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Delayed cerebellar ataxia complicating falciparum malaria: a clinical study of 74 patients

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Abstract We report the clinical features of 74 patients with delayed cerebellar ataxia (DCA) following falciparum malaria, who were prospectively followed up at two centres. This unusual complication has an acute onset, with signs suggesting a predominantly midline cerebellar lesion without any evidence of cerebral involvement. There was a delay of a median 13 days between the onset of fever and the onset of ataxia. DCA has a good prognosis, with spontaneous and complete recovery within 3 months. In our opinion, it is an example of a post-infective neurological syndrome possibly mediated via an immune mechanism.

Key words Cerebellar ataxia
Falciparum malaria

Introduction

Delayed cerebellar ataxia (DCA) is an unusual complication of falciparum malaria, first reported in Sri Lanka in 1984 [17]. It is characterised by the development of a self-limiting, isolated cerebellar ataxia in otherwise well, conscious patients following an attack of falciparum malaria. Since its first description, there have been several other reports of this condition, all except two case reports originating from Sri Lanka [6, 7, 11, 12, 14–16, 23]. Of the patients reported outside Sri Lanka, one had pancytopenia in addition to cerebellar ataxia [12] and the other was poorly investigated [15]. More recently, Chaine et al. [4], reported a patient with falciparum malaria who developed isolated cerebellar signs several days after the onset of fever. However, in contrast to other reports of patients with DCA, the electroencephalogram was abnormal and suggested a more diffuse encephalopathy in their patient.

This paper presents the clinical features of a large series of patients with DCA seen at two different centres. This enabled us to describe its clinical course and prognosis in more definitive terms. We have also performed detailed investigations, particularly with a view to excluding other possible causes of a self-limiting cerebellar ataxia, which are lacking in earlier descriptions of the syndrome.

Patients and methods

Patients admitted to the Teaching Hospital Peradeniya and the General Hospital Colombo between August 1986 and August 1988 with ataxia following a documented attack of *Plasmodium falciparum* malaria or febrile illness highly suggestive of malaria were studied prospectively. Information was elicited with regard to the malarial attack, treatment received, source of malaria, previous attacks of malaria and any drugs taken after each attack. Details of the ataxia and associated symptoms were recorded, and a complete physical examination was performed. Results of investigations were also entered into data sheets. All patients were offered follow-up in the outpatient clinics.

Results

A total of 74 patients were studied. They were aged between 16 and 56 years (median 28). Sixty-six of them were males. Thirty-two of the patients were permanent residents and 2 were temporary residents (stay < 3 months) in areas endemic for malaria. Of the others 16 had made multiple visits to malarial areas, and 10 only a single visit, whilst 14 denied visiting a known malarial area. The malarial areas referred to by the patients were scattered throughout the country. Cerebellar ataxia was preceded by a well-documented attack of falciparum malaria confirmed by a positive blood film and treated

with chloroquine in 56 patients, while in 7 the febrile illness had been very suggestive of malaria clinically and therefore treated with anti-malarials. Eleven patients had not received any anti-malarial treatment. A previous history of malaria (1 to about 30 attacks) with no accompanying or subsequent symptoms was obtained in 38 patients. The delay between the onset of the last episode of fever and the onset of ataxia was 3–41 days (median 13). In 62 patients the ataxia developed after an afebrile period of 1–38 days (median 5), and they continued to be afebrile during cerebellar dysfunction. In 12 patients fever was present at the onset of ataxia and lasted for a further 9 days (median 2), but there was no hyperpyrexia. None of the patients had impaired consciousness or seizures. Ataxia was maximal in 2–14 days after its onset.

The cerebellar signs were predominantly midline-truncal, with gait ataxia being pronounced in all 74 patients. Other findings were: abnormal heel-knee-shin test, 53; abnormal finger-nose test, 44; dysarthria, 42; dysdiadochokinesia, 41; and nystagmus, 18. Nystagmus was horizontal, phasic and bidirectional. Other systems were normal except for hepatomegaly in 7 and splenomegaly in 19 patients. The patients were conscious, rational and alert, and had no signs of cerebral involvement. There were no features suggestive of an alternative cause of cerebellar pathology. Particular attention was paid to a history of alcohol abuse, exposure to heavy metals, drug history, recent vaccination, other febrile illnesses (including exanthemata), and family history – all of which were negative (except the use of anti-malarials to treat the attack of malaria in 63 patients). There was no clinical evidence of malignancy.

Investigations

Peripheral blood films showed *P. falciparum* in 33 and mixed infection in 1 (rings in 15-including the 11 patients who had not been given anti-malarials; rings and gametocytes in 10; and only gametocytes in 8). Serum antibody titres to *P. falciparum* (measured in 48 patients) were positive at a significant level. The following investigations showed no significant abnormalities: full blood count, blood glucose, urea, creatinine and electrolyte concentrations, liver function tests, Widal's test, serology for Japanese encephalitis, Coxsackie B (types 1–6) and echovirus infection, VDRL (42 patients), cerebrospinal fluid examination including culture for bacteria (52 patients), thyroid stimulating hormone levels (32 patients), chest radiographs (32 patients), electroencephalography, and brain CT with contrast enhancement (11 patients). Nerve conduction and electromyography of limb muscles were performed in the initial phase of the study but were abandoned later on as they were consistently normal.

Plasma chloroquine levels were assayed by a colorimetric method in 20 specimens (12 patients and 8 controls). The 12 patients (10 males and 2 females) were aged 16–52 years (median 29) with cerebellar ataxia 18–26 days following a documented attack of falciparum malaria. Blood was collected on admission 22–31 (median 26) days after onset of the malarial attack. The controls 7 males and 1 female, aged 23–46 years (median 25), who 21–26 (median 24) days after the onset of an attack of falciparum malaria had not developed cerebellar symptoms. The chloroquine levels were less than 60 μg/l in all specimens tested, with no significant difference in levels between patients and controls.

Patients with ring stages of *Plasmodium* were treated with chloroquine and primaquine, while the patients with only gametocytes were treated with primaquine alone. Subsequent blood films in these patients showed clearance of parasitaemia, but the cerebellar signs did not improve. Three of the patients with severe ataxia were empirically given prednisolone 60 mg/day for 7 days and the dose was then tailed off. In 1 patient the ataxia lasted only 7 days and in the other 2 it lasted 30 days. The others were given only symptomatic treatment and physiotherapy.

Sixty-six (89.2%) patients were followed up until they recovered completely. Recovery was spontaneous and complete within 3 months of the onset of ataxia. The other 8 patients had also improved by the time they were discharged from hospital, but were lost to follow-up. Several patients attended outpatient clinics for some time after complete recovery. A further attack of malaria developed in 3 patients and the attack was followed by ataxia in 2 of them.

Discussion

We describe in detail the clinical features of DCA following an attack of falciparum malaria. DCA is an acute-onset, predominantly midline cerebellar lesion without any evidence of cerebral involvement. It occurs a median of 13 days following the onset of an attack of otherwise uncomplicated falciparum malaria, and has an excellent prognosis with spontaneous and complete recovery within 3 months.

Unlike the earlier descriptions of DCA, this study has excluded many other possible causes of a self-limiting cerebellar ataxia. Some of these merit further discussion. In most of our patients with DCA, the attack of malaria had been treated with chloroquine. The possibility that DCA may be due to a toxic effect of chloroquine or due to a toxic contaminant of the drug has been previously suggested [14, 16]. However, the plasma chloroquine levels were found to be less than 60 μg/l in all the samples tested, and adverse reactions to chloroquine usually develop when plasma concentrations exceed 250 μg/l [13, 22]. There was also no significant differences in chloroquine concentrations between patients with DCA and the

controls, who did not develop DCA after falciparum malaria. Furthermore, several patients in the present study and some of those described earlier by Senanayake [16] had in fact not received any chloroquine prior to developing ataxia. DCA has also not developed in any patient following vivax malaria treated with chloroquine, in spite of the fact that this is the commoner type of malaria in Sri Lanka [1]. It is therefore very unlikely that either chloroquine or a toxic contaminant in the drug is responsible for DCA. Acute cerebellar ataxia can also follow a wide variety of infections: viral, bacterial, fungal and protozoal [19, 20, 21]. However, in the patients we describe, there was no clinical or serological evidence of any infection other than malaria. Japanese encephalitis virus infection, which can give rise to cerebellar ataxia, was specifically excluded, as this infection is also endemic in parts of Sri Lanka where malaria is prevalent. Hyperpyrexia is unlikely to have been the cause of cerebellar ataxia, because 62 of the 74 patients developed DCA after an afebrile period of 1–38 days (median 5) and continued to be afebrile during the entire period of cerebellar dysfunction. Furthermore, none of the 12 patients who were febrile at the onset of ataxia had hyperpyrexia.

A causal relationship between falciparum malaria and DCA is therefore most likely. The parasitaemia had not completely cleared in about one-third of the patients (*P. falciparum* rings present in the peripheral blood films) at the onset of ataxia. However, the delay between the onset of fever and onset of ataxia, and the fact that treatment with anti-malarial drugs did not improve the ataxia despite clearance of parasitaemia, could be taken as evidence against the possibility that *P. falciparum* was directly responsible for the cerebellar syndrome. Quite distinct from DCA, in instances where cerebellar signs occur during an acute attack of falciparum malaria, *P. falciparum* is thought to be directly responsible for cerebellar dysfunction [2, 5]. In this situation, the patients are febrile during the ataxic period and respond dramatically to antimalarials, with complete neurological recovery usually occurring within 48 h of starting treatment [2, 3, 5, 18]. The selective involvement of the cerebellum and especially the delay between the onset of fever and the onset of cerebellar dysfunction suggest that immune mechanisms are involved in its pathogenesis. The favourable response to treatment with steroids seen in some patients [16], and the finding of elevated cytokine levels, tumour necrosis factor α, interleukin 2 and interleukin 6, in the sera and cerebrospinal fluid of patients with DCA suggesting immune activation [8] further support the immunological hypothesis. The delayed onset of the cerebellar lesion and its very focal distribution within the brain raises the possibility of molecular mimicry between *Plasmodium* antigens and epitopes within the cerebellum with cerebellar dysfunction resulting from antibody cross-reactivity. There has, however, been no experimental evidence to support antibody mediation, and it has been suggested that cell-mediated immune mechanisms may be more important than humoral mechanisms in its pathogenesis [9]. The self-limiting nature of the cerebellar dysfunction with full recovery within 3 months is suggestive of a demyelinating process. However, there was no evidence of demyelination on CT and owing to the essentially benign nature of the condition, it has not been possible to perform pathological studies on these patients. Furthermore, because not all persons who contracted falciparum malaria developed DCA, host susceptibility factors which are yet to be defined are also likely to be important in the pathogenesis of this syndrome.

There have been no descriptions of DCA complicating falciparum malaria prior to 1984 even though *P. falciparum* infection had been endemic in parts of Sri Lanka for many years and also caused several epidemics. Some of our patients had previously suffered several attacks of malaria, but not develped cerebellar dysfunction. The complication occurred in patients who were permanent residents of areas endemic for malaria and presumably had a certain degree of immunity. Yet they seemed as susceptible to DCA as those who contracted falciparum malaria during a single visit to an endemic area. That a new strain of *P. falciparum* was responsible for this complication is a possible explanation. results of an epidemiological survey performed in the North Central region of Sri Lanka support this hypothesis [10]. The survey confirmed clinical impressions of the epidemic nature of DCA, and showed that the frequency of DCA between 1986 and 1991 corresponded very closely with an epidemic of falciparum malaria which occurred between 1984 and 1988 [1]. Both the epidemic of malaria and the frequency of DCA reached a peak in 1987. DCA of such epidemic proportions has been reported solely from this country; only 2 cases of this complication have originated outside Sri Lanka. The condition, in our opinion, is an example of a post-infective neurological syndrome due to a new strain of *P. falciparum,* mediated via an immune mechanism.

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