

CHLOROQUINE-INDUCED PRURITUS: FAMILIAL AGGREGATION AND POSSIBLE GENETIC BASIS

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Summary

1152 attendants comprising 40% male and 60% female subjects at urban private clinics and rural health centres in Ghana were interviewed by questionnaire. Enquiry was made into the occurrence of chloroquine-induced pruritus in themselves, their spouses, their children, their siblings and their parents. The questionnaire included the following details:-

- (a) self-medication for febrile illnesses
- (b) the number of tablets of chloroquine that induced pruritus.
- (c) the time of onset and duration of pruritus
- (d) the method of relief of pruritus

44.8% of respondents had experienced itching on taking chloroquine. 23.3% itched on being given chloroquine intramuscularly and 95% of these itched on oral chloroquine. The rate of itching on self-medication with chloroquine alone or with other drugs was 41%. 33.9% itched each time they took chloroquine and 30.9% itched at least once after taking chloro-

quine. The prevalence rate of chloroquine-induced pruritus in this study was found to be between 30.9% and 44.8%. Of the respondents who knew about itching among their close relatives, 50.7% (309/609) had siblings who itched, 29.3% (184/628) had children who itched, and 21.9% (166/759) had parents who itched on taking chloroquine.

The results describe a pattern suggestive of strong familial aggregation and thus a possible genetic basis for chloroquine-induced pruritus. In addition, a pathway of inheritance leading to male preponderance in off-springs of respondents who itch has been established.

The minimum number of tablets required to induce itching was found to be 2, equivalent to 300mg base chloroquine. 42.2% of respondents started itching within 2 hours, 24.1% between 2 and 6 hours, and 33.3% after 6 hours. Of the 57.6% who took drugs for relief of pruritus, 89.7% took antihistamine preparations. However there was no significant difference between those who took the drug before or after chloroquine ingestion, with regard to relief of pruritus.

Key Words:

Pruritus, Chloroquine, Familial Aggregation

Introduction

Chloroquine is the drug of choice for the treatment of malaria in Ghana. It is also used without medical supervision in the treatment of febrile episodes.^{1,2} One side effect that makes its use unacceptable to some patients is pruritus (itching). Prevalence rates of between 8% and 15% have been reported from Nigeria,³ with other data indicating that the prevalence is rising.^{2,4,5} The reaction has also been observed in other ethnic groups.^{4,6} Pruritus occurs whether

chloroquine is used for prophylaxis or chemotherapy. It has been suggested that chloroquine-induced pruritus may have a pharmacogenetic basis.^{2,4} The aim of this study was to find the prevalence of chloroquine-induced pruritus among out-patient attendants at some clinics in Ghana. The familial aggregation of chloroquine-induced pruritus i.e., the tendency of members in the same family to itch after taking chloroquine, was also studied.

Patients and Methods

Outpatient attendants at three urban private clinics in Accra, one district hospital and one rural health centre in the Suhum District in Ghana consented to answer a questionnaire administered by trained interviewers.

Respondents answered questions relating to the occurrence of pruritus in themselves and the practice of self-medication for febrile illness. They were also asked about the occurrence of chloroquine-induced pruritus in their children and spouses, their parents and their siblings. Other information obtained included:-

- (a) minimum number of tablets of chloroquine that induced pruritus.
- (b) the onset and duration of pruritus
- (c) medications used to achieve relief from itching

The occurrence of skin rash with chloroquine-induced itching and of itching with other medications were also sought.

Analysis of Data

The responses were coded and processed using a Wang 2200 MVP miniframe computer. Chi-square test and the critical ratio (Z) for the comparison of independent proportions were performed whenever it was appropriate. Analyses were based on unequivocal responses to questions and differences in responses were considered significant at the 5 per cent significance level.

Results

Prevalence and Self-medication

1152 consecutive out-patient attendants were interviewed. The group comprised 40% males and 60% females, their mean age \pm SD being 31.4 ± 10.1 years. Prevalence rate was estimated by different questions as well as from itching related to self-medication for febrile illness. 1138 respondents gave unequivocal responses about their itching status and of these 44.8% itched on taking chloroquine, 42.5% being male and 57.5% female. 23.3% admitted

to itching on being given chloroquine intramuscularly and 95% of these also itched on taking chloroquine orally. 30.9% have itched at least once after taking chloroquine and 33.9% itched each time they took chloroquine.

36 (3.1%) respondents did not self-medicate for a febrile episode. Of the remaining 1116 who self-medicated, 980 used chloroquine, paracetamol or aspirin either alone or in combination and 136 used other preparations including herbs and antibiotics with or without any of the above three drugs; of these 389 (34.8%) itched irrespective of the drug. 805 respondents took chloroquine alone or in combination with paracetamol and/or aspirin and 330 (41.0%) itched on these medications. 7.4% of those who took aspirin and/or paracetamol alone also itched.

Thus in this study, other agents apart from chloroquine on their own induce pruritus, but a 35% itching rate is associated with chloroquine alone as compared with 7.4% for analgesics, suggesting that there is a greater propensity to itch to chloroquine. The prevalence of pruritus when chloroquine is orally administered in the study population is between 30.9% and 44.8%.

Familial aggregation

Of 552 respondents who knew about itching in their spouses, 144 (26.1%) said their spouses itched on taking chloroquine. 184 of 628 respondents (29.3%) gave a definite response of itching among their children and 309 (50.7%) of 609 respondents had siblings who itched. 166 of 759 respondents (21.9%) had parents who itched on taking chloroquine. Chi-squared analyses indicate a significant relationship in the itching rates of respondents and their parents, siblings and children ($p < 0.05$). Where both the respondent and his or her

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parent or spouse did not itch, a higher proportion of the respondents' off-springs did not itch. A similar relationship exists between respondents, their parents and their siblings. The occurrence of pruritus in off-springs (differentiated by sex) in relation to itching in the respondents' spouses was investigated and two family trees constructed. In one the gender of the respondent and spouse was not known (Fig. 1).

In the other the gender of the respondent and spouse was known (Fig. 2). Nearly 1 in 2 (45.9%) of off-springs itch if both parents are itching as opposed to 1 in 10 (10.2%) when neither parent itches (Fig. 1). When only one parent itches, between 1 in 6 (16.2%) and 1 in 5 (19.8%) of the off-springs itch. In the event of both parents itching the sex ratio (Male:Female) of the off-springs who itch is 1:1. When only one parent itches the sex ratio is approximately 2:1.

Other Characteristics

The minimum number of tablets required to induce itching in the 510 respondents who itch on taking chloroquine was two (range 1 to 10). 12.9%, 57.5%, 5.7% and 18.1% of those itching did so on taking 1, 2, 3, and 4 tablets of chloroquine respectively. 42.2%, 24.1% and 33.3% started itching within 2 hours, between 2 to 6 hours and after 6 hours respectively. Itching lasted for less than a day in 21.1%, for 2 days in 22.5% and more than 2 days in 56.3%. 16.4% of those itching had an associated skin rash. Whereas 42.4% of those itching on taking chloroquine did nothing to relieve it, 57.6% (294) took drugs to achieve relief. (264) 89.7% of these took antihistamine preparations; a third of them before and the rest after taking chloroquine. (206) 78% felt that the antihistamine helped their itching. However, the time of administration did not significantly affect the response to the antihistamine as indicated by a Z value of 0.47 between the two proportions, 76.4% before and

78.9% after. (Probability of 0.638, 2-tailed test).

Discussion

44.8% of the population of 1152 interviewed had experienced pruritus in relation to chloroquine ingestion. The estimated prevalence of pruritus in chloroquine related self-medication of 41% is close to the interviewed population rate of 44.8%. The figure of 44.8% may be an over estimation since medications other than chloroquine used for febrile episodes may be referred to as chloroquine. In addition, there is an itching rate of 7.4% in those taking aspirin, paracetamol or both for febrile illnesses in this study. 30.9% of respondents admitted to itching the last time they took chloroquine. 33.9% itched each time they took chloroquine. The low prevalence rate of 23.3% for intramuscularly administered chloroquine may be related to the route of administration or the dose given. A single intramuscular injection of chloroquine of 4-5ml contains 160-200mg of chloroquine base, whilst one tablet of chloroquine contains 150mg of chloroquine base. The median of the minimum number of tablets required to induce itching was found to be 2 or 300mg base. The prevalence of itching induced by chloroquine between 30.9% and 33.9% is similar to the 28% reported by Olatunde and Obih.² However, it is less than the recently reported prevalence rates of 51.8%⁵ and 74.3%⁴ from Nigeria.

Various studies on chloroquine-induced pruritus have either suggested a familial tendency⁵ or a pharmacogenetic basis for the itching.^{2,4-5} The familial tendency is confirmed in this study by the strong association, ($p < 0.05$) between respondents, their siblings, parents and children with respect to itching induced by oral chloroquine. Thus the results describe a pattern which suggests a strong familial as well as a genetic basis for chloroquine-induced pruritus.

Fig. 1

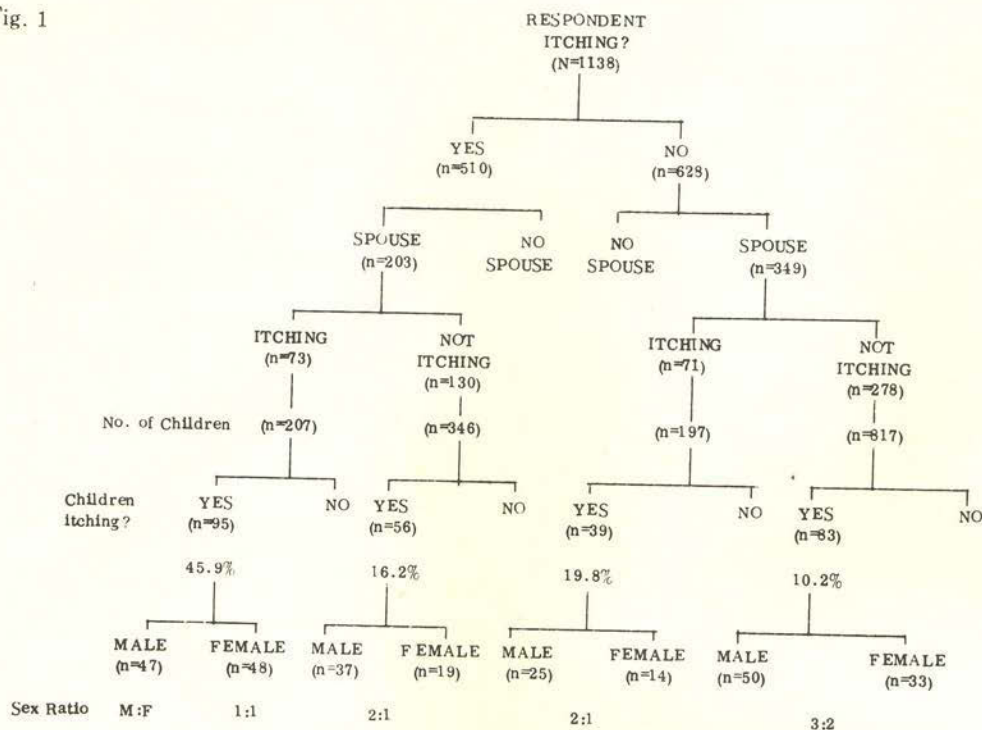
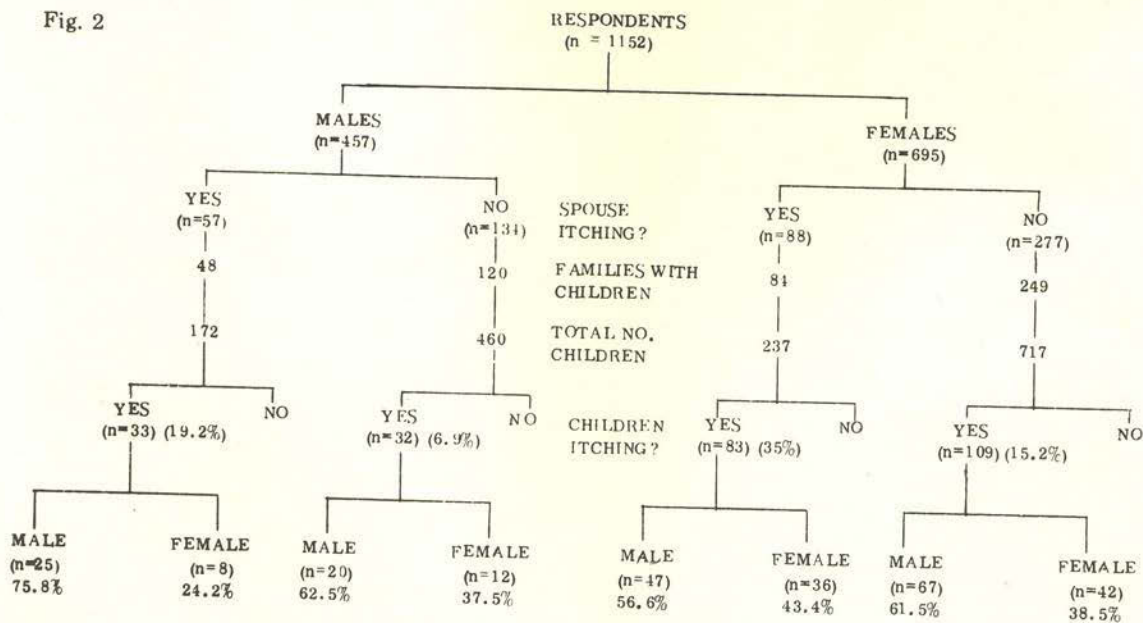


Fig. 2



In addition, our results indicate a possible pathway of inheritance of chloroquine-induced pruritus in the offsprings of the respondents. It also shows a strong male preponderance of those who itch where only one parent itches. These observations require further studies.

The onset of itching occurred within 6 hours of chloroquine intake in two-thirds of the respondents. This figure is lower than the reported latency period of 11 ± 9 hours in Nigerian subjects.⁴ The duration of the itch reaction is greater than 2 days in the majority of patients (56.3%). The itch was accompanied by a rash in 84 out of 510 (16.4%) respondents. Itching caused by chloroquine is usually not accompanied by cutaneous manifestations. The rash may therefore be due to associated drug intake or dermatological problems.

The absence of cutaneous manifestations in the majority of respondents also makes histamine an unlikely pruritogenic agent in the itch reaction. The time of administration of antihistamines does not seem to influence benefit. The role of antihistamines in the relief of itching is not clear. There are other putative pruritogenic substances, like serotonin and prostaglandins, and it would be instructive to study the effects of their specific antagonists on chloroquine-induced pruritus.

Chloroquine-induced pruritus is common in the population studied. The reaction shows a tendency to familial aggregation and a male preponderance in offsprings and there may be

a genetic basis for this observation.

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