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Malaria and the problem of drug resistant *Plasmodium falciparum*

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The optimism which greeted the malaria control activities of the sixties has been replaced by pessimism [1]. There has been a resurgence of the disease as it affects 102 countries, with an estimated 270 million cases and approximately one million deaths annually. Ninety per cent of these deaths come from Africa south of the Sahara [1] making it mainly an African problem. The background to this scenario is the increasing prevalence of drug resistant *P. falciparum* [2]. The resultant effect has been increased morbidity and mortality from malaria.

Cerebral malaria

Cerebral malaria which is defined as altered consciousness in a patient who has *P. falciparum* parasites in the blood and in whom no other cause of coma can be found [3], is the most lethal complication of malaria [4]. Mortality from this form of malaria is rather high and may be up to 50% in some instances [4,5,6]. In our environment it was previously thought that cerebral malaria was uncommon in persons above the age of 11 years as pointed out in one of the articles in this edition of the Journal. This has since changed [7].

The background to this change in the presentation of the disease can be attributed to an increase in the prevalence of drug resistant malaria which was first authenticated in Ibadan in 1987 [8]. This simple cause and effect relationship may not be all that there is to it, as the pathogenesis of this complicated form of malaria may be multifactorial.

Current evidences indicate that mechanical obstruction by sequestration of parasitized red cells in the microcirculation of the small vessels of the brain may be the main pathology of the disease. This has been demonstrated in post-mortem specimens from fatal cases [6,9]. The reduction of cerebral blood flow may therefore lead to anaerobic cerebral glycolysis with increased lactate production. White *et al.* [10] have demonstrated higher lactate levels in fatal compared to non-fatal cases. Immune mechanisms have also been implicated through tumour necrosis factor, (TNF) a cytokine produced by monocytes and macrophages. There is indeed evidence that plasma levels of TNF are elevated in adults with cerebral malaria [11] and children with *P. falciparum* malaria [12]. High levels of TNF have been shown to be associated with increased risk of a poor outcome in malaria [12,13]. The role of raised intracranial pressures in the pathogenesis of the disease is not clear as they have been demonstrated to be raised in Kenyan children[14]. Post-mortem data from Ibadan have provided confirmatory evidence for this [6]. Evidence from adults are to the contrary as raised intracranial pressure and cerebral oedema are not prominent features of the disease in adults [15].

To reduce the high mortality associated with cerebral malaria, it is essential that treatment must be prompt and adequate doses of sensitive anti-malarials given. Since the question of resistance is very important in endemic areas, the current studies on artemether in our environment and other parts of the world is therefore timely [16,17]. It is also a welcome alternative to the current intravenous regimes of chloroquine and quinine which are not suited for the rural areas [3,6]. Various other agents have been suggested as adjuncts to specific drug treatment. They include urea, mannitol, corticosteroids, heparin, cyclosporin, tumour necrosis factor antibody and recently desferrioxamine [18]. All these are still being closely studied as they are not proven beyond doubt to reduce mortality or morbidity.

Prophylaxis

The question of the use of prophylactics is an obvious one to raise in view of the grim picture presented above. The article on prophylaxis that appears in this edition of the journal is timely [19]. The problem has always been that of adequately protecting the population at risk. For example, the authors in that article show that although chloroquine does protect against malaria while the children in the study used it prophylactically, the prevalence of severe malaria is increased in the later ages when they are withdrawn from

al. Dexamethasone proves deleterious in cerebral malaria. A double-blind trial in 100 comatose patients. New England Journal of Medicine 1982; 306: 313–319.
6. Walkers O, Salako LA, Sowunmi A, Thomas JO, Sodeinde O, Bondi FS. Prognostic risk factors and post mortem findings in cerebral malaria in children. Trans. R. Soc. Trop. Med. Hyg. 1992: 86: 491–493.
7. Sowunmi A, Walker O, Salako LA. Cerebral malaria in non-paediatric subjects resident in South Western Nigeria. Afri. J. Med. med. Sci. 1993; 1: 49–53.
8. Salako LA and Aderounmu AF. *In-vitro* chloroquine and mefloquine-resistant *Plasmodium falciparum* in Nigeria. Lancet 1987; 572–573.
9. Thomas JO. Clinical and histopathological correlation of cerebral malaria. Trop. Geogr. Med. 1971; 23: 232–238.
10. White NJ, Warrell DA, Looareesuwan S, Chanthavanich P, Phillips RE, Pongpaew P. Pathophysiological and prognostic significance of cerebrospinal fluid lactate in cerebral malaria. Lancet 1985; i: 776–778.
11. Kern P, Hemmer CJ, Van Damme J, Gruss HJ, Dietish M. Elevated tumor necrosis factor alpha and interleukin-6 serum levels as markers for complicated *Plasmodium falciparum* malaria. Am. J. Med. 1989; 87: 139–143.
12. Kwiatkowski D. Tumor necrosis factor, fever and fatality in falciparum malaria. Immunol lett. 1990; 25: 213–216.
13. Grau GE, Piguet PF, Vassalli P, Lambert PH. Tumor necrosis factor and other cytokines in cerebral malaria. Experimental and clinical data. Immunol. Rev. 1982; 112: 49–70.
14. Newton CRJE, Kirkham FJ, Winstante PA, *et al.* Intracranial pressure in African children with cerebral malaria. Lancet 1991; 572–573.
15. Looareesuwan S, Warrell DA, White NJ, *et al.* Retinal haemorrhage, a common sign of prognostic significance in cerebral malaria. Am. J. Trop. Med. Hyg. 1983; 32: 911–915.
16. White NJ, Waller D, Crawely J, *et al.* Comparison of artemether and chloroquine for severe malaria in Gambian children. Lancet 339: 317–321.
17. Walker O, Salako LA, Omokhodion SJ, Sowunmi A. An open comparative trial of intramuscular artemether against intravenous quinine in cerebral malaria in Nigerian children. Trans. R. Soc. Trop. Med. Hyg. 1993. In press.
18. Editorial. Desferioxamine and cerebral malaria. Lancet 1992; ii: 1386–1387.
19. Oyediran ABOO, Topley E, Osunkoya BO, *et al.* Severe morbidity among children in a trial of malaria chemoprophylaxis with pyrimethamine or chloroquine in Ibarapa, Nigeria. Afr. J. Med. med. Sci. 1993. In press.
20. Greenwood BM, Greenwood AM, Bradley AK, *et al.* Comparison of two strategies for control of malaria within a primary health care programme in the Gambia. Lancet 1988; i: 1121–1127.
21. Nahlen BL, Akintunde A, Alakija T, *et al.* Lack of efficacy of pyrimethamine prophylaxis in pregnant Nigerian women. Lancet 1989; 2: 830–834.
22. Limsonwong N, Pang LN, Singharay P. Malaria prophylaxis with proguanil in children living in a malaria endemic area. Amer. J. Trop. Med. Hyg. 1988; 38: 231–236.
23. Quinghaosu. Antimalarial Coordinating Research Group. Antimalarial studies on quinghaosu. Chinese Medical Journal 1979; 92: 811–816.
24. Ezeamuzie IC, Ojinnaka MC, Uzogara EO, Oji SE. Anti-inflammatory, antipyretic and anti-malarial activities of a West African medicinal plant *Picralima nitida.* Afr. J. Med. Sci. 1993. In press.
25. Makinde JM, Awe SO, Agbadakin JM. Effect of *Khaya grandifolioles* on *Plasmodium berghei berghei* in mice. Phytotheraphy Research 1988; 2: 30–32.
26. Makinde JM, Amusan OO and Adesogan EK. The antimalarial activity of chromatographic fraction of *Spathodia campanulata* stem bark extracts against *Plasmodium berghei berghei* in mice. Phytotheraphy Research 1990; 4: 53–56.
27. Obih PO and Makinde JM. Effect of *Azadirachtha indica* on *Plasmodium berghei berghei* in mice. Afr. J. Med. med. Sci. 1985; 14: 51–54.
28. Makinde JM and Obih PO. Screening *Morinda lucida* for antimalarial action on *Plasmodium berghei berghei* in mice. Afr. J. Med. med. Sci. 1985; 14: 59–63.
29. Makinde JM, Obih PO and Jimoh AA. The effect of *Solanum erianthum* aqueous leaf extract on *Plasmodium berghei berghei* in mice. Afr. J. Med. med. Sci. 1987; 16: 195–196.

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