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# MR of Cerebral Malaria

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**Summary: In three cases of cerebral malaria, MR imaging disclosed either cortical infarcts (one case) or hyperintense areas of white matter (two cases) on T2-weighted and fluid-attenuated inversion-recovery sequences. These white matter abnormalities were, in one case, sharply limited, symmetrical, hyperintense, and unenhanced; in the other case, they were diffuse, hyperintense, and had a more limited focus. The diffuse hyperintensity was probably due to edema, whereas focal lesions were probably associated with gliosis.**

Cerebral malaria occurs in 2% of patients infected by *Plasmodium falciparum.* The neurologic signs, caused by diffuse involvement of the brain, are usually nonspecific (1). The pathogenesis of cerebral malaria may be explained by two mechanisms: capillaries blocked by infected red blood corpuscles constitute one important factor, and potential cerebral toxicity by cytokines has also been implicated (2). MR imaging, which is rarely performed in cases of cerebral malaria, has disclosed cortical infarcts (3, 4) or lesions of the white matter (5, 6). We describe findings in three patients with cerebral malaria who had either cortical or white matter lesions.

## Case Reports

Since 1992, we have examined 12 patients who had, during the previous days or weeks, suffered from cerebral malaria. MR examinations performed on a 1.5-T unit included sagittal 5-mm-thick T1-weighted images, axial 4-mm-thick T2-weighted images, axial 4-mm-thick T1-weighted images, before and after contrast injection, and axial fluid-attenuated inversion-recovery (FLAIR) sequences in four patients. In patients with abnormal findings, sagittal or coronal T2-weighted images were also obtained. Among these 12 patients, three had abnormalities on MR examination. Those three are reported here.

### *Case 1*

A 13-year-old girl from Cameroon was admitted to our hospital because of recurrent seizures. One month before, she had suffered an attack of malaria, which had been diagnosed by blood smears containing *P. falciparum.* The neurologic examination was normal, but the EEG showed $\theta$ spikes in the right frontotemporal areas. An MR examination showed a few hemorrhagic cortical lesions, which were presumed to be cortical infarcts (Fig 1). She received antiepileptic therapy and was discharged. At follow-up no other seizures had occurred. The abnormal EEG findings disappeared 3 months later, and the MR abnormalities were no longer detectable after 6 months. Antiepileptic medication was progressively reduced and the treatment was finally stopped after the normal EEG and MR studies were obtained.

### *Case 2*

A 30-year-old man returned to France from a 4-week visit in Niger. During his stay in Africa, he had neglected his malaria chemoprophylaxis. Upon his return, he reported feeling faint and having headaches, and soon thereafter he lost consciousness. At neurologic examination, he had a score of 6 on the Glasgow Coma Scale (GCS). Blood smears showed a huge infestation by *P. falciparum*, with high-grade parasitemia (approximately 50%). Treatment by intravenous quinine dihydrochloride was initiated. MR examination, performed 36 hours after the onset of coma, showed diffuse abnormalities of the white matter in the centrum semiovale and the splenium of the corpus callosum (Fig 2A). With treatment, the patient regained consciousness, but defects in memorization tasks, as determined by neuropsychological testing, remained. A follow-up MR study, performed 1 week after the onset of neurologic symptoms, showed the disappearance of the white matter hyperintensities of the centrum semiovale and minimal decrease in the size of the lesion of the splenium of the corpus callosum (Fig 2B). Five months later, neuropsychological test scores were normal but the lesion of the corpus callosum remained unchanged at MR examination.

### *Case 3*

A 23-year-old man traveling in Thailand contracted cerebral malaria, which resulted in coma (GCS score = 8). He partially recovered and returned to France, but then suffered a relapse. Blood smears confirmed infestation by *P. falciparum*, and treatment by intravenous quinine dihydrochloride was initiated. Recovery was incomplete and the patient had a residual left-sided facial palsy and left-sided hemiparesis. MR imaging, performed 4 weeks after the onset of illness, showed bilateral hyperintense areas in the deep white matter (Fig 3). No additional treatment was prescribed and the patient was discharged. Three months later, neurologic findings were normal except for slight weakness of the upper left limb. A CT study showed two hypodense foci of the centrum semiovale. The patient did not have subsequent clinical or imaging follow-up.

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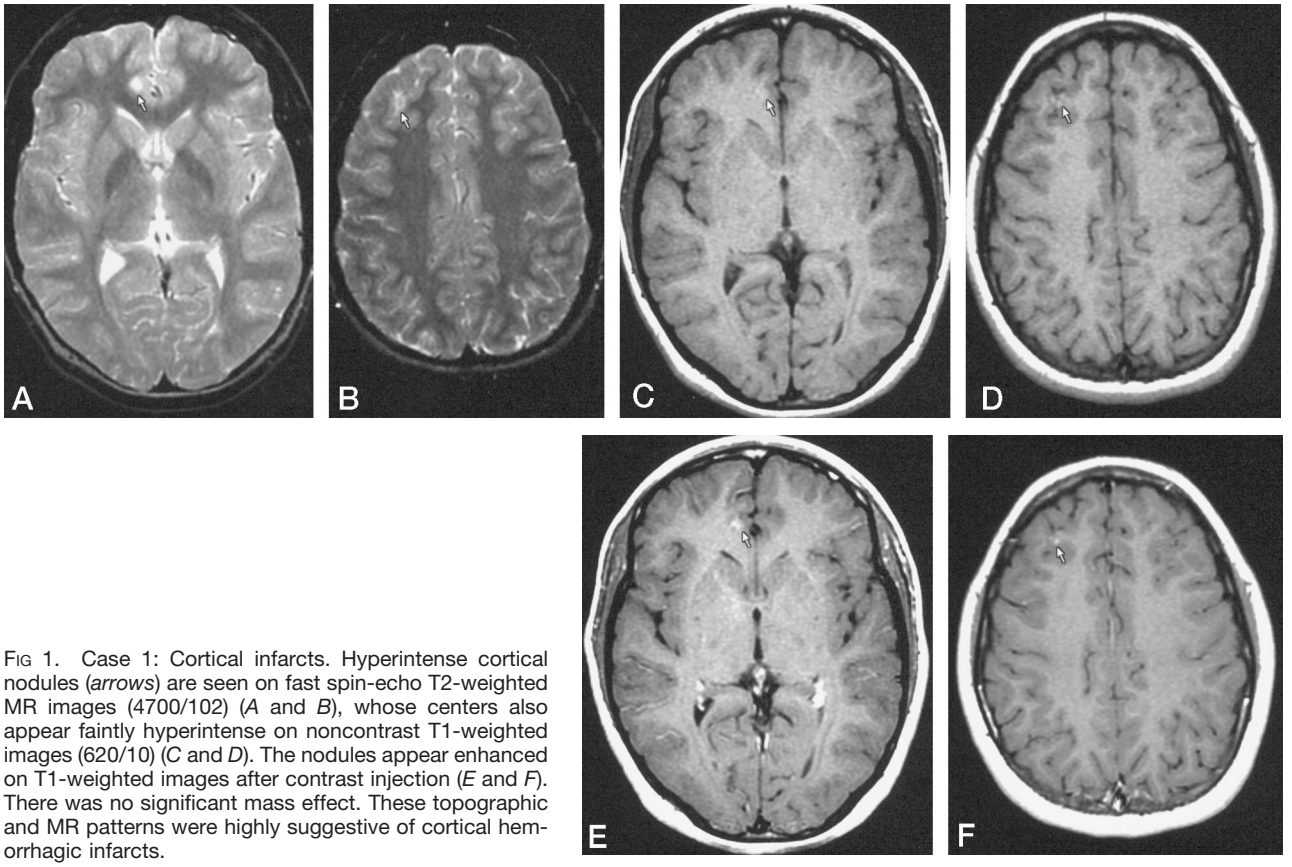


FIG 1. Case 1: Cortical infarcts. Hyperintense cortical nodules (*arrows*) are seen on fast spin-echo T2-weighted MR images (4700/102) (*A* and *B*), whose centers also appear faintly hyperintense on noncontrast T1-weighted images (620/10) (*C* and *D*). The nodules appear enhanced on T1-weighted images after contrast injection (*E* and *F*). There was no significant mass effect. These topographic and MR patterns were highly suggestive of cortical hemorrhagic infarcts.

## Discussion

Cerebral malaria is a life-threatening complication of *P. falciparum* infestation that occurs in approximately 2% of the cases. In endemic areas it affects mainly children. Occurrence in adults is far less frequent, yet it is seen among persons who have lived away from endemic areas for a sufficient time to have lost their immunity. Progressive clinical changes occur along with high fever and chills. The neurologic manifestations are nonspecific because of diffuse involvement of the brain. Transient extrapyramidal and neuropsychiatric manifestations as well as isolated cerebellar ataxia may occur, but localizing signs are rare (1). Coma may ensue, and approximately one third of patients die.

Since 1992, we have treated 12 patients with cerebral malaria, of whom three had brain abnormalities on MR studies.

There are few reports of neuroimaging findings in cerebral malaria. Looareesuwan et al (7) reported the absence of conspicuous lesions on CT scans. In a prospective MR study of 24 patients with cerebral malaria imaged on a 0.2-T system in which 10-mm-thick T2-weighted images were obtained, the same authors confirmed the lack of cerebral edema but found a slightly increased brain volume, which they attributed to an increase in cerebral blood flow caused by vasodilatation and sequestration of infected erythrocytes. Apart from this moderate brain swelling, MR imaging revealed no abnormalities (8). In another study (4), cortical and subcortical ischemic brain lesions were reported in a case of cerebral malaria, but since the patient was a 71-year-old man, it could not be asserted that cerebral malaria was the cause of these lesions. Other reported brain lesions include central pontine myelinolysis (5) and myelinolysis in the upper medulla (6), the latter following a simple attack of *P. falciparum*, and cerebellar syndrome with microinfarcts of the cerebellar hemispheres (3).

The histologic findings in cerebral malaria include sequestration of infected erythrocytes in brain vessels, mainly cortical and perforating arteries, with perivascular ring hemorrhages and white matter necrosis (9, 10). Presence of edema is more difficult to document pathologically because, in postmortem studies, brain edema may not be appreciated (8, 11).

Our observations illustrate two kinds of cerebral lesions, which correspond to the mechanisms usually suggested to explain neurologic symptoms, namely, blockage of capillaries of the brain by infected red blood cells and white matter ischemia or toxicity. In our first case, taking into account the age of the patient, small infarcts of the cortex were thought to be due to the blockage of capillaries by infected erythrocytes. In the other cases, either focal or diffuse hyperintensity of the white matter was seen, with regression paralleling the favorable course of the disease in one case. The hyperintensity had the characteristics of edema, which may have been due to ischemia or toxic injury. Recent pathologic and experimental studies have focused on the effect of

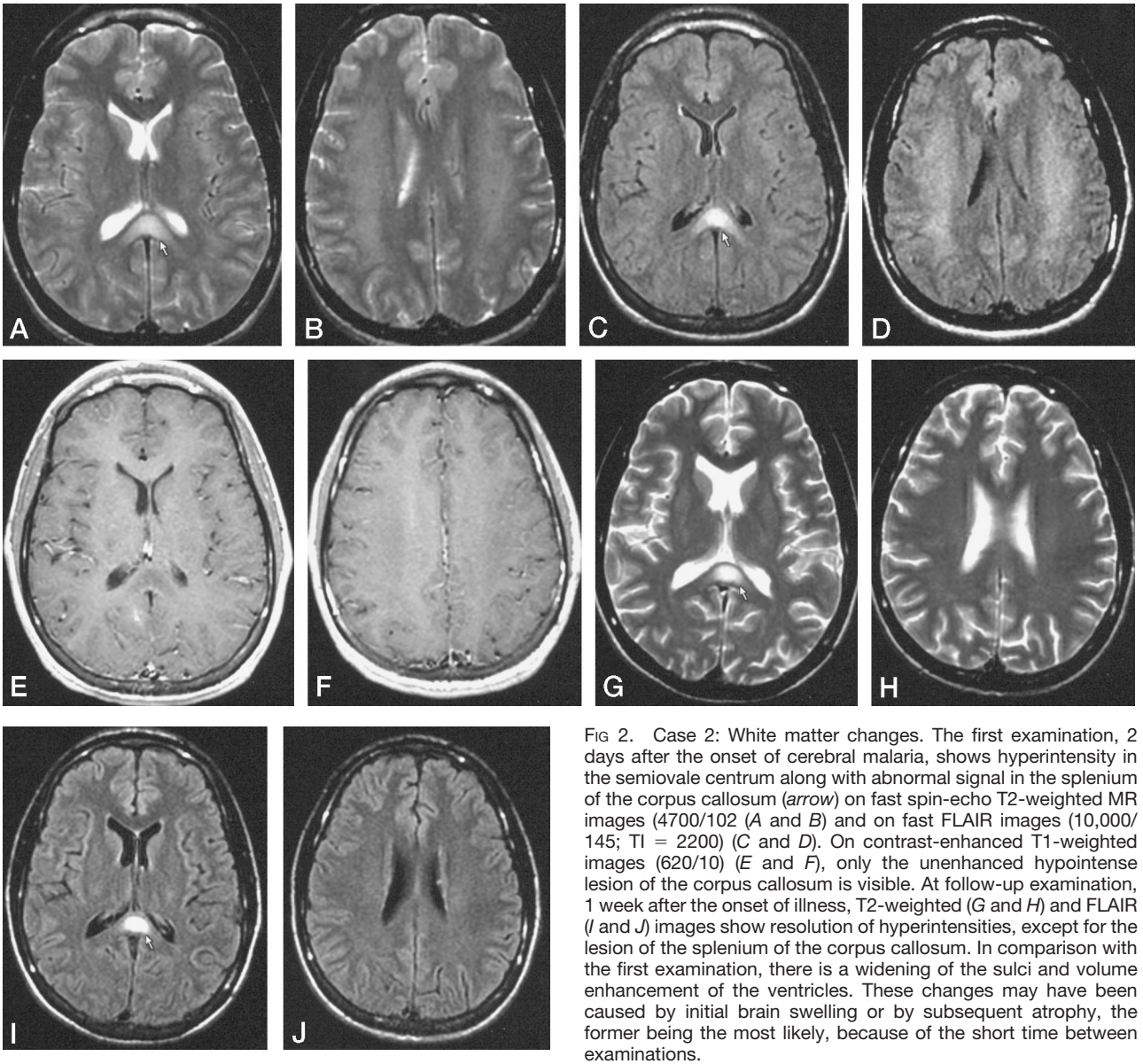


FIG 2. Case 2: White matter changes. The first examination, 2 days after the onset of cerebral malaria, shows hyperintensity in the semiovale centrum along with abnormal signal in the splenium of the corpus callosum (*arrow*) on fast spin-echo T2-weighted MR images (4700/102 (*A* and *B*) and on fast FLAIR images (10,000/145; TI = 2200) (*C* and *D*). On contrast-enhanced T1-weighted images (620/10) (*E* and *F*), only the unenhanced hypointense lesion of the corpus callosum is visible. At follow-up examination, 1 week after the onset of illness, T2-weighted (*G* and *H*) and FLAIR (*I* and *J*) images show resolution of hyperintensities, except for the lesion of the splenium of the corpus callosum. In comparison with the first examination, there is a widening of the sulci and volume enhancement of the ventricles. These changes may have been caused by initial brain swelling or by subsequent atrophy, the former being the most likely, because of the short time between examinations.

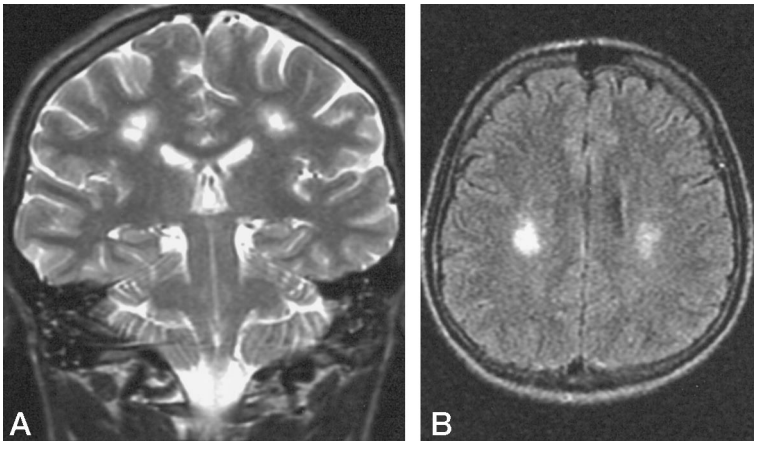


FIG 3. Case 3: White matter gliosis. Coronal fast spin-echo T2-weighted MR image (4700/102) (*A*) and fast FLAIR image (10,000/145; TI = 2200) (*B*) obtained 4 weeks after the onset of cerebral malaria show bilateral foci of hyperintensity in the centrum semiovale. There was no enhancement on T1-weighted contrast-enhanced images (not shown).

endothelial activation, nonspecific immune inflammatory response, and subsequent release of cytokines (2, 12, 13). These factors could lead to vascular engorgement and vasodilatation with reduction of cerebral blood flow and edema, which might explain the presence of raised intracranial pressure and brain swelling. Our findings in the second case are consistent with those described by Looareesuwan et al (8), with moderate brain swelling detected only by comparison with follow-up MR studies. Signal abnormalities in this case were faint, as were the microinfarcts in the first case. It is possible that such abnormalities could be missed on a low-field system, since the lower signal-to-noise ratio prevents use of thin sections. This would explain the lack of abnormalities, other than brain swelling, found in the study by Looreesuwan et al. The hypothesis of brain swelling resulting from vasodilatation and edema may explain the reversal of clinical and MR imaging signs with successful treatment, as in our second case.

Lack of effective treatment of cerebral malaria may lead to irreversible necrotic and hemorrhagic lesions of the perivascular myelin, which have been found to be similar to lesions caused by fat emboli (9). Such necrosis, without hemorrhage, may have occurred in our third case, in which transient facial palsy and hemiparesis were associated with areas of gliosis or demyelination in the centrum semiovale.

## Conclusion

In addition to brain swelling, cortical infarcts and white matter lesions can be seen on MR examinations obtained during the course of cerebral malaria. White matter lesions can regress with effective treatment. The MR pattern is compatible with toxicity leading to intravascular engorgement and edema and, in some cases, to irreversible myelin damage.

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