patients attempt to reduce and/or prevent pruritus. None of these children had used steroid group of drugs or dapsone for treatment or prevention of chloroquine-induced pruritus. Studies have established corticosteroids and dapsone as being more effective than antihistamines in the reduction or prevention of itching to chloroquine (Adebayo *et al*, 1997; Ademowo & Sodeinde, 2002; Onwubuya *et al*, 1996).

The 9/43 (20.9%) without positive family history otherwise had similar characteristics to those 34/43 (79.1%) who had positive family history. Notwithstanding the chloroquine-induced pruritus, 28/43 (65.1%) of these children continued to use chloroquine for the treatment of malaria. The effectiveness and availability of chloroquine and amelioration by other drugs were proffered as reasons. In addition to the foregoing, the fact that some other antimalarial drugs including the newer ones like halofantrine produced pruritus in Nigerian (Sowunmi *et al*, 1998) children should underscore the need to elucidate the mechanism of chloroquine-induced pruritus in this population.

Chloroquine-induced pruritus is thought to involve a complex interaction between the host, the parasite and the drug. Some genetic markers notably haemoglobin genotype and glucose-6-phosphate dehydrogenase (G6PD) have been found to be associated with chloroquine-induced pruritus. It is noteworthy that about 43% (12/28) of our respondents still used chloroquine because their itching was alleviated by antihistamines. Antihistamines (H-1) have not been found to be effective in the prevention or alleviation of chloroquine-induced pruritus in some studies. Chloroquine-induced pruritus is characterised by initial response to antihistamines as may be suggested by this study, and failure of response to even steroid at a later time (unpublished observation).

Chloroquine is still an effective antimalarial drug in some parts of Nigeria and the West African sub-Region. Efforts at prolonging its effectiveness as in resistance reversal with chlorpheniramine are further evidence of the potential of this drug. In view of the foregoing, availability and safety profile of the drug more efforts should be directed at ameliorating pruritus induced by the drug. This study indicates wide acceptability of chloroquine for chemo-suppression of malaria and that pruritus evolved with age and positive family history correlates well with prevalence of chloroquine-induced pruritus in children living in Ibadan, south-western Nigeria. Verification would require larger epidemiological and experimental studies

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Received: January 2004
Revised version accepted: June 2004