

Evoked potentials in pediatric cerebral malaria

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Abstract

Cortical evoked potentials (EP) provide localized data regarding brain function and may offer prognostic information and insights into the pathologic mechanisms of malaria-mediated cerebral injury. As part of a prospective cohort study, we obtained somatosensory evoked potentials (SSEPs) and brainstem auditory EPs (AEPs) within 24 hours of admission on 27 consecutive children admitted with cerebral malaria (CM). Children underwent follow-up for 12 months to determine if they had any long term neurologic sequelae. EPs were obtained in 27 pediatric CM admissions. Two children died. Among survivors followed an average of 514 days, 7/25 (28.0%) had at least one adverse neurologic outcome. Only a single subject had absent cortical EPs on admission and this child had a good neurologic outcome. Among pediatric CM survivors, cortical EPs are generally intact and do not predict adverse neurologic outcomes. Further study is needed to determine if alterations in cortical EPs can be used to predict a fatal outcome in CM.

Introduction

Cerebral malaria (CM) is a common cause of mortality and morbidity among children, especially in those younger than 5 years.¹⁻⁵ CM is traditionally defined as being unarousable coma in the presence of *P. falciparum* parasitemia with no other coma etiology evident.⁶

A CM-specific retinopathy has recently been described that further enhances diagnostic certainty.^{1,6-9} Of children with CM who reach care, 15-25% die. Risk factors for death include more profound coma, younger age, seizures, hypoglycemia and hyperparasitaemia.^{10,11} Neurologic sequelae, including cortical blindness, gross motor deficits, ataxia and language regression are also common and occur in ~30% of survivors.¹¹⁻¹² No prior studies of pediatric CM have included evoked potentials (EP) during the acute coma. Despite extensive research, the pathogenetic mechanisms of CM-induced coma, CNS injury, and death remain unclear.¹³ We obtained cortical EPs, specifically somatosensory evoked potentials (SSEPs) and auditory evoked potentials (AEPs), in children with CM coma to determine if the presence or absence of cortical EPs predicts adverse neurological outcomes.

EPs are the electrical responses to sensory stimulation. The SSEPs are presynaptic and postsynaptic responses recorded over the limbs, spine and scalp following the stimulation of peripheral nerve trunks (median and/or posterior tibial nerves). They provide a measure of sensory conduction and thereby detect lesions in proximal peripheral nerves, spinal cord, brainstem and the brain.¹⁴ AEPs consist of auditory (click) stimuli delivered to each ear following which responses are recorded in the brainstem and cortex. They are mainly used for evaluation of peripheral and central auditory circuits in the brainstem.

Cortical responses obtained on SSEPs and AEPs have been widely used to prognosticate neurological outcome and survival in patients with coma due to hypoxic, anoxic, traumatic and ischemic brain injury.¹⁵⁻¹⁸ The absence of cortical responses of SSEPs and AEPs (in the absence of peripheral nervous system or auditory system dysfunction) is indicative of irreversible cerebral damage and poor prognosis.¹⁵

EPs are obtained quickly and easily at the bedside with inexpensive equipment, provide information on brainstem function and could be readily used in endemic areas if shown to contribute usefully to the diagnosis, management or prognosis in patients with CM. malaria endemic regions, CT technology is the most commonly available brain imaging option but routine protocols provide very limited views of brainstem anatomy due to bony artifact.¹⁹

Materials and Methods

From January to June 2008 (the malaria season), children admitted to Queen Elizabeth Central Hospital (QECH) with CM underwent SSEPs and AEPs as part of their clinical assessment. Inclusion criteria for this study were admission the Pediatric Research Ward, a

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Key words: cerebral malaria, evoked potentials, AEP, SSEP, outcome, mortality.

Acknowledgements: many thanks to Clara Antonio and Juliet Simwinga whose contributions through patient follow-up made this work possible. We are grateful to the children and their parents and guardians who took part in the study. The Department of Paediatrics of the College of Medicine and the Queen Elizabeth Central Hospital provided ward accommodation and essential support for these studies.

Contributions: MB, study design, conception, EP interpretation, review and editing; TET, study design and conception, patient enrollment and care, staff supervision, review and editing; MEM, study design and conception, patient enrollment and care, staff supervision, review and editing; MSO, data collection, logistics and design, review and editing; GLB, study conception and design, staff training and oversight, data analysis, manuscript writing.

Conflict of interest: the authors report no conflicts of interest.

Funding: for this work was provided by: NIH/NINDS K23 NS046086-01(GB), NIH/NIAID R01 AI034969-10AI (TT). The Wellcome Trust (MM) 074125/Z/04/Z

Received for publication: 9 September 2011.
Accepted for publication: 28 September 2011.

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Licensee PAGEPress, Italy
Neurology International 2011; 3:e14
doi:10.4081/ni.2011.e14

Blantyre Coma Score (BCS) of <3, *P. falciparum* parasitemia, and the presence of CM retinopathy identified by an ophthalmologist. EPs were generally only available during daytime hours. Children who died or regained consciousness before EPs could be obtained were not eligible for inclusion in this analysis.

AEPs and SSEPs were completed using an XLTEK Neuromax 1004 System. AEPs were performed by inserting small ear buds into the external auditory canal for delivery of auditory stimulus. The auditory stimuli consisted of clicks delivered at a rate of 10/sec at stimulus intensity of 60 dB per SPL (decibels peak equivalent sound pressure level) and duration of 0.1 microseconds. The contralateral ear was masked with white noise. The responses were recorded between the vertex and ipsilateral

mastoid processes. The right and left ear were stimulated independently and at least two separate trials were given consisting of 2000 stimuli that were amplified and averaged with band pass filters at 100 and 3000Hz. The waveforms were analyzed for the presence or absence of waves III and V.¹⁴ SSEPs were obtained after stimulation of the median and tibial nerves bilaterally. Median nerves were stimulated using a surface cathode 3 cm proximal to the wrist crease and anode 2 cm distal to the cathode. The electrical stimulus consisted of square-wave pulses at 7 per second. The intensity of the stimulus was adjusted to produce a visible thumb twitch. The responses were recorded at the elbow, Erb's point (N9), over the seventh cervical spine process (N13), and the contralateral parietal cortex (N20) corresponding to C3 or 4 of the 10-20 international system. A common reference electrode was attached at Fz of the 10-20 system. The ground electrode was placed on the arm. Each study consisted of 500 trials averaged and filtered with a band width of 30-3000 Hz. Similarly, tibial SSEPs were obtained by placing the stimulating electrode (cathode) at the ankle between the medial malleolus and Achilles tendon. The anode was placed 3 cm distal to the cathode and the ground was placed on the calf. The stimulus intensity was adjusted to produce a small plantar flexion of the toes. The responses were recorded at the T12 spinous process (LP), C5 spinous process (N34), ipsilateral cortex between C3 or C4 and P3 or P4 of the 10-20 system (CPI) and midline between Cz and Pz (CPz). A common reference electrode was placed at the Fpz position of the 10-20 system. The waveforms were recorded and averaged over 1000 trials and filtered with bandpass of 30-3000 Hz. The presence or absence of cortical responses for the median stimulation was based upon the N20 responses and for the tibial stimulation it was based upon the P37 responses.¹⁴

Survivors were followed up for at least 12 months after discharge, to assess for any adverse neurological outcome. The discharging physician completed a neurologic examination and subsequent assessments were completed at 1 month post discharge and quarterly thereafter by study nurses. These follow-up assessments included The Epilepsy Screening Questionnaire and The Ten Questions. The Epilepsy Screening Questionnaire is a nine-item instrument that has been previously used to screen for epilepsy in the developing world with 79.3% sensitivity and 92.9% specificity.²⁰ The Ten Questions instrument has been shown to be valid for identifying moderate neurodisabilities in children as young as two years with good reliability ($\kappa=0.67$) with 85% sensitivity for detecting moderate to severe neurodevelopmental disabilities.²¹ Both instruments were

forward and back translated into the local language with discrepancy resolution prior to use. Any child screening positive for potential problems by the nurses was seen by a neurologist to confirm and characterize the nature of the neurologic sequelae.

This study was approved by the University of Malawi College of Medicine Research Ethics Committee and Michigan State University's Biomedical IRB. Written informed consent was obtained from the parent or guardian of all children included in this study.

Results

Twenty-seven children met inclusion criteria and underwent EP studies during their acute admission. The study population was characterized by a mean age of 4.2 years (median 2.7; IQR 2.3-5.8) and 13 were male (48.1%). The average time from admission to regaining a BCS ≥ 3 was 20.4 hours (median 10.5; IQR 6.0-25.5). Two children died and among survivors 7/25 (28.0%) had at least one adverse neurologic outcome including epilepsy (3 children), behavioral disorders (3 children) and/or gross neurodisabilities (4 children) characterized by language regression, motor or sensory deficits or ataxia. Cortical responses were present on EPs in 26 patients (96.3%), including the two who later died. Only a single subject had absent EPs during the acute CM infection and this child had a good neurologic outcome.

Discussion

The presence or absence of cortical responses on SSEPs and AEPs during acute coma due to CM does not predict long term neurologic sequelae. Some limitations to this study include technical challenges such as the lack of age specific normative data and documentation of limb temperature. More sophisticated assessments including changes in absolute or inter-peak latencies need to be further assessed. Neurodiagnostic staff were available only during daytime hours, so we were not able to assess some children, who recovered or died before EPs could be obtained. This likely excluded a higher than random proportion of patients with fatal CM, which is reflected by the fact that the mortality rate in our study was 7% in comparison to the pediatric research ward's overall rate of 16%. Further studies are needed that include a greater number of CM fatalities to determine whether EPs offer prognostic information for survival.

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