Neurological Dysfunction Following Malaria: Disease- or Drug-Related?

SIR—The artemisinin derivatives are very important new antimalarial drugs, which are being used increasingly throughout the world. The possibility that these otherwise extremely well tolerated and highly effective drugs may damage the CNS is of great concern. Unfortunately, the case report by Elias et al. [1] contains unjustified speculation on this subject that may cause unnecessary alarm.

The authors described a 55-year-old expatriate patient who was treated with an inadequate course (5 days) of artesunate (parenteral? oral?) for acute falciparum malaria in Ghana and, when recrudescence of the infection occurred 3 weeks later, was again treated with artesunate. He developed tremors of the hands and unsteadiness, neurological sequelae of acute malaria which are well described [2-5]. However, the authors chose to ascribe this to the artesunate treatment rather than to the malaria and, as evidence to support their hypothesis, misquote a reference describing 74 patients with cerebellar dysfunction following malaria [6] (of whom none had received artemisinin derivatives and 11 had not received any antimalarial treatment at all).

Some antimalarial drugs are potentially neurotoxic. Mefloquine is associated with a self-limiting syndrome characterized by psychosis or encephalopathy, with an incidence of ~1 in 10,000 in healthy individuals, 1 in 200–1000 among people who have had uncomplicated malaria, and 1 in 20 among people who have had cerebral malaria [7]. Chloroquine may also (rarely) produce neuropsychiatric reactions. In contrast, large numbers of patients have developed tremor or encephalopathy, with an incidence of 9.000 in healthy individuals, 1 in 200–1000 among people who have had cerebral malaria [6] (of whom none had received artesinin derivatives and 11 had not received any antimalarial treatment at all).

Tremor has been described most commonly in adults, with an overall incidence ranging from <0.1% to 3% of all cases of acute falciparum malaria [1, 7]. Self-limiting tremor has been reported to occur before or after treatment with chloroquine, quinine, mefloquine, and (in this case) artesunate, which suggests strongly that it is a result of the disease rather than its treatment. Different types of tremor have been observed: (1) as part of a Parkinsonian syndrome; (2) rarely, in association with the well-described delayed cerebellar ataxia that may follow acute falciparum malaria; and (3) sometimes in isolation.

It is highly likely that the neurological abnormalities in this case resulted from malaria and not artesunate. However, instead of discussing this probable explanation, Elias et al. have provided unjustified and misleading recommendations that would unnecessarily restrict the use of artemisinin derivatives for the treatment of malaria.

Nicholas J. White
Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

References

Diagnosing Postneurosurgical Meningitis

SIR—It is unclear why the authors of a report of a recent study regarding surrogate markers for the diagnosis of postneurosurgical bacterial meningitis [1] thought there was a need for any additional surrogate marker beyond the CSF concentrations of total and polymorphonuclear leukocytes, since they regarded these as “gold standard” tests for defining the presence or absence of bacterial meningitis. CSF leukocyte counts are as readily obtainable as CSF lactate and glucose levels, and
SIR—We appreciate the comments of J. R. Johnson regarding our study [1], which demonstrated higher predictive values for CSF lactate (cutoff, 4 mmol/L) than CSF : blood glucose ratio (cutoff, 0.4 mmol/L) for the diagnosis of bacterial meningitis in neurosurgical patients. We agree that it would be clinically important to study the outcome of patients with “presumed bacterial meningitis” who did not receive antimicrobial therapy. However, at the time that we performed our study, all patients who qualified for our category “presumed bacterial meningitis” received antimicrobial therapy. We planned and performed our study because we had some doubt that leukocyte counts in the CSF are reliable as a single test for the diagnosis of bacterial meningitis in neurosurgical patients.

Neutrophilic CSF pleocytosis as a consequence of subarachnoid-space inflammation is found in various infectious and noninfectious forms of meningitis. The gold standard for the diagnosis of bacterial meningitis is the documentation of bacteria in CSF by use of gram stain or culture. Both CSF leukocyte count and documentation of microbial pathogens are inconclusive in patients who are receiving steroids or antimicrobial therapy. In spontaneously occurring meningitis, CSF lactate and CSF : blood glucose ratio have been found to discriminate bacterial from nonbacterial causes of meningitis [2–7]. Neurosurgery involving the posterior fossa can result in aseptic meningitis (“posterior fossa syndrome”). Signs of meningeal irritation appear rapidly, and although CSF analysis shows polymorphonuclear pleocytosis with elevated protein and low glucose mimicking bacterial meningitis, cultures remain negative. The obvious clinical dilemma is whether to treat these patients with antimicrobial therapy or withhold it.

Standard CSF studies (i.e., gram stain, leukocyte counts, or glucose and protein concentration) have proven unreliable for the diagnosis of bacterial meningitis after neurosurgery [8]. Therefore, in addition to standard CSF analysis, CSF : blood glucose ratio and CSF lactate levels are used in some centers to help differentiate postoperative bacterial meningitis from aseptic meningitis. In a retrospective study, we assessed which of the 2 ancillary tests, CSF lactate or CSF : blood glucose ratio, yielded better predictive values for the diagnosis of bacterial meningitis after neurosurgery. As correctly pointed out by J. R. Johnson, CSF leukocyte count accurately discriminated nonbacterial meningitis from presumed and proven bacterial meningitis, as shown in figures 1 and 2. However, this observation does not render CSF lactate or CSF : blood glucose ratio determination redundant, as the leukocyte count was used to categorize patients into the predefined groups. Our study showed that CSF lactate is superior to CSF : blood glucose ratio for the diagnosis of post-neurosurgical bacterial meningitis. This finding might prove helpful for designing a prospective study, as suggested by J. R. Johnson, that addresses the question: which patients need antimicrobial therapy?

Stephen L. Leib and Werner Zimmerli
Institute for Medical Microbiology, University of Bern, and Division of Infectious Diseases, University Hospital, Basel, Switzerland

References
7. Nelson N, Eeg-Olofsson O, Larsson L, Ohman S. The diagnostic and pre-