Case Report

Psychosis consequent to antimalarial drug use in a young child

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Abstract

The empirical use of anti-malarial agents in patients of unexplained pyrexia is a common practice in developing countries especially where the prevalence of malaria is high. The use of artemisinin-based combined therapies has gained prominence since some time, but chloroquine is still commonly utilized as monotherapy or in combination. Neuropsychiatric adverse effects of artemisinin are rarely reported, while chloroquine is associated with a range of such events. Further, the reporting of such side effects was more so in the 1980s and 1990s, and with the turn of this century, very few cases of chloroquine-induced psychosis especially in child and adolescent population have been reported. Herein, we report the development of psychosis in a young child who was exposed to chloroquine.

Keywords: Antimalarial drugs, artesunate, chloroquine, malaria, psychosis

Introduction

Neuropsychiatric symptoms consequent to malaria and anti-malarial agents have been reported in the literature. The psychiatric manifestations of malaria fever may occur in the form of dreamlike states, amnesias, reduced attention and concentration, insomnia, anxiety, depression, mania, confusional psychosis, and delirium.[1] However, the description as well as the association of malarial fever as an etiology of the neuro-psychiatric syndrome has been doubted since some time. Furthermore, almost every anti-malarial agent, other than the artemisinin derivatives, has been linked with neuropsychiatric manifestations.[2-4] Herein, we report the development of psychiatric symptoms in a child following exposure to anti-malarial drugs.

Case Details

A 91/2-year-old boy was admitted to psychiatry inpatient with complaints of abnormal behavior and insomnia for 3 days. His medical history revealed that he recently suffered from a fever that was intermittent, high-grade (102°−103°F), and associated with chills and rigors. However, no cough or cold, nausea and vomiting, diarrhea, headache, seizures or rash was reported. In view of flu-like symptoms, he was initially treated with only oral paracetamol. However, despite taking oral paracetamol (500 mg at every 6 − 8 hours), the fever did not remit. Hence, investigations in the form of complete hemogram and peripheral blood film examination, a chest roentgenogram, ultrasonography of the whole abdomen, card test for malaria, dengue, and serology for typhoid were performed. All the investigations were normal, and a diagnosis of pyrexia of unknown reason was entertained. In addition to paracetamol, amoxycillin and clavulanic acid (250 mg/62.5 mg every 8 hours) were prescribed, but despite a 5-day course, the fever did not remit. Thereafter, he was treated as inpatient and empirically treated with intravenous artesunate at a dosage of 2.4 mg/day for the next 3 days, and his fever subsided. Following this, he was prescribed oral chloroquine at dosages of 300 mg stat followed by 150 mg after 6 hours and then 150 mg/day for the next 2 days. However, one day after the completion of anti-malarial therapy, a new set of symptoms appeared. The child could not sleep properly for the next 3 days. He also complained of irritation

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in his eyes due to impaction of hair/eyelash, though his parents did not find it. Consequent to repeated rubbing, he developed redness and excessive lacrimation in eyes. He also voiced that hairs grew from his nails and that he could see them and this led to significant distress. Additionally, he reported seeing ants crawling over his body which others could not see. Along with this, he heard voices of his relatives in clear consciousness when they were not around and bore the characteristics of auditory hallucinations. He remained conscious, though parents reported certain instances when he mis-recognized them. Sensory symptoms in the form of increased sensitivity to sound, light, and touch were also reported. Certain psycho-social stressors could be elicited in the form of an authoritarian style of parenting by father and very permissive parenting by mother. At the time of admission, he was afebrile, weighed 33 kg, and had a body mass index of 16.41 Kg/m^2. His physical examination including detailed neurological examination was normal. His mental state examination revealed increased psychomotor activity, increased speech output, irritable mood, normal cognitive functions, and comprehension. He reported auditory, visual, and tactile hallucinations with preserved insight. He scored 29 on mini-mental state examination which ruled out delirium. Differential diagnosis of malaria, focal encephalitis, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections was ruled out by physical examination and investigations [Table 1]. In view of this and screening on MINI-KID 6.0,[5] a DSM-5 diagnosis of medication-induced psychotic disorder (due to chloroquine) was kept, and he was started on olanzapine 5 mg/d along with clonazepam 0.5 mg at bedtime. The dose of olanzapine was increased to 10 mg/day in a week in view of minimal response. All the symptoms subsided within the next 3 days, and he was discharged. The child has maintained in remission after a month of discharge.

Discussion

The World Health Organization (WHO) recommends artemisinin-based combination therapies for the treatment of uncomplicated malaria.[6] A typical regimen includes once daily dose of artemisinin for 3 days followed by an oral anti-malarial drug. Artesunate has an extremely short half-life (0.5 − 3 hours), and has minimal risk of neuropsychiatric adverse effects. Although high dosages of artemisinin derivatives are associated with neurotoxicity in animal models, evidence is scarce for humans.[2,3] Only, one case report of induction of mania consequent to arteether treatment in a young child is available.[7] On the other hand, chloroquine has a low safety margin, it tends to accumulate in the body, and has a long plasma half-life. Therefore, the neuropsychiatric adverse effects consequent to chloroquine may even develop when prescribed in standard doses. The proposed neuro-toxicity is akin to methamphetamine (i.e. due to an excess of dopamine) and fluoroquinolones antibiotics (leading to N-methyl-d-aspartate excitotoxicity and gamma-aminobutyric acid inhibition).[8] A total of 13 cases of chloroquine-induced psychosis in children have been reported. Biswas *et al.* (2014)[9] had differentiated psychosis following chloroquine exposure (PFC) from equal number of age-matched patients with brief psychotic disorders (BPD). It was observed that the PFC group had an early onset of psychosis, comprised of mixed affective psychosis, was more restless, irritable, agitated, and had more disturbed thought content, orientation, while insight was better than the BPD group. Further, visual hallucination and derealization were also frequently observed in the PFC group.

In the index case, psychosis was precipitated after the remission of fever, was unlikely to be due to malaria (as tests for it were

Table 1: Investigation results in an index patient

Investigation	Result
Complete hemogram	Hb-12.8g/dl; TLC-4510/cmm, DLC-N30L57M10E1; Platelets count: 5.5 lac/cmm
Peripheral blood examination	Normocytic normochromic RBCs, platelets raised on smear, and no hemoparasites
Liver function test	SGPT/SGOT=23/17 U/L; Total bilirubin 0.74mg/dl, direct bilirubin: 0.16mg/dl, total proteins: 7.35g/dl, albumin 4.39g/dl, ALP: 250U/L
Kidney function test	Urea: 20mg/dl, Creatininge: 0.73mg/dl
Fasting blood sugar	80 mg/dL
Blood culture	Sterile
Typhoid IgG/IgM rapid card test	Non-reactive
Malaria antigen rapid card test	Negative
Serum sodium/Potassium/Chlorides	138/4.76/103 mmol/L
Serum calcium	10 mg/dl
Throat swab	No growth was observed on aerobic incubation
Widal test	Titers for Salmonella Typhi O and H and Paratyphi AH antigen was <1:20
Dengue IgM/IgG by rapid card test	Negative
Anti-streptolysin O antibody titres	Negative
Serum Vitamin B 12 level	298 pg/mL
Serum ceruloplasmin	28 mg/dL
Thyroid panel	Free T3/T4-2.38 pg/mL, 1.33 ng/dL; TSH: 1.13mIU/L
Electrocardiogram	Normal
Electroencephalography	Normal
Ophthalmological examination	Normal
Magnetic resonance imaging of brain	Normal

negative), occurred within a week of initiating anti-malarial therapy (artesunate and chloroquine), with prominent visual hallucinations, sensory symptoms, and historical evidence of disorientation. As all the medications were prescribed in right dosages, and according to WHO guidelines, and that artesunate is rarely shown to lead to neuropsychiatric adverse effects, so the adverse side effect of psychosis possibly occurred consequent to chloroquine (Naranjo Algorithm score = 4).

To conclude, the primary care physicians, pediatricians, and psychiatrists must remain aware of the severe psychiatric side effects of a commonly prescribed anti-malarial drug.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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