Chorea in a 29-year-old Nigerian following antimalarial treatment with artesunate

There are about 300—600 million episodes of clinical *Plasmodium falciparum* infections globally every year. Malaria remains a major cause of morbidity and mortality in tropical countries. Because of the relentless increase in resistance of malaria parasites to conventional drugs, including chloroquine, sulfadoxine—pyrimethamine, and mefloquine, new therapeutic approaches have been developed. The key one among these has been artemisinin-based combination therapy (ACT). The artemisinin group of drugs was discovered in China from a crude extract of the wormwood plant *Artemisia annua* (qinghao). Artemisinin is the parent compound that can be variedly modified at the C10 position to produce artesunate, arteether, arteether, dihydroartemisinin, or artelinc acid. Artesunate is a water-soluble hemisuccinate derivative of dihydroartemisinin. The hemiscuccinate group in the molecule confers water solubility and relatively high oral bioavailability. Artesunate is highly active against both the sexual and asexual forms of the four species of *Plasmodium* that affect humans. The antimalarial action of artemisinins has been attributed to their ability to generate free radicals. The endoperoxide moiety, which is essential bonds with key parasite proteins, such as membrane transporters, thereby impairing their functions. An alternative mechanism of action based on inhibition of the calcium ATPase (sarcoplasmic endoplasmic reticulum cal-
cium ATPase, SERCA) of the malarial parasites has been suggested.7

A 29-year-old public servant presented with a 6-hour history of repetitive, jerky, and involuntary movements of the body, which started gradually after the second dose of a brand of oral artesunate. The purposeless spasms were said to have started in the limbs and later involved the whole body. He had been having moderate-grade intermittent fever, headache, and generalized body weakness for three days and decided to do self-medication for presumptive malaria fever by using artesunate tablets. There was no neck pain or rigidity, no photophobia, altered sensorium, weakness of the limbs, or upper respiratory tract symptoms. There was no previous or concurrent history of trauma to the head. He was not on any other medications besides artesunate, and there was no known prior use of artemisinin derivatives. There was no personal or family history of chorea or any movement disorders, no history of seizure disorder, and his hemoglobin genotype was AA.

Physical examination revealed an anxious young man who was conscious and fully oriented. There was no pallor, jaundice, or cyanosis, and his right axillary temperature was 37.6°C. There were repetitive, jerky, and uncontrollable movements of the whole body with spasms mostly affecting the lower limbs. His cognitive functions were intact. There were neither facial ticks nor signs of meningeal irritation, ataxia, or asterixis. All cranial nerves were intact. Muscular tones, power and tendon reflexes were normal, and sensations were intact. Other systems were essentially normal.

He was admitted, and blood samples were taken for malarial parasite blood films, serum electrolytes, BUN and creatinine, and random plasma glucose assays. The blood films were positive for malarial parasites, but the serum electrolytes, BUN, creatinine, and glucose were within normal limits. Other appropriate investigations were done. He was reassured and counseled and the offending drug, artesunate, was stopped. Intramuscular diazepam (20 mg) was administered. The same dose was repeated one hour later and subsequently followed with oral diazepam 5 mg every 6 hours for the next 48 hours. The patient improved considerably with chorea completely subsided within 24 hours of admission. He was treated with amodiaquine and sulfadoxine—pyrimethamine and discharged after 36 hours. He was followed up for more than 9 months after discharge and there was no recurrence of chorea.

ACT has become the therapy of choice for malaria in some African countries following treatment disappointments and attendant increased ill health, deaths, and enormous economic losses associated with chloroquine resistance. The most commonly reported adverse effects of artemisinins include transient gastrointestinal disturbance, which may be a feature of the acute malaria in itself.8 However, neurotoxicity, principally in the form of brain stem lesions, has been identified in animals receiving high doses over long periods.9–13 The neurotoxicity included gait disturbances, loss of spinal and pain response reflexes, loss of brain stem and eye reflexes, seizure-like activity, and stereotypic movement disorders. Ataxia, slurred speech, tremor, and hearing loss have also been reported in a small number of humans.14–19 Toovey and Jamieson15 reported that treatment of uncomplicated malaria with co-artemether (artemether–lumefantrine) was associated with hearing loss among subjects working at a construction site in Mozambique. However, these neurological effects may not likely be of clinical significance, particularly because of limited penetration of artemisinin derivatives into the cerebrospinal fluid.20–27 Although chorea per se has not been reported in humans following the use of artemisinin derivatives for malaria, Brewer et al.9 reported the onset of a clinical neurologic syndrome with dose-related changes in seizure-like activity and stereotypic movement disorders in Sprague–Dawley rats exposed to high doses of artemether and arteether over long periods. Neurotoxicity appears to be partly mediated through artemisinin induced oxidative stress in exposed brainstems.28

Chorea is a neurologic disorder characterized by involuntary spasmodic movements of the body. Movements are jerky and arrhythmic, and may involve the whole body. Drugs are one of the recognized causes of chorea. It may occur as a result of increased dopaminergic activity in the projections from substantia nigra to the striatum, resulting in decreased GABAergic activity from the striatum to the globus pallidus.29,30 Drug treatment of chorea includes: dopaminergic blockers (e.g., haloperidol), dopaminergic depletors (e.g., tetrabenazine), benzodiazepines (e.g., diazepam), or anticonvulsants (e.g., phenytoin). We used a benzodiazepine, diazepam, for our patient and the response was dramatic.

This report is to sensitize health professionals to the possibility of human neurotoxicity, particularly chorea, with the use of artemisinin derivatives. It also calls for increased vigilance for the adverse reactions of these increasingly used antimalarial drugs. Neurotoxicity should be evaluated particularly in children, as the susceptibility of the developing nervous system to injury could be greater than in adults. There is urgent need to develop the next generation of artemisinins with reduced toxicity, increased potency, and improved stability.

Conflict of interest: No conflict of interest to declare.

References

Correspondence

17. Van Vugt M, Angus BJ, Price RN, Mann C, Edwards G, Ward SA, Park BK, et al. Artesunate and gentamicin for four weeks. We were unable to recover any further details about this period.

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Kytococcus Schroeteri, a rare agent of endocarditis

We report herein the case of a prosthetic valve endocarditis due to Kytococcus Schroeteri.

A 70-year-old man with a bioprosthetic valve was admitted to Laveran Hospital in Marseilles, France in September 2004 with a fever (39 °C), headache, and cough. Blood cultures were sterile. He was treated with vancomycin and gentamicin for four weeks. We were unable to recover any further details about this period.

In March 2005 he was admitted to Timone Hospital in Marseilles for a new episode of fever and shivers. On admission, his white blood cell count was 11.53 × 10^9/L (80.8% polymorphonuclear cells), his hemoglobin level was 13.1 g/dL, the erythrocyte sedimentation rate was 24 mm in the first hour, and his C-reactive protein level was 83 mg/L. Transeosophageal echocardiography showed a 4-mm vegetation on the aortic bioprosthetic valve and an intratinal abscess (Figure 1). Computed tomography examination showed an embolic cerebral stroke and bilateral renal emboli.

An endocarditis diagnostic kit was performed, as previously described.1 The first blood culture of the kit was performed using a set of Bactec® Plus Aerobic/F and Bactec® Lytic/10 Anaerobic/F bottles (BD Diagnostic Systems, Sparks, MD, USA). The specimen volume is 10 ml for each bottle. The second and third blood cultures of the kit were collected in Bactec Plus Aerobic/F bottles, with 2-h intervals between samples. Blood bottles were incubated for 5 days at 37 °C under continuous automated monitoring for bacterial growth in the medium. One blood culture grew Gram-positive cocci.