Clinical Infectious Diseases

BRIEF REPORT

Adult cerebral malaria: acute and subacute imaging findings, long-term clinical consequences

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Cerebral malaria is an important cause of mortality and neurodisability in endemic regions. We show MRI features suggestive of cytotoxic and vasogenic cerebral edema followed by microhemorrhages in two adult UK cases, comparing them with an Indian cohort. Long-term follow-up images correlate ongoing changes with residual functional impairment.

Key words: malaria; cerebral malaria; neuro-imaging; MRI; neuro-disability

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DOI: 10.1093/cid/ciad651

CASE SUMMARIES

Case 1: A 28-year-old female presented to her local hospital two weeks after returning from Ghana with five days of fever, diarrhea, vomiting, and confusion. She had not taken antimalarial prophylaxis. She was febrile, agitated and confused, with tachycardia and hypotension. Blood film showed 22.1% *Plasmodium falciparum* trophozoites. There was lactic acidosis (pH 7.2, pCO2 33 mmHg, lactate 8mmol/L), hemolytic anemia (Hb 105g/L, unconjugated bilirubin 1.30mg/dL), severe thrombocytopenia ($6x10^9$ cells/L), raised inflammatory markers (white cell count $20x10^9$ cells/L, C-reactive protein 150mg/L), acute kidney injury (serum creatinine 2.85mg/dL) and disseminated intravascular coagulation (INR 1.5, fibrinogen 0.6g/L). She was intubated and ventilated and treated with intravenous artesunate, broad-spectrum intravenous antibiotics, inotropes, continuous veno-venous hemodiafiltration and multiple red cell, platelet and fresh frozen plasma transfusions. Blood cultures were negative and there was no other evidence of bacterial sepsis.

On transfer to our center (day 4), cumulative fluid balance was 10L positive. She received nine days of IV artesunate and five days of oral artemether-lumefantrine. Malaria films were negative from day 5. A lumbar puncture was not done due to the patient's low platelet count, so the possibility of concurrent bacterial meningitis was not completely excluded. On day 7 GCS was 4. Magnetic resonance imaging (MRI) demonstrated a right-sided subacute striatocapsular infarct, restricted diffusion in the corpus callosum, basal ganglia, and the hippocampus, and diffuse severe vasogenic edema, particularly affecting the posterior subcortical and deeper white matter tracts, with brain swelling and effacement of the posterior sulci (Figure 1A, B). By day 14, GCS was 7. Day 15 MRI showed significant reduction of brain swelling with diminishing vasogenic edema, resolved restricted diffusion (Figure 1A, B) and striatocapsular infarct remodelling. Signal alteration in the hippocampus and adjacent limbic structures persisted. Susceptibility weighted imaging (SWI) showed numerous new susceptibility artefacts in the subcortical white matter, corpus callosum, basal ganglia and cerebellum (Figure 1A). On day 23, the patient was extubated, was GCS 10, and was able to follow one-step commands. By day 30, she could speak in short sentences, with pseudoathetoic movements and clumsiness in her left arm. Day 50 MRI showed complete edema resolution and maturation of the right striatocapsular infarct. The hippocampus, parahippocampal gyrus and insula continued to show T2-hyperintensity, suggestive of gliosis, and persistent microhemorrhages (Figure 1A).

Upon discharge (day 62) she could walk with assistance and communicate in full sentences, with subtle word-finding difficulties. Her Montreal Cognitive Assessment score was 21/30. Days 70 and 253 neurocognitive assessments (Supplementary Data) showed reduced mental processing speed and semantic fluency, and fatiguability on prolonged concentration. All indices except language function improved between the two timepoints; she remained aware of word-finding difficulties and reduced short-term memory a year later.

Case 2: A 17-year-old female travelled to Sierra Leone and Morocco for 3 weeks, taking malaria prophylaxis intermittently, and becoming unwell 12 days after her return to the UK, with 5 days fever, vomiting, confusion, and unsteadiness. Blood film showed *P. falciparum* parasitemia 1.1%. Hemoglobin was 7.3 g/L, white cell count normal (8.74 x10^9/ L), platelets 26 x10^9/ L. There was lactic acidosis, with pH 7.1 and lactate 7.7mmol/L, normal renal function and no evidence of respiratory or renal compromise. GCS was 14 on admission and subsequently dropped to 11. She was treated with IV artesunate (ten days total) and ceftriaxone (5 days total) and transferred to our unit. Malaria treatment was completed with three days of oral artemether-lumefantrine.

Lumbar puncture showed <1 white blood cell/ cu mm, 6 red blood cells/ cu mm, CSF protein 0.84 g/L, CSF glucose 3.8 mmol/L (plasma glucose 6.2), CSF lactate 2.54 mmol/L. Blood cultures were negative and there was no evidence of bacterial sepsis. By day 4, GCS was 6 and MRI on day 5 showed restricted diffusion in the corpus callosum and subcortical white matter, vasogenic edema in the basal ganglia and microhemorrhages or microthrombi in the subcortical white matter, corpus callosum and internal capsule (Supplementary Figure 1A). She was extubated on day 8 and by day 15 could walk with assistance, was orientated to time but not place, with limited attention and slow processing, and able to follow one-stage commands. MRI on day 21 showed nearly complete resolution of the restricted diffusion as well as the vasogenic edema, with more prominent microhemorrhages or microthrombi (Supplementary Figure 1B). Upon discharge on day 27, she was fully orientated and ready to return to school. Neurocognitive testing (WAIS III) on day 117 showed mild to moderate under-functioning in verbal and non-verbal domains from high average premorbid estimates. Poor visual recall memory and executive functioning tests suggested medial temporal and frontal weakness.

DISCUSSION

We present two cerebral malaria (CM) cases in non-immune patients returning from West Africa, comparing MRI changes with our cohort of 85 cases in Rourkela, India [1], a malaria-endemic setting with seasonal transmission. Follow-up imaging and detailed psychometric assessments provide unique insights into the evolution of neurologic changes in adult patients.

Both UK and Indian cases had diffusion restriction and vasogenic edema in hypoxia-sensitive areas of the brain (Figure 1, Supplemental Figure 1) [2,4]. Restricted diffusion with decreased ADC values likely represents cytotoxic edema secondary to ischaemia caused by *P. falciparum* sequestration in the CNS microvasculature [3]. Whilst diffusion restriction can also be caused by intramyelinic edema (more common in toxic and metabolic conditions), , it appears less likely to be the cause for diffusion restriction observed here.

In Case 1, MRI after one week showed generalised brain swelling and significant vasogenic edema with mild cytotoxic edema in the subcortical and deep white matter [2]. There was also a

basal ganglia infarct likely resulting from extensive sequestration [5]. Case 1 might not have survived outside of this well-resourced setting. Case 2 was less severely affected, with cytotoxic edema in the subcortical white matter and corpus callosum and milder generalised brain swelling and vasogenic edema in the basal ganglia. The vasogenic edema in Case 1 was unusually marked, possibly due to the initial aggressive fluid resuscitation [6]. The same brain areas were involved in our cohort of Indian CM patients imaged at admission, but cytotoxic edema was the dominant feature with a lesser degree of vasogenic edema. (Figure 1, Supplemental Figure 1) [1].

We suggest that cytotoxic edema develops first in hypoxia-sensitive regions during the acute stage of CM, followed by vasogenic edema in the subacute stage (Figure 1A-D), as described in other forms of hypoxic brain injury. Depending on the degree of cytotoxic edema, it can reverse completely e.g. in rapidly recanalized stroke patients, or turn into vasogenic edema in more severely affected brain regions. This mechanism of initial cytotoxic edema development may explain why adjunctive steroids, hypertonic saline and mannitol are not efficacious in adult CM [7].

In both settings, reversal of brain swelling was accompanied by the development of numerous susceptibility artefacts in the subcortical grey matter, corpus callosum, internal capsule and basal ganglia, representing microhemorrhages or intravascular microthrombi (Figure 1C, Supplemental Figure 1). Both microthrombi at autopsy and SWI abnormalities consistent with microhemorrhages are associated with pediatric CM [8]. Damaged or previously thrombosed microvessels cannot withstand the pressure of normalised blood flow following parasite clearance, leading to rupture and microhemorrhage. Similar changes have been reported in COVID-19, severe respiratory failure and disseminated intravascular coagulation [9,10]. There was no clinical evidence of bacterial sepsis or significant hypoxia in the UK cases although DIC could have contributed to the microhemorrhagic pattern in Case 1.

While brain swelling and vasogenic edema persisted for weeks in Case 1, repeat neuroimaging within 48-72 hours of treatment in the adult Indian cohort showed a much faster resolution of these changes [1]. The UK cases had severe disease with longer ICU stays and slower neurologic recoveries compared to the Indian cases, all of whom showed a GCS improvement to 14 or 15 within 72 hours. Long-term neurocognitive follow-up testing showed ongoing functional deficits. In Case 1 these were in memory and processing, correlating with persistent imaging changes in the hippocampus.

CONCLUSION

We describe imaging findings consistent with acute cytotoxic edema and subacute vasogenic edema and likely microhemorrhage in two UK adults with CM. These findings are similar to those described in a large Indian cohort, despite different genetic backgrounds, degrees of pre-existing immunity, and geographical settings. Our findings support the hypothesis that CM is

caused by hypoxia-induced edema through sequestration of *Plasmodium falciparum*-parasitized erythrocytes within the cerebral microvasculature [1], followed by vasogenic edema. These are the first cases we are aware of where long-term neurocognitive follow-up testing shows ongoing functional deficits and, in Case 1, sequential imaging showing persistent brain alterations correlating with these functional impairments.

Historically, long-term neurologic sequelae of CM have been considered rare in adults [7]. CM is a major cause of childhood epilepsy and neurodisability in endemic regions [11] and there is mounting concern that it may cause unrecognised lifelong neurocognitive deficits in pediatric and adult survivors [12,13]. With emerging evidence of neuroimaging changes in adults with both uncomplicated and severe non-cerebral malaria [14], there is an urgent need to investigate long-term neurocognitive outcomes following falciparum malaria.

FUNDING: S.C.W. is supported by the National Institute of Allergy and Infectious Diseases of the NIH under award number U19AI089676, and the Medical Research Council UK under award number MR/S009450/1. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

ACKNOWLEDGEMENTS: The authors would like to thank the patients and their families for their permission to publish their clinical details.

CONTRIBUTORSHIP STATEMENT: CC, AC, SW and AH wrote the manuscript. AH, RJ and FC analysed the radiological images. All authors commented on the manuscript.

CONFLICT OF INTEREST: HRJ reports royalties from Springer Nature Publishers for editing textbook of Clinical Neuroradiology; participation on Parexel MS Study Merck KGaA MS700568_0022 (Evaluation of Potential Progressive Multifocal Leukoencephalopathy (PML) Lesions on Imaging). SCW reports grants unrelated to this work (NIH, USA (ref: R21AI142472) and Wellcome, UK (ref: 214227/Z/18/Z)). The authors have no conflicts of interest to declare.

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FIGURE LEGENDS

Figure 1. Comparative MRI findings between Case 1 and a patient from an Indian cerebral malaria series [1] . Images highlighted in red illustrate the acute stage of the disease; in light blue, the early subacute disease stage; in dark blue, the late subacute stage; and in yellow, the residual imaging changes at about 2 months. **(A)** representative T2-weighted images, apparent diffusion coefficient (ADC) maps and susceptibility-weighted images of Case 1 are displayed at the level of the basal ganglia. Day 7 (GCS 4): The T2-weighted image shows a right T2 hyperintense striatocapsular infarct (arrow, first row). In addition, there is more ill-defined T2 hyperintense signal in the subcortical white matter bilaterally (arrowhead) and corona radiata representing vasogenic edema with corresponding increase in ADC. There is sulcal effacement posteriorly (and to a lesser degree, anteriorly) indicating brain swelling. In addition to the striatocapsular infarct, there is symmetrical ADC decrease in the putamen bilaterally (arrows, second row) and in the corpus callosum, consistent with mild cytotoxic edema. The SWI shows subtle areas of punctate susceptibility artefact in the internal capsules and subcortical white matter. Day 15 (GCS 7): T2 hyperintensities in the right striatum and posterior internal capsule and corona radiata remain, while sulci are now clearly visible, indicating brain swelling reversal. There is no longer evidence of cytotoxic edema with reduced ADC. The areas of increased T2 signal show increased ADC corresponding to residual vasogenic edema in the subcortical white

matter and corona radiata. Numerous areas of susceptibility artefact are now much more clearly visible in the subcortical white matter (arrowhead points at susceptibility artefacts in the occipital subcortical white matter), corpus callosum, corona radiata and internal capsules, corresponding to microthrombi or microhemorrhages. Day 50 (GCS 15): A well-defined T2 hyperintensity indicates maturation of the right capsular infarct (arrow). The ADC signal has normalised. Extensive areas of susceptibility artefact persist within the same distribution as at day 15, appearing more prominent as imaging has been performed at 3T compared to 1.5T previously (arrowhead points at susceptibility artefacts in the occipital subcortical white matter). Thus, at day 50 brain swelling has completely reversed, with a mature right striatocapsular infarct and microthrombi/microhemorrhages in the subcortical white matter, corpus callosum, corona radiata and internal capsules. **(B)** ADC maps at the level of the superior corona radiata/centrum semiovale of Case 1 show an ADC decrease at day 7 (arrows), a mildly increased ADC on day 15 (arrow) and a fully normalised ADC at day 50. **(C)** representative T2-weighted images, ADC maps and susceptibility-weighted images of a 32-year-old Indian male with CM are displayed at the level of the basal ganglia. Day 1 (GSC 5): An increased T2 signal is evident in the cortex and the slightly swollen lateral basal ganglia (putamen, arrows). Sulci are narrowed. ADC decrease is seen in the subcortical white matter (arrowhead) and basal ganglia (putamen, arrows), as in 1A. On SWI no clear pathological signal is apparent. Brain swelling is evident with mild cytotoxic edema in the subcortical white matter and basal ganglia. Day 4 (GCS 15): The T2 signal in the basal ganglia (arrows) and the cortex has normalised. Residual ADC decrease is seen in the occipital white matter (arrowhead). On the SWI image multiple susceptibility artefacts are seen in the subcortical white matter, corpus callosum and basal ganglia. Thus, brain swelling has reversed with remaining slight cytotoxic edema in the occipital white matter and newly apparent microthrombi/microhemorrhages in the subcortical white matter (arrowhead), corpus callosum and basal ganglia. Microthrombi/microhemorrhages have the same distribution as in 1A. **(D)** ADC map of a 22-year-old Indian male with CM at the level of the corona radiata. Day 1 (GCS 5): Cytotoxic edema, evidenced as ADC decrease is evident in the subcortical white matter (arrowhead) with sparing of the corona radiata. Day 4 (GCS 15): Cytotoxic edema, evidenced as ADC decrease is now apparent in the corona radiata (arrows), while most of the previously affected subcortical white matter does not show an ADC decrease anymore, similar to the appearance in 1B. Diffusion restriction was also present in the basal ganglia on day 1, resolved by day 4 (not shown).