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Psychosis following chloroquine ingestion: a 10-year comparative study from a malaria-hyperendemic district of India☆

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ABSTRACT

Objectives: Serious adverse effects such as acute psychoses have been reported following treatment with chloroquine. Chloroquine can cause cell death, including neurons. We aimed to identify the most frequent type of psychiatric manifestation and symptomatological characteristics of psychosis following chloroquine ingestion (PFC).

Method: Out of a total of 4471 randomly selected recent-onset psychosis patients, 3610 consecutive patients who had responded to standard treatment were screened for entry in the study. We compared background clinicodemographic profile information and psychopathology of 51 PFC patients, who were either drug free or drug naive, to 51 brief psychotic disorder (BPD) patients who were matched in terms of age, sex and education. Only those patients who remitted within 8 weeks (PFC patients) or 4 weeks (BPD patients) were included. Cranial computed tomography, electroencephalography and lumbar puncture of the entire experimental group were normal, and none had Mini Mental Status Examination score <22. Group difference and correlational statistics (parametric and nonparametric) have been used to test the hypotheses and explain the results.

Results: The most common (76.2%) type of psychiatric disturbance in PCF group was mood disorder (mixed episode) accompanied by predominant irritability with little blunting of affect. PFC patients characteristically had prominent positive symptoms with visual hallucination and derealization experiences. They were more restless, agitated and anxious and had more disturbed thought content and orientation, but better preserved insight. There was no linear relationship between the amount of chloroquine consumed and the severity of psychosis.

Conclusion: Considering the large number of patients still receiving chloroquine especially in developing countries, this study has been presented to draw attention of the psychiatrists and other health professionals to the hazardous effect of chloroquine on mental health.

1. Introduction

Chloroquine is a commonly prescribed, inexpensive antimalarial drug that is widely used for the presumptive treatment of malaria. Although chloroquine has been replaced by artemisinin-based combination therapies in some developed countries, it is still one of the most used drugs in the world, and enormous amounts of this drug have been prescribed to patients and travelers to endemic areas in the last 6 decades. Chloroquine is also indicated for treatment of amoebic abscess and autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis [1]. Adverse effects of chloroquine include gastrointestinal problems, dermatologic reactions, blood dyscrasia, myopathy, neuropathy, cramps, anaphylactic shock, headache, vertigo, tinnitus and extrapyramidal syndrome [2]. Serious adverse effects such as acute psychoses have been reported to occur at a high doses (2–6 g/day) [3–5] as well as standard antimalarial doses (cumulative dose of 1500 mg of base) [2]. Symptoms vary widely from insomnia [6] to catatonia [7], toxic psychosis [8,9] and suicide [10]. A wide range of behavioral symptoms has been published, including most frequently increased irritability, restlessness, abusiveness, distractibility, pressure of speech with flight of ideas, delusions of grandeur, and the presence of auditory and visual hallucinations [11].

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Depersonalization and derealization have also been reported [12,13]. However, in addition to the clinical picture, longitudinal course is also important because there may have been a relationship between the duration of drug use (thus, cumulative dose) and the intensity of symptoms as it has been observed in hallucinogens [14].

Being a weak base, chloroquine concentrates in acidic vesicles such as lysosomes and raises their pH, an effect that has been shown to disrupt the function of lysosomal enzymes [15]. Chloroquine-induced death has been described in many cell types, including immature neurons and HeLa cells, and has been shown to be regulated by members of the Bcl-2 family [16].

Apart from discrete case reports, there is still no systematic study of psychosis following chloroquine ingestion (PFC). The index study of patients with PFC (includes both psychotic and mood disorder) as defined by *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) [17] has addressed the following questions. (a) Which are the more frequent manifestations: psychosis or mood disorder or mixed type symptoms? (b) Are there any symptomatological characteristics in PFC patients? (c) Is there any relationship between the duration of drug use (and thus cumulative amount of choloroquine) and the intensity of symptoms? (d) How are the symptoms of PFC different from another early remittent psychosis: brief psychotic disorder (BPD)? We hypothesized that BPD and PFC had distinct demographic profile, premorbid functioning, severity of symptoms and psychopathology and that there would be a linear relationship between the amount of chloroquine consumed and the intensity of symptoms.

2. Material and methods

2.1. Study site

The study area is in West Bengal, India, where the climate is equatorial. In this area, malaria is hyperendemic, predominantly caused by *Plasmodium vivax*. Our outpatient department treats mental patients from three districts, including 22 malaria-endemic villages (approximately 15,000 inhabitants) covering an area of 1950 km^2.

2.2. Sample selection

We randomly selected a total of 4471 patients with recent-onset psychosis from those referred from different peripheral and district general hospitals to our State Mental Hospital during the study period of 10 years (2002–2012). Among them, 3610 patients who responded to standard treatment were screened for entry in the study.

The participants of PFC group were diagnosed by consultant psychiatrists of the institute according to criteria set by the research team (from descriptions reported in the literature [18–20] and DSM-IV-TR [17] criteria for substance-induced psychotic disorder): (a) no psychiatric history before starting chloroquine; (b) prominent hallucinations or delusions not exclusively during delirium; (c) psychiatric symptoms continuing for at least 1 week; (d) onset of psychotic disorder within 6 weeks after starting chloroquine; (e) the individual took at least one tablet of chloroquine (equivalent to 150 mg of base); (f) the symptoms have to be severe enough to cause hospitalization or referral for specialist treatment; (g) symptoms must be resolved within 8 weeks of cessation of chloroquine ingestion; (h) disturbance is not better accounted for by a psychotic disorder that was not substance induced. A control group had been constituted with patients of BPD diagnosed according to DSM-IV-TR criteria [17] (298.8). We excluded those who had family history of any psychotic disorder in first- and second-degree relatives, prior history of significant head injury, major medical or neurological disorders and concomitant prescribed or illicit drug use. Kappa coefficients for diagnosis of PFC and BPD ranged from 0.66 to 1.00.

All the finally selected PFC (59) and BPD (58) patients were structurally interviewed by the authors P.S.B. and D.S. The malarial fever subsided in 53 PFC patients before the onset of psychosis. Our experimental group ($n=51$) consisted of 47 patients who took chloroquine due to malarial fever (39 *P. vivax* and 8 *P. falciparum*) and 2 patients with an inadvertent use of chloroquine. Two patients whose blood tests were normal were on chloroquine prescribed by less well trained local doctors as presumptive treatment of fever. Forty-six patients of the PFC group were drug naive during first contact. The remaining five took one to two doses of either tablet alprazolam (0.25–0.5 mg) or tablet diazepam (5–10 mg). One of the PFC patients had a previous one episode of PFC, but he was drug free (no oral psychotropic drugs within the past 4 weeks or depot antipsychotics within the past 8 weeks) at the time of the interview. Subsequently, 51 patients with BPD were selected after matching with PFC group with respect to age, sex and education. Forty-eight BPD patients were drug naive. Four BPD patients had previous completely remittent psychosis in the form of either BPD (two patients) or psychosis not otherwise specified (two patients), but were drug free.

Our treatment protocol for PFC group was comprised of (a) discontinuation of chloroquine, (b) initiation of flexible dose of antipsychotic drugs (risperidone 6–8 mg/day or olanzapine 10–20 mg/day with or without trihexyphenidyl 2–4 mg/day) and (c) acidification of the urine by using vitamin C (500 mg/day). The BPD group was treated with only antipsychotics and anticholinergic in the same dose. We defined *response to treatment* as attaining a 50% or greater decrease in mania, depression or psychosis ratings [21]. *Remission* was defined as a decrease in Young Mania Rating Scale (YMRS) [22], Hamilton Depression Rating Scale (HDRS) [23] and Brief Psychiatric Rating Scale (BPRS) [24] scores to less than 9, 8 and 30, respectively, that persisted for <2 months [21]. *Recovery* was defined as a virtual absence of symptoms for 2 months or more [21].

2.3. Assessment

Information concerning sociodemographic variables, clinical history and diagnostic assessment were collected during a semistructured interview, which included BPRS (for psychopathology) and YMRS and HDRS (for current mood) during the first interview and subsequently during follow-up over the next 6 months. Good reliability ratings were obtained, with intraclass correlation coefficient of above 0.92 for total scores and levels of agreement above 0.80 ($P<.001$) for all individual items. In addition, we assessed type of hallucination (if present) and presence of derealization and depersonalization in a 7-point Likert scale. None of the PFC or BPD patients had MMSE score <22 at the time of the first interview. We analyzed only those data that were collected at the time of the first interview. Malaria fever was diagnosed with thick and thin peripheral blood film and/or card antigen (OptiMal) test. Cranial computed tomography, electroencephalography (EEG) and lumbar puncture of the entire experimental group were normal. None of the participants had clinical features of hepatocellular failure, making any other possibility very unlikely. During chloroquine consumption, none noticed any difficulty with eyesight or had an abnormal retinal examination. The Institutional Research and Ethics Committee of the State Mental Hospital reviewed and approved the protocols, and after a complete description of the study to the subjects, written informed consent was obtained.

2.4. Statistical analyses

Pearson χ^2 tests and t tests were used to compare group differences for dichotomous variables and continuous variables, respectively. A nonparametric Mann–Whitney U test was used when data were not normally distributed. Pearson correlation and point biserial correlation were done between sociodemographic–