Can Magnetic Resonance Imaging R2* Quantitation Elucidate Acute Cerebral Malaria Pathology?

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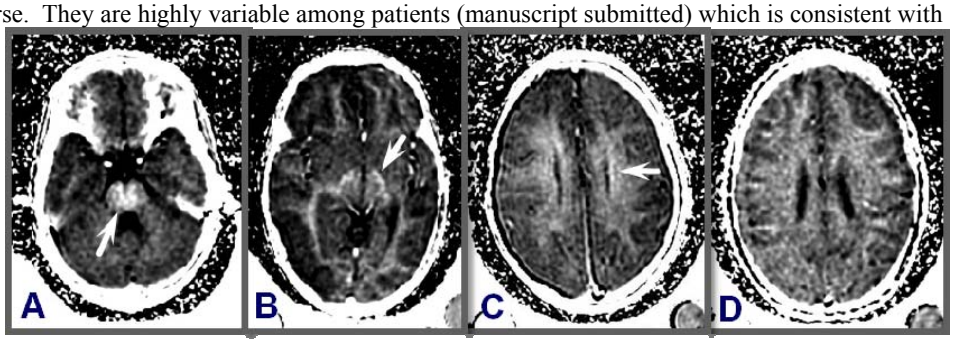
PURPOSE Approximately one million children per year worldwide die from malaria at an average age of ~3.6 years. The vast majority succumb to cerebral malaria (CM), which is endemic to sub-Saharan Africa. The first-ever MR center dedicated to CM research was built in Blantyre, Malawi funded by US NIH.[1] The malaria parasite produces and accumulates a highly-paramagnetic characteristic molecule of polymerized heme called hemozoin.[2] One aspect of the CM MR project investigates the potential for R2* quantitation to measure local CM disease processes via R2* modulation by [hemozoin] and microhemorrhage (no prior MR literature exists). A review of observations and insights from the first year's acquired R2* data sets are presented.

METHODS A permanent-magnet-based 0.35 T MRI scanner (GE Signa Ovation 5) was used to acquire axial 2D GRE images at 5 TE values: 8.0, 11.5, 27.5, 31.0, 47.0 ms, which occur at constant effective fat-water phase. Acquisition parameters: TR 2400, 87° flip, 128x128, 5.0 mm thick at 26 locations, flow comp, NEX 1, 25 cm FOV, 0.75 phase FOV, 122.1 Hz/pixel, single channel head coil. Each TE was acquired in an individual series as no multi-echo sequence is available. Custom MATLAB software computed R2* maps by pixelwise fitting of the registered TE images to the monoexponential relaxation model, $S(TE) = S_0 e^{-R2^* \cdot TE}$, using nonlinear least squares estimation of initial signal intensity S_0 and R2*. When required, image registration between the 5 TE series was performed using AFNI normalized mutual information registration (Medical College of Wisconsin). R2* maps were evaluated unblinded with access to the other MR images. A stringent clinical case definition of CM, including ocular funduscopy, was used.[3,4]

RESULTS AND DISCUSSION Assessable multi-TE image sets were obtained for 9 pediatric acute comatose CM patients and 3 pediatric normal volunteers (consented; approved by US and Malawi IRBs). Careful evaluation of the R2* maps revealed that the most prevalent locations for elevated R2* values were: (A) the pons, where 100% of the CM patients had ROI values averaging 14.0±0.77 s^{-1} (±sd) within the range 12.9–15.3 s^{-1} while the normal subjects were largely separable having mean 12.5±0.83 s^{-1} (Fig. A shows the R2* map for a CM pons example having R2*=15.0 s^{-1}); (B) the posterior limb of the internal capsule, where 78% of CM patients had elevated R2* regions (Fig. B) compared to no such features in any of the normals; and (C) the periventricular white matter, where 89% of CM patients had significant regions of high R2* (Fig. C) compared to no such periventricular features in the normals, as absent in the normal shown in Fig. D.

CM MRI manifestations are dramatic and diverse. They are highly variable among patients (manuscript submitted) which is consistent with the observations in the ongoing autopsy study.[4,5] The R2* maps among the CM patients show marked and varied findings, compared to the first 3 normal children in whom the R2* maps were consistent and simple. The 3 CM R2* maps in the figures give suggestion to the variable presentation of CM. A significant proportion of the information portrayed in the R2* maps is also seen in the T2 weighted images but with different amplitudes, inverted image contrast, and qualitative voxel values. Variable pathophysiologic responses to CM can complicate discriminating what R2* measurements arise from the [hemozoin] located in the microvasculature. Eventually we aim to identify such associated findings through analysis of autopsy specimens.



The aim of this effort is to develop a quantitative MR measurement of the mechanism hypothesized to be central to malaria pathogenesis: the sequestration of parasitized red cells in the cerebral microvasculature. These data will help advance ongoing studies of malaria pathogenesis. R2* map quality was compromised by clinically limited scan time forcing scan protocols having low spatial resolution and SNR, and the reduced paramagnetic effects at 0.35 T. The realities of no local cryogens support and frequent electrical power interruptions necessitated using a permanent magnet scanner and 0.35 T was the highest available B_0 at the time. There are indications that small but significant areas of high R2* are blurred or lost by low spatial resolution, for example as following the internal capsule when it turns more in-plane and fades from partial volume averaging in the slice thickness direction. Lab analysis of autopsy specimens may enable identification and verification of the cause of the R2* values—hypothesis is that they arise from concentrations of hemozoin and/or microhemorrhage blood products.

CONCLUSIONS These preliminary observations of the initial CM R2* maps suggest that there is a detectable MR signal, even at 0.35 T, arising from brain areas which commonly show histological evidence of hemozoin and microhemorrhage at autopsy. The pons, periventricular white matter, and internal capsule appear to be common locations of elevated R2*. Further development effort is warranted.

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