PURPOSE: To correlate imaging abnormalities, clinical features, and postmortem findings in patients with proved cerebral malaria.

MATERIALS AND METHODS: Twenty-one patients aged 17–50 years with cerebral malaria consented to undergo transverse nonenhanced (10-mm sections) and contrast material–enhanced (8-mm sections in posterior fossa and 10-mm sections in supratentorial region) CT on admission (n = 21) and on day 10 (n = 6), with thin sections (5 mm) obtained in the area of abnormality. CT scans were evaluated for diffuse cerebral edema, focal parenchymal abnormalities, and hemorrhage. CT findings were categorized as normal, diffuse cerebral edema, and edema with thalamic hypoattenuation without or with cerebellar hypoattenuation. Spearman rank correlation test was performed.

RESULTS: Initial scans were normal in seven patients with mild disease (median Acute Physiology and Chronic Health Evaluation [APACHE] II score of 7, median Glasgow Coma Scale [GCS] score of 10), and all survived. Of eight patients with diffuse cerebral edema (GCS ≥ 8; median APACHE II, 21), six survived. Cerebral edema with thalamic and cerebellar white matter hypoattenuation was seen in five patients. All had GCS score of 6 or less, median APACHE II score of 26, and multiorgan failure; none survived. One patient (GCS = 6) had thalamic hypoattenuation without cerebellar lesions. He survived with mild residual hemiparesis. Diffuse petechial hemorrhages were seen in the cerebrum and cerebellum at autopsy in all seven patients who died. These petechial hemorrhages were not visualized on CT scans. CT findings did not correlate with degree of parasitemia.

CONCLUSION: CT findings correlate well with level of consciousness and severity of disease but underestimate the extent of disease at pathologic examination. A normal CT scan indicates a favorable outcome, whereas cerebellar hypoattenuation portends a poor outcome.
undergo computed tomography (CT) and were evaluated for the study after providing informed consent and according to the protocol approved by the institution’s ethics committee. Patients had varying severity of cerebral involvement. The diagnosis of malaria was confirmed by demonstration of ring forms of *Plasmodium falciparum* on a peripheral smear examination. Cerebral malaria was diagnosed if the patient had altered consciousness (Glasgow coma scale [GCS] score ≤ 10) in the absence of hypoglycemia. History and physical signs were documented in all patients. Severity of malaria was assessed by the degree of parasitemia (parasite index [ie, percentage of red blood cells that had demonstrable parasitic invasion]), Acute Physiology and Chronic Health Evaluation (APACHE) II score on day 1, and presence of organ failure. Patients were treated with intravenously administered quinine followed by orally administered quinine after the admission. One of the patients had hypoglycemia at admission but made an uneventful recovery. None of these patients showed any focal neurological deficits. No follow-up CT scan was obtained in these patients.

**RESULTS**

The parasite index varied from 1% to 25%, and the day 1 APACHE II score varied from 6 to 31 (Table). Systemic manifestations in the form of organ failure were seen in 10 patients.

**Imaging Findings**

*Normal CT findings.*—A normal CT scan was seen on day 1 in seven patients. Although these patients had a low GCS score on admission, all seven improved to a GCS score greater than 10 within 24 hours of admission. One of the patients had hypoglycemia at admission but made an uneventful recovery. None of these patients showed any focal neurological deficits. No follow-up CT scan was obtained in these patients.

**Diffuse cerebral edema.**—This was the only abnormality seen in eight of the 21 patients (Fig 1) and was characterized by small ventricles, absence of sulci, and compression of the perimesencephalic

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**Clinical Observations in 21 Patients with Cerebral Malaria**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CT Findings</th>
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<tbody>
<tr>
<td></td>
<td>Normal (n = 7)</td>
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<tr>
<td>GCS score on admission*</td>
<td>10 (9–11)</td>
</tr>
<tr>
<td>Day 1 APACHE II score*</td>
<td>7 (6–8)</td>
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<tr>
<td>Paratube index (%)*</td>
<td>7 (1–15)</td>
</tr>
<tr>
<td>Organ or system failure†</td>
<td>1 (0–1)</td>
</tr>
<tr>
<td>Renal</td>
<td>0</td>
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<tr>
<td>Thrombocytopenia</td>
<td>0</td>
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<tr>
<td>Disseminated intravascular coagulation</td>
<td>0</td>
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<tr>
<td>Hepatic</td>
<td>0</td>
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<tr>
<td>Acute respiratory distress syndrome</td>
<td>0</td>
</tr>
<tr>
<td>Severe hemolysis‡</td>
<td>1</td>
</tr>
<tr>
<td>No. of organs or systems affected*</td>
<td>0 (0–1)</td>
</tr>
<tr>
<td>Deaths†</td>
<td>0</td>
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</tbody>
</table>

* Data are the median score. Numbers in parentheses are the range.
† Two-tailed Spearman rank correlation test.
‡ Data are number of patients.
§ Hemoglobin level of 7 g/dL (70 g/L) or less or the patient required blood transfusions.
† Two-tailed χ² test for trend.

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**Figure 1.** Contrast-enhanced transverse CT scan obtained on day 1 in a 31-year-old female patient shows effacement of cerebral cortical sulci and compression of the body of the ventricles, suggestive of generalized cerebral edema.
and chiasmatic cisterns. All these patients had a GCS score between 8 and 10. Two (25%) of the eight patients with diffuse cerebral edema died of systemic complications; the deaths were not due to the cerebral edema. Both had renal failure, and one also had disseminated intravascular coagulation.

The six patients who survived showed no focal neurologic deficits. A repeat CT scan on day 10 in all six survivors showed complete resolution of the cerebral edema.

Postmortem examination of the brain in the two patients who died showed diffuse cerebral edema and petechial hemorrhages in the gray and white matter all over the cerebral hemispheres (Fig 2).

Diffuse cerebral edema with bilateral thalamic hypoattenuation.—One patient had bilateral thalamic lesions without cerebellar lesions (Fig 3a). At presentation, this 17-year-old boy had coma (GCS score of 6), seizures, and mild right hemiparesis. CT showed diffuse cerebral edema with well-defined, well-circumscribed areas of hypoattenuation involving both thalami. No evidence of hemorrhage was seen in any of these lesions. He made a gradual recovery over 5 days, but mild hemiparesis persisted at the time of discharge from the hospital on day 29. Repeat CT scan on day 10 showed complete resolution of the cerebral edema, but the thalamic lesions were still visible, although no clinical manifestations of these could be detected (Fig 3b).

Diffuse cerebral edema with bilateral thalamic and cerebellar hypoattenuation.—This was seen in five patients (Fig 4). CT showed these lesions as well-defined, well-circumscribed areas of hypoattenuation involving both thalami and the cerebellum. No evidence of hemorrhage was seen in any of these lesions. These patients were the most seriously ill, with a GCS score less than 6, a median day 1 APACHE II score of 26 (range, 21–31), and failure of two or more organs or systems. All these patients died.

Postmortem examination was performed in these five patients. Autopsy findings revealed diffuse cerebral edema with multiple petechial hemorrhages diffusely scattered in the brain. Areas of softening due to infarction were seen in the thalamus and involved predominantly the white matter of the cerebellum (Fig 5). Histopathologic findings revealed ring hemorrhages around the smaller blood vessels, Durck granulomas (aggregates of parasitized red blood cells, inflammatory cells, and necrotic tissue seen in the perivascular region), and parasitized red blood cells in the intracranial vessels (Fig 6).

CT Findings, Severity of Illness, and Mortality

When the data were assessed with the Spearman rank correlation test, a significant correlation was noted between the type of finding on the CT scan and the day 1 APACHE II score (Spearman r = 0.8831, P < .001). A significant negative correlation was noted between the type of CT finding and the GCS score at the time of scanning (Spearman r = −0.8716, P < .001). The number of other organs...
affected also correlated significantly with increasing degree of cerebral abnormality on CT scan (Spearman \( r = 0.4798, P < .001 \)). Thus, patients with more severe abnormalities on the CT scan also had greater severity of illness, lower levels of consciousness, and involvement of other organ systems due to malaria (Table). There were no deaths in patients with normal CT findings. Prognosis was worse in the eight patients with cerebral edema, two of whom died (relative risk, 4.4, vs normal scans). Mortality was highest in patients with thalamic hypoa attenuation with or without cerebellar hypoa attenuation (five of six patients died), with a relative risk of 12.8 when compared with patients with normal CT findings. However, no correlation was noted between the degree of parasitemia (defined as number of red blood cells harboring parasites expressed as a percentage of the total number of red blood cells visible in the field of the microscope at peripheral blood smear examination) and the type of abnormality on the CT scan.

**DISCUSSION**

Red blood cells parasitized by *P falciparum* adhere to capillary endothelium at a certain phase of the intraerythrocytic phase of the life cycle of the parasite. Presumably, the parasites derive some nutrition from the endothelium. This phenomenon occurs maximally in the capillaries of the brain, resulting in the serious complication, cerebral malaria (3). Neuropathologic features of cerebral malaria are not specific, and altered consciousness is the most common manifestation followed by seizures. Even with appropriate antimalarial therapy and intensive care, 15%–25% of patients die, and mortality may reach 50% if more than 10% of erythrocytes are parasitized (4). In our series as well, seven of the 21 patients died.

Our study clearly shows four major patterns of CT brain findings that closely correlated with the clinical severity of malaria, as well as outcome. In previous studies, investigators reported a normal CT scan as the most common finding (5). This was seen in seven of our 21 patients with cerebral malaria. Newton et al (5) observed that 50% of their patients with cerebral malaria had normal scans. However, these authors did not emphasize the clinical significance of this finding. In a study of 10 Thai patients, Looa reesuwan et al (6) found a normal CT scan in four patients, and outcome was better in these patients than in those with abnormal scans. Clinical correlation in our patients revealed that those with normal CT findings had the mildest cases of cerebral malaria, and they had an excellent prognosis. They regained consciousness rapidly after initiation of antimalarial therapy and recovered without residual neurologic deficits; no deaths occurred in this group of patients.

Diffuse cerebral edema was the most common abnormality seen in our patients with cerebral malaria. This was observed in 14 (67%) of our patients. It occurred as an isolated finding in eight patients and along with thalamic and cerebellar lesions in six. Patients with isolated cerebral edema had moderately severe malaria, as evidenced by the APACHE II and GCS scores at admission, and their outcome was worse than that in patients with a normal scan but better than that in patients with thalamic or cerebellar hypoa attenuation.

Cerebral edema is believed to be both vasogenic and cytotoxic in origin. The cause of edema probably is an increase in the intracerebral blood volume, which results from sequestration of the parasitized erythrocytes and compensatory vasodilatation, damage to cerebral capillary endothelium, and cerebral microvascular occlusion (7). The exact incidence and clinical significance of cerebral edema in patients with malaria have been a subject of some controversy. In an early study, Looa reesuwan et al (6) found cerebral edema on CT scans in only two of 10 patients, all of whom died within hours of scanning. This led the authors to conclude that cerebral edema is not common, even in comatose patients. They suggested that it occurred only as a terminal event. However, Newton et al (5) reported the presence of cerebral edema in four of 14 patients, all of whom survived. In a later article, Looa reesuwan et al (7) reported this abnormality in 17 of 24 patients (four of whom died), and these authors now suggest that cerebral edema is common in patients with cerebral malaria. Our observations also suggest that cerebral edema is frequently encountered and not necessarily a terminal phenomenon.

Focal hemorrhagic or nonhemorrhagic infarcts in the cortex, basal ganglia, thalamus, pons, and cerebellum in patients with cerebral malaria occasionally have been described in isolated case reports (1,5,8–10); these infarcts have resulted in residual neurologic deficits such as hemiparesis, quadriparesis, blindness, epilepsy, and aphasia. Newton et al (5) reported multiple low-attenuation areas suggestive of ischemic damage in four of their 14 patients. All four patients had severe neurologic sequelae. They attributed these lesions to a critical reduction in cerebral perfusion pressure, hypoglycemia, and widespread blockage of small vessels by the parasitized erythrocytes and anemia. Occlusion of the basal arteries was seen in this series in one Kenyan child who developed hemiparesis caused by cerebral malaria (5). Only one patient (aged 17 years) in our study had right hemiparesis and showed diffuse cerebral edema.
and isolated symmetric thalamic hypooptenuation. Complete resolution of the cerebral edema with decrease in size of thalamic lesions was noted on the follow-up CT scan at day 10 of admission, but hemiparesis persisted at discharge.

It is noteworthy that all reported cases of focal infarction of the brain were in children with cerebral malaria. Such focal deficits may occur in 9%–14% of African children (5,11,12). In contrast, we found focal neurologic deficits in only one of our 21 patients, who was also the youngest in our series. One possible reason for this difference in clinical manifestations may be because all our patients were adults or adolescents. This lack of focal areas of infarction is also evident from the two previous reports by Looareesuwang et al (6,7) in which none of the 34 adult Thai patients studied had this abnormality.

Bilateral, symmetric, isolated, and thalamic and cerebellar areas of hypooptenuation were seen in five of our patients with the most severe illness. All were deeply comatose, had higher APACHE II scores than those of patients with any other abnormalities on CT scans, and had 100% mortality. CT showed these lesions as well-defined, well-circumscribed areas of hypooptenuation involving both thalami and the cerebellum. There was no evidence of hemorrhage seen in any of these lesions. To the best of our knowledge, this finding has not been reported in literature before. Antemortem MR imaging was not possible in our patients, as they were too critical to be transported to another hospital (MR imaging was not available at our center). Postmortem studies performed in all five patients revealed diffuse cerebral edema with symmetric ischemic changes involving the thalamus and the cerebellum. There was mild swelling of the brainstem. These findings were possibly caused by sequestration of the parasitized red blood cells in the cerebral microvasculature and led to capillary occlusion and damage (7). Major branches of the cerebral, vertebral, and basilar arteries were patent. The imaging modality highly underestimated the abnormalities at pathologic examination. The diffuse petechial hemorrhages seen on the autopsied brain in all patients were not visualized on CT scans. Histopathologic examination revealed parasitized red blood cells in the intracranial microvasculature. Because we were unable to perform MR imaging at presentation in our patients, we had to rely on CT for detection of low attenuation in the cerebellum.

Bilateral, symmetric infarction of the thalami has been seen in internal cerebral vein thrombosis, Japanese encephalitis, and occlusion of both paramedian thalamic and mesencephalic arteries caused by atherosclerosis or tuberculous meningitis (13–16). There was no evidence of cerebral venous thrombosis, meningitis, or arterial occlusion at autopsy in any of our patients. Hypoglycemia, which occurs in 8%–32% of patients with cerebral malaria (17,18), may also cause serious cerebral damage. The cortex, hippocampus, basal ganglia, and the substantia nigra (but not the thalamus or cerebellum) are particularly vulnerable to this (19). One of our patients had hypoglycemia at admission, but this patient had a normal scan and an uneventful recovery.

Cerebellar demyelination following falciparum malaria has been reported in several patients from Sri Lanka and India (20). However, this occurs several days after recovery from acute falciparum malaria, and the preceding malarial infection is usually mild. CT scans in these patients have shown no abnormality. The condition has a chronic course and is not fatal. However, cerebellar involvement on CT scans was found during the acute stage of cerebral malaria in five of our patients and was fatal in all. Sien et al (21) showed that the number of mi-
Radiology

crovessels with parasitized red blood cell sequestration is greater in the cerebellum than in the cerebrum (21). Findings at autopsy studies also have confirmed the selective clogging of the cerebellar capillaries with parasitized red blood cells, which leads to microscopic infarcts, perivascular hemorrhages, shrinkage of the Purkinje cells, and perivascular clusters of microglia (20–23).

In conclusion, our study findings confirm that abnormalities on CT scans are common in patients with cerebral malaria. In adult patients, CT findings may conform to four characteristic patterns: a normal scan, isolated diffuse cerebral edema, diffuse cerebral edema with bilateral thalamic hypoattenuation, and diffuse cerebral edema with bilateral thalamic and cerebellar hypoattenuation.

Areas of petechial hemorrhage, which are the hallmark of cerebral malaria at pathologic examination, are not seen on CT scans. One could argue that the petechial hemorrhages could have developed after the initial CT scan or that they may have been missed on the CT scans obtained on day 1. Notwithstanding the limitations of our CT technique, wherein 10-mm sections in the supratentorial brain parenchyma and 5-mm sections through the cerebellum and thalamus were obtained if there was a suspicion of a focal abnormality on the nonenhanced scans, our study findings clearly demonstrate that the severity of CT findings correlates well with the level of consciousness, severity of illness, and mortality. A normal CT scan indicates a favorable outcome, but cerebellar hypoattenuation may indicate a poor prognosis. These areas of hypoattenuation represent infarction in the territories supplied by the thalamoperforating and cerebellar vessels as a result of microvascular occlusion.

A focal area of infarcts in the distribution of the ophthalmic and major cerebral arteries, which is common in children, seems to be rare in adults. This suggests that the thalamoperforating and cerebellar vessels tend to be more commonly affected in adults, whereas the larger cerebral vessels may be spared. Whether these differences are related to differences in the caliber of the arteries or in the density of endothelial receptors to which parasitized erythrocytes adhere is not yet clear.

References