

# Cerebral malaria in the United Kingdom

IVAN JANOTA AND BALA DOSHI

From the Institute of Psychiatry, Denmark Hill, London SE5 8AF, UK

**SUMMARY** Four fatal cases of cerebral *Plasmodium falciparum* malaria in English travellers returning from Africa have been seen in the last 13 years. The haemorrhages, accumulations of microglia, and destruction of cerebral white matter around small veins as a result of blockage of cortical capillaries by parasitised red blood corpuscles resemble the effect of fat embolism. Microglia in the lesions is demonstrated by special neuropathological techniques. Attention is drawn to the need for a prompt recognition of malaria since appropriate treatment can be successful.

Malignant tertian cerebral malaria due to *Plasmodium falciparum* is not rare in the United Kingdom. Between 1968 and 1977 there were 56 deaths reported due to malaria; a further eight deaths occurred in the first nine months of 1978, when a total of 1533 cases of malaria, 201 of them due to *P. falciparum*, were imported into this country. These figures reflect the mean fatality of 4% in the past decade (British Medical Journal, 1972; Bruce-Chwatt, 1978), and most if not all deaths due to malaria are in cases of *P. falciparum* infection. Emphasis on the clinical and pathological involvement of different systems of the body in malaria is reflected in various classifications. Our cases fall into the cerebral malaria group.

Malaria is particularly dangerous in those exposed to it for the first time. The four fatal cases reported in this paper were in adult English travellers returning from Africa in the last 13 years. Three had not taken antimalarial prophylactics. A delay in diagnosis and treatment is more likely in this country than in territories where malaria is endemic (Sheehy, 1975) and increases the likelihood of a fatal outcome. In the brain of the victims of falciparum malaria there is destruction of white matter around small veins as a result of blockage of the capillaries in the cerebral grey matter by red blood corpuscles containing the parasite (Spitz, 1946; Greenfield, 1958; Scheidegger, 1958; McMenemey, 1966; Winslow *et al.*, 1971; Escobar and Nieto, 1972). The cerebral lesions resemble those found in fat embolism, which when it affects the brain is also often fatal (Spitz, 1946; Zülch and Tzonos, 1964; Watson, 1970; Zülch, 1971).

## Case histories

### CASE 1 (MH No. 4528)

A 61-year-old toy merchant returned from a 17-day visit to Ghana on 1 May 1965. He had taken no anti-malarial prophylactics. On 3 May he felt hot, sweated, shivered, and complained of anorexia, nausea, vomiting, diarrhoea, headache, and double vision on looking up. His urine was dark brown. On 8 May he became drowsy and was admitted to hospital. He was confused, jaundiced, and hypotensive. His temperature was 39.4°C (103°F). Blood films then showed a heavy infection with *P. falciparum*. He was treated with intravenous fluids, antibiotics, and hydrocortisone. The next day (9 May) he was transferred to the intensive care unit. He was drowsy but lucid. The liver was enlarged, soft, and tender, and the spleen was just palpable. He had fine nystagmus but no other abnormal neurological signs. Chloroquine was given intravenously from 9 May; altogether six doses of 200 mg were given over four days. He deteriorated. Oliguria developed and a daily peritoneal dialysis was started. From 13 May on, there were no malarial parasites in the peripheral blood. The oliguria persisted and he suffered respiratory distress. Intermitent assisted respiration was given. On 15 May the peritoneal dialysate seeped into extraperitoneal tissues and *Pseudomonas pyocyanea* was found on blood culture. On the next day haemodialysis was carried out. He died on 17 May, 15 days after the onset of symptoms. Necropsy showed congested, soft, deeply brown liver and spleen and oedematous lungs. The kidneys were haemorrhagic with necrotic tubules.

### CASE 2 (MH No. 5330)

On 12 December 1968 this 64-year-old housewife

returned from a two-month visit to her son in Kenya; she had taken proguanil hydrochloride (Paludrine). On arrival at London Airport she felt unwell and thought that she had influenza. The next day she was seen by her doctor and treated for influenza and gastroenteritis. On 14 December she had a high fever and diarrhoea and she vomited. For the next three days her temperature was normal and she felt better. On the morning of 18 December she became jaundiced and in the evening she collapsed and was unconscious for 5 minutes. Her blood pressure was 90/50 mmHg and her temperature 39.7°C (103°F); the faeces were watery and blood stained. She had rigors and was admitted to hospital at 1840. She became very restless and lost consciousness and 15 minutes later she died. A blood film showed a mixed infection of *Plasmodium vivax* and *falciparum*. A coroner's postmortem showed jaundice and a few cutaneous petechial haemorrhages.

#### CASE 3 (MH No. 40/74)

A 53-year-old business executive wrote to his wife from Ghana on 8 December, and from France where he had flown on 17 December 1973, that he had a bad cold. On arrival in England on 22 December he appeared to have a very bad cold. He was seen by his doctor and given an antibiotic. On 25 December his temperature was 40°C (104°F). Next day his temperature was normal; he was then thought to have influenza. On 28 December he became drowsy and shivered. On 29 December at 1745 he was admitted to hospital. A blood film showed *P. falciparum*. He had not taken any antimalarial prophylactics. He died at 2130, eight days after arrival in England and 13 days after leaving Ghana. A coroner's postmortem showed gross oedema of the lungs, bronchopneumonia, a soft heart, a large, soft spleen, and an enlarged liver. There were diffuse peritoneal petechial haemorrhages.

#### CASE 4 (BH No. N65/75)

A 20-year-old housewife returned from a three-week visit to Nigeria on 26 July 1975. She had not taken any antimalarial prophylactics. She felt unwell and complained of loin pains. On 28 July, in the morning, she went to see her doctor complaining of headache, blurred vision, vomiting, and urinary frequency. The urine was dark. In the evening she suddenly began to have fits and became unconscious. She was admitted to hospital at 2125. Her temperature was 37.8°C (100°F). The pupils were dilated and there were haemorrhages in the retina, and the optic discs were oedematous. A lumbar puncture showed a clear, colourless fluid with 1.170 g/l of protein and 4 red blood cells/mm<sup>3</sup>. Blood films showed infection with *P. falciparum*. At 2345 she was given chloro-

quine and dexamethasone intravenously. She remained unconscious. On 29 July at 1320 an EEG showed an abnormal depressed cerebral activity. She suddenly developed cardiac arrest and died at 1620, two days after the onset of the symptoms. The coroner's postmortem showed a congested liver and spleen, and oedematous lungs.

The macroscopic abnormalities in the viscera at necropsy are listed with the case histories; in two cases where histological examination was possible there were corresponding microscopic changes. Details of these are not included in this report.

### Macroscopic findings in the brain

#### CASE 1

The brain weighed 1370 g. There were petechiae in the cerebellar leptomeninges, numerous small red patches around the vessels in the white matter, and ill-demarcated, larger, soft red areas in the internal capsules, lentiform nuclei, and fornices. The globus pallidus on both sides was necrotic.

#### CASE 2

The brain weighed 1268 g. It looked normal apart from congestion.

#### CASE 3

The brain weighed 1330 g. It was swollen and congested with slit-like lateral and third ventricles. There were a few small haemorrhages in the corpus callosum and in the white matter of the posterior half of the cerebral hemispheres.

#### CASE 4

The brain weighed 1330 g. It was swollen with slit-like ventricles and unusually dark grey cortex and deep grey matter.

### Material and methods

The brains were fixed in formol saline. Frozen sections of cerebral hemispheres and cerebellum were stained with Sudan III and IV for neutral lipid and impregnated with silver for microglia. Representative blocks of cerebral hemispheres, brain stem, and cerebellum were embedded in paraffin wax, and sections were stained with standard histological techniques. Sections of the brain from cases of fat embolism were treated in the same way.

### MICROSCOPIC FINDINGS

The changes in cases 2, 3, and 4, who survived for six, eight (or possibly 13 days or longer), and two days and in whom malaria parasites were found in the peripheral blood within hours of death, were

similar. There were masses of pale, somewhat swollen, red corpuscles containing malaria parasites and pigment in the capillaries in the grey matter, especially in the cerebral and cerebellar cortex and in the dentate nucleus of the cerebellum (Fig. 1). Some of the red corpuscles were pale. Small perivascular haemorrhages were particularly marked in the molecular layer of the cerebellar cortex, but the extravasated red corpuscles did not contain any parasites. Frozen sections revealed a generalised excess of microglia in the grey matter with concentrations of such cells near some capillaries. There was some neutral lipid in the microglial processes. Some Purkinje cells in the cerebellum were shrunken with a dark acidophil cytoplasm. Scattered nerve cells showing similar anoxic-ischaemic changes were found in the deep grey matter and in the cerebral cortex. In the white matter there were haemorrhages and cuffs of lymphocytes and microglia with a little neutral lipid around the veins. In case 2 there were large perivascular clusters of microglia in the dentate nucleus of the cerebellum.

In case 1, who survived for 14 days, small infarcts were found in the cerebral cortex. Some capillaries in the infarcts contained malaria pigment, but generally the cerebral cortex was free of malaria parasites and pigment. Many of the nerve cells were shrunken with acidophil cytoplasm. In the white matter, including the internal capsule, corpus callosum, and fornix, there were many large perivascular lesions. They consisted of dense clusters of microglial

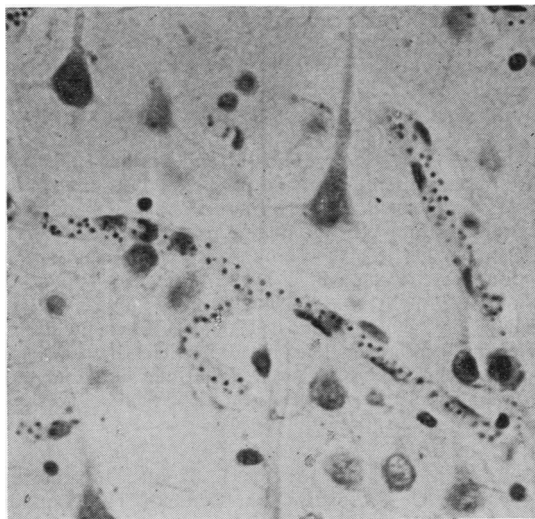


Fig. 1 Parasitised red blood corpuscles in cortical capillaries. Case 4. Luxol fast blue/Nissl,  $\times 320$ .

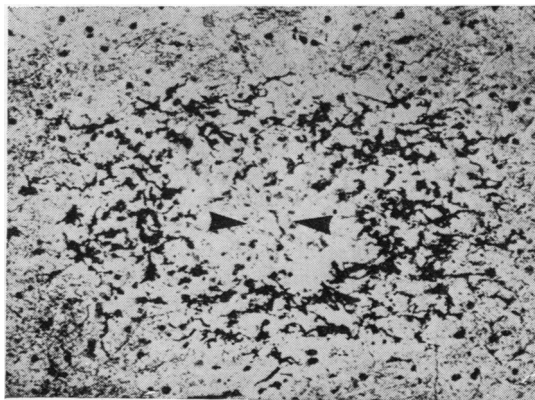


Fig. 2 Microglial cluster around a small vein (arrows) in the white matter. Case 1. Weil-Davenport,  $\times 90$

cells containing neutral lipid and iron pigment. These were well shown in frozen sections impregnated with silver (Fig. 2). Rings of ghostly or well-preserved red blood corpuscles around a pale necrotic zone including microglia and a central vein were often found. These lesions appeared as pale patches in the sections stained for myelin because of displacement and destruction of nerve fibres and oedema. In the cerebellum there were swollen nerve fibres in some such lesions. Microglial clusters were also seen in the dentate nucleus of the cerebellum, the inferior olivary nuclei, and the anterior grey horns of the spinal cord. Large pale infarcts were found in the dorsomedial part of the globus pallidus and in the posteromedial part of the cerebellar hemispheres. *Pseudomonas pyocyanea* was grown in blood culture of this patient on the day before death, and Gram-negative bacilli were found in some larger blood vessels deep in the cerebral hemispheres.

An unusual finding was patchy infarction of the anterior lobe of the pituitary in case 3, the only case in which the pituitary was examined. Malaria parasites were present in the small blood vessels in the pituitary.

## Discussion

Our four cases illustrate the known effects of malignant tertian malaria on the brain. The parasitised red blood corpuscles in the cerebral capillaries, even though there is no evidence of organising thrombi, appear to interfere with the cerebral circulation in a way similar to that found in fat embolism (Spitz, 1946; Watson, 1970). In that condition, fat globules of a diameter similar to that of swollen red blood corpuscles (Zülch and Tzonos, 1964; Zülch, 1971) accumulate in the cortical capillaries. Although

ischaemic changes occur in the nerve cells of the cerebral grey matter in both conditions, the more obvious lesions are found around the veins in the white matter. The haemorrhages, microglial nodules often referred to as Dürck's nodules, and areas of necrosis and oedema in the white matter in cerebral malaria closely resemble the white matter lesions in fat embolism. In our material, specific impregnation showed that most cells in the nodules are microglial. These cells were present in all our cases. They could well be missed or wrongly identified in sections of paraffin-embedded material stained with routine techniques. The involvement of the white matter is probably due to an increase in permeability and necrosis of the vessel wall after a slowing down or arrest of the blood flow, but the mechanism of production of the lesions is not fully understood. Edington (1954) lists mechanical blockage, sludging, anoxaemia, and toxins as the factors involved. Spitz (1946) also refers to stagnation of blood in the capillaries, thromboses, and anoxia from other causes, for example, fat embolism and spotted fever; she illustrates a similar picture of extreme engorgement of cerebral capillaries following anoxia due to flying at high altitudes. We have found changes similar to those in malaria and in fat embolism in acute herpes simplex encephalitis in the white matter underlying necrotic oedematous cortex (unpublished). The lesions in the basal ganglia in case 1 may not be due directly to malaria: they resemble the lesions encountered when blood pressure is low or when the oxygen content of the blood is lowered.

Although two of the brains (cases 3 and 4) appeared swollen on macroscopic examination, there was no microscopic evidence of generalised oedema of any severity in them. The infarction of the anterior lobe of the pituitary in case 3 was patchy, probably related to the presence of malaria parasites in the blood vessels. The infarction was less extensive than the pituitary necrosis found with severe cerebral oedema and often in patients who have been kept on a respirator when the intracranial blood supply to the pituitary is interrupted (Daniel *et al.*, 1973). The pituitary does not appear to have been examined routinely or often in malaria. If pituitary infarction in cerebral malaria were common it would be another factor contributing to the fatal outcome. Three of our four patients had not taken any antimalarial prophylactics. In all four, the disease became apparent soon after return to England but the correct diagnosis was delayed. In case 3, milder symptoms of 'cold' had started earlier in Africa. The presentation of four fatal cases of cerebral malaria in England is intended to draw attention to the need for a ready

recognition of malaria since early diagnosis and appropriate treatment can be successful.

We are grateful to Dr D. Haler, Professor A. K. Mant, and Dr I. G. Williams, who performed the coroner's postmortems, for referring three of the cases to us.

#### References

- British Medical Journal (1972). Malaria in the UK. (News and notes.) *British Medical Journal*, **3**, 652.
- Bruce-Chwatt, L. J. (1978). Preventing deaths from malaria (Letter). *British Medical Journal*, **2**, 1085-1086.
- Daniel, P. M., Spicer, E. J. F., and Treip, C. S. (1973). Pituitary necrosis in patients maintained on mechanical respirators. *Journal of Pathology*, **111**, 135-138.
- Edington, G. M. (1954). Cerebral malaria in the gold coast African. Four autopsy reports. *Annals of Tropical Medicine and Parasitology*, **48**, 300-306.
- Escobar, A., and Nieto, D. (1972). Malaria. In *Pathology of the Nervous System*, edited by J. Minckler, Vol. 3, p. 2506. McGraw-Hill, New York.
- Greenfield, J. G. (1958). Malaria. In *Neuropathology*, edited by J. G. Greenfield, p. 212. Edward Arnold, London.
- McMenemey, W. H. (1966). Malaria. In *Systemic Pathology*, edited by G. Payling Wright and W. St. C. Symmers, Volume 2, p. 1187. Longmans, London.
- Scheidegger, S. (1958). Malaria. In *Handbuch der speziellen pathologischen Anatomie und Histologie*, edited by W. Scholz, Volume 13, Part 2A, pp. 1113-1124. Springer, Berlin.
- Sheehy, T. W. (1975). Disseminated intravascular coagulation and severe falciparum malaria (Letter). *Lancet*, **1**, 516.
- Spitz, S. (1946). The pathology of acute falciparum malaria. *Military Surgeon*, **99**, 555-572.
- Watson, A. J. (1970). Genesis of fat emboli. *Journal of Clinical Pathology*, **23**, Supplement (Royal College of Pathologists) 4, 132-142.
- Winslow, D. J., Connor, D. H., and Sprinz, H. (1971). Malaria. In *Pathology of Protozoal and Helminthic Diseases*, edited by R. A. Marcial-Rojas, Chapter 10. Williams and Wilkins, Baltimore.
- Zülch, K. J. (1971). Fat embolism. In *Pathology of the Nervous System*, edited by J. Minckler, Volume 2, p. 1524. McGraw-Hill, New York.
- Zülch, K. J., and Tzonos, T. (1964). Transsudationsphänomene an den tiefen Hirnvenen nach Blockade von Arteriolen oder Kapillaren der Rinde durch Mikroembolien. *Naturwissenschaften*, **51**, 539-540.

Requests for reprints to: Dr I. Janota, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, UK.