Cerebrospinal fluid lactate in P. falciparum malaria: measurement by chemical shift imaging at 3 Tesla

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Introduction

To determine the feasibility of using magnetic resonance spectroscopy (MRS) for serial determinations of cerebrospinal fluid (CSF) lactate in patients infected with *P. falciparum* malaria, we prospectively examined 10 adults admitted to the Bangkok Hospital for Tropical Disease with acute falciparum malaria. Globally, the incidence of malaria has *increased* 2- to 3-fold over the past 4 decades, with as many as 500 million people now being infected each year and more than 2 million dying[1]. Cerebral malaria, a clinically complex complication of infection, is a rapidly progressive encephalopathy that is likely the most common cause of coma in the world. Without treatment, cerebral malaria is almost inevitably fatal; even with the best available antimalarial therapy and intensive care, mortality remains high at 20% or more. The concentration of lactate in the CSF, obtained by lumbar puncture, is the single best indicator of prognosis in patients with cerebral malaria[2,3]. *P. falciparum* modifies the surface of infected erythrocytes so that the parasitized red blood cells sequester by adhering to endothelial cells lining the microvasculature, obstructing blood flow and causing ischemia. CSF lactate is thought primarily to reflect the severity of anaerobic glycolysis and microvascular ischemia in the brain.

Materials and Methods

Antimalarial treatment was begun and signed informed consent obtained before enrollment into the study. Standard MRI scans (3DT1, FLAIR, T2W) and single slice 2-dimensional spectroscopy (MRS) data were collected with a 6 channel SENSE-Head Coil on a Philips 3.0T Achieva scanner (Best, The Netherlands) in the Ramathibodi Hospital, Bangkok, Thailand. New broadband refocusing pulses[4] in combination with a single spin-echo localization technique was used to limit destructive interference in lactate detection by chemical shift artifacts. 2D chemical shift imaging (CSI) [BW =2000; TR=2000; TE=288; 1024 samples, NSA=1, 20x20 matrix, FOV 240, 12 mm slice] data were acquired at a slice chosen to maximize the CSF contribution from the anterior ventricles. An echo time (TE) of 288 ms was chosen to ensure that the lactate methyl and methine groups have a spatially homogeneous coupling evolution leading to an upright methyl group lactate peak[5,6]. Ten outer volume suppression (OVS) slabs (25mm) were used to suppress the signal from extracranial lipids[7]. MRI and 2DCSI were repeated after clearance of peripheral malarial parasitemia and at 28 days in the patients with uncomplicated malaria.

Results

Nine patients with acute uncomplicated malaria and one patient with cerebral malaria were enrolled in the study and first examined on the day of hospital admission. On initial examination, 2D-CSI found no detectable lactate in 7 of the patients with uncomplicated malaria (Fig. 1A). In the remaining 2 uncomplicated patients, a lactate peak was evident in the initial CSI study (Fig. 1B). On initial examination of the patient with cerebral malaria, 2D-CSI showed a CSF lactate/creatine integral that was at least three times larger than those found in the 2 patients with uncomplicated malaria (Fig. 1C). Repeat CSI studies in the patient with cerebral malaria (Fig. 2) found a rapid decline in the CSF lactate/creatine integral, coinciding with clearance of the peripheral malarial parasitemia. Subsequently, persistent low CSF lactate/creatine integrals were found throughout the follow-up period, comparable to those observed in the 2 uncomplicated cases.

Discussion and Conclusion

These first measurements of CSF lactate using 2D-CSI in patients infected with *P. falciparum* (Figure 1) demonstrate that MRS can detect increases in some patients with infection classified diagnostically as "acute uncomplicated malaria." As anticipated from clinical studies[2,3], a substantially greater increase in CSF lactate was found initially in a patient with cerebral malaria. After treatment with potent artemisinin antimalarials, the CSF lactate in this patient with cerebral malaria declined rapidly and then remained at low levels over the period of follow-up studies. Repeated non-invasive MRS measurement of CSF lactate will be clinically useful for the diagnosis and management of patients with cerebral malaria, provide a valuable investigatory tool to examine the still undetermined pathogenesis of this lethal complication of falciparum malaria and permit rapid evaluation of neuroprotective treatments for the prevention of persistent neurological disorders in survivors.

References

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Figure 1: MR Spectroscopy in *P. falciparum* malaria

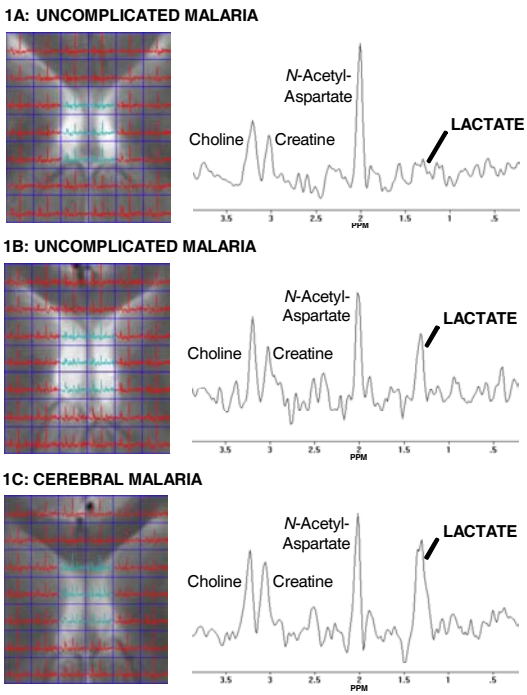

Fig. 1. CSI spectra from three patients shown overlying transverse T2-weighted images alongside the corresponding average spectra from 6 CSF-containing voxels in the anterior ventricles. The CSI has been zero filled to a 6mm voxel resolution and smoothed with a 5Hz Gaussian filter. 1A: lactate-negative uncomplicated malaria, 1B: lactate-positive uncomplicated malaria, 1C: cerebral malaria.

Figure 2: Ratio of lactate to creatine in a cerebral malaria patient

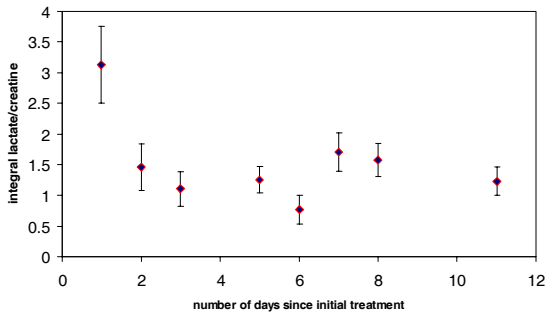

Fig 2. CSF lactate to creatine ratio of a patient with cerebral malaria in 8 examinations performed over 11 days. The ratio of the lactate integral in a single voxel containing mostly CSF is taken with respect to the integral of the creatine in 6 normal appearing brain matter voxels. Error for the peak integration is estimated based on the comparison of the creatine integral in the left and right brain hemispheres which is assumed to be constant.