Original Article

Noninvasive measures of brain edema predict outcome in pediatric cerebral malaria

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Abstract

Background: Increased brain volume (BV) and subsequent herniation are strongly associated with death in pediatric cerebral malaria (PCM), a leading killer of children in developing countries. Accurate noninvasive measures of BV are needed for optimal clinical trial design. Our objectives were to examine the performance of six different magnetic resonance imaging (MRI) BV quantification measures for predicting mortality in PCM and to review the advantages and disadvantages of each method.

Methods: Receiver operator characteristics were generated from BV measures of MRIs of children admitted to an ongoing research project with PCM between 2009 and 2014. Fatal cases were matched to the next available survivor. A total of 78 MRIs of children aged 5 months to 13 years (mean 4.0 years), of which 45% were males, were included.

Results: Areas under the curve (AUC) with 95% confidence interval on measures from the initial MRIs were: Radiologist-derived score = 0.69 (0.58–0.79; P = 0.0037); prepontine cistern anteroposterior (AP) dimension = 0.70 (0.56–0.78; P = 0.0133); SamKam ratio [Rt. parietal lobe height/(prepontine AP dimension + fourth ventricle AP dimension)] = 0.74 (0.63–0.83; P = 0.0002); and global cerebrospinal fluid (CSF) space ascertained by ClearCanvas = 0.67 (0.55–0.77; P = 0.0137). For patients with serial MRIs (n = 37), the day 2 global CSF space AUC was 0.87 (0.71–0.96; P < 0.001) and the recovery factor (CSF volume day 2/CSF volume day 1) was 0.91 (0.76–0.98; P < 0.0001). Poor prognosis is associated with radiologist score of ≥7; prepontine cistern dimension ≤7 mm; SamKam ratio ≥6.5; and recovery factor ≤0.75.

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**BACKGROUND**

Pediatric Cerebral malaria (PCM) is a leading killer of children in developing countries.\(^{[15,21]}\) In 2016, there were 216 million malaria cases worldwide, with 445,000 deaths, most of these in under 5 children in Sub-Saharan Africa.\(^{[21]}\)

The pathophysiology of PCM is not fully understood, but there is wide consensus that sequestration of parasitized red blood cells in cerebral microcirculation is the pathological hallmark of the disease.\(^{[18]}\) Vascular sequestration and a variety of other processes are associated with coma, seizures, and death,\(^{[8-12,14,15,17]}\) with PCM mortality being caused by diffuse cerebral edema, herniation, respiratory arrest, and death.\(^{[15]}\) No effective adjuvant therapies have been identified. Accurate assessment of brain edema is crucial in the design of clinical trials of anti-edema therapies. Research over the past decade shows that noninvasive edema assessment can be achieved by magnetic resonance imaging (MRI) using a variety of methods. These methods provide brain edema assessments that can be used to predict clinical outcome, bypassing invasive intracranial pressure (ICP) measurements, which are fraught with infection risk in resource-challenged settings.\(^{[4]}\) More accurate noninvasive measures of increased brain volume (BV) are needed for optimal clinical trial design utilizing edema reduction measures to decrease the PCM mortality rate of 15–25%.\(^{[8,17]}\)

**Objectives**

The objectives are to examine the features of the performance of six different MRI BV quantification methods for predicting mortality in PCM using the receiver operator characteristic (ROC) curves and to review the advantages and disadvantages of each method.

**MATERIALS AND METHODS**

**Study design**

Retrospective case–control study of children with PCM who had MRIs completed between 2009 and 2014 was conducted comparing survivors and fatal cases.

**Inclusion criteria**

- All patients had retinopathy positive PCM\(^{[1,7]}\)
- Fatal cases were matched to the next available survivor with two or more MRIs.

**Exclusion criteria**

- All cases needed sagittal T1 flair and axial T2 pulse sequences for analysis. Cases without complete sag T1 flair and axial T2 sequences were excluded from the study.

**Clinical procedures and image processing**

All children underwent fundoscopy by an ophthalmologist to determine retinopathy status. Malarial retinopathy increases the specificity of the clinical diagnosis of cerebral malaria (CM) as it correlates with the presence of cerebral vascular sequestration, the pathological hallmark of CM.\(^{[17,14]}\) BV scores were determined by two radiologists with consensus on discrepant reads. Readings were entered into Neurointerp.\(^{[13]}\) Linear measurements and cerebrospinal fluid (CSF) volumetric quantification were also determined by a radiologist. Cisternal CSF was quantified manually using ClearCanvas on a subset of 10 cases (5 survivors and 5 case fatalities) independently by a radiologist and an MRI technologist to establish interobserver agreement in the CSF quantification method.

**MRI scanning protocols**

Scanning protocols used since 2009 have been published before\(^{[14,15]}\) and included sagittal T1 flair, coronal T2, axial T2, and axial diffusion weighted imaging pulse sequences. The sagittal T1 flair sequence used 6 mm slices with 1.5 mm spacing.

**Statistical analysis**

The ROC curves for predicting outcome (death vs survival) were derived using six methods—a radiologist-derived brain volume, the SamKam ratio,\(^{[5]}\) prepontine cistern measurement, cisternal CSF volume manually assessed using ClearCanvas on day 1 and day 2 and the recovery factor(CSF volume day 2/CSF volume day 1).

**Radiologist-derived brain volume (BV) 1–8 score\(^{[14,15]}\)**

This method is performed by an experienced radiologist evaluating the axial T2 pulse sequence images through the cerebral hemispheres [Table 1; Figure 1]. The method is dependent on a radiologist’s experience in pattern recognition of brain edema.

**SamKam ratio\(^{[5]}\)**

The SamKam ratio is the ratio of the mid-height of the right parietal lobe measured on the first coronal slice.
behind the splenium of the corpus callosum and the sum of the preopticine cistern and the fourth ventricle anterior–posterior dimensions in the mid-sagittal slice. The rationale of this method is that brain edema expels cranial CSF, hence, a representative “brain/CSF” ratio should measurably change with worsening edema.

Prepontine cistern dimension
A linear prepontine cistern anteroposterior dimension in the mid-sagittal plane was used to assess brain edema [Figure 2; left panel].

Global CSF Volume Day 1
The cisternal CSF volume around the brainstem was manually quantified by ClearCanvas. Reproducibility of this volume quantification approach has been shown elsewhere.[3,20] In this method, the cranial cisternal CSF is quantified [Figure 3] as follows:

1. On ClearCanvas, using the sagittal T1 and axial T2 pulse sequences, CSF is quantified on T1 by tracing out the cisternal space areas and the presence of fluid in them is ascertained by cross-referencing with axial T2 slices.
2. The boundaries for sampling are as follows (white lines):
   a. Inferior boundary: Foramen magnum line (left panel)
   b. Superior margin: Tentorium cerebelli (left panel)
   c. Lateral margins for sampling the cerebellopontine angle cisterns: The sagittal slices through the exits of the 7/8 cranial nerves from the cerebellopontine angle cisterns (middle panel).
   d. Lateral margins for sampling the suprasellar and ambient cisterns: The sagittal slices through the lateral margins of the cerebral peduncles (right panel).
3. Pitfalls:
   a. Slow flowing blood causes abnormal T1 signal. It should be included in quantification.
   b. The uncus (encroaches into the suprasellar cistern in severe edema); the pituitary stalk and the basilar artery should not be included in quantification.
4. Infratentorial cisternal CSF volume (cubic centimeters) = Sum of cisternal areas × slice thickness.

A subset of children (n = 37) who survived long enough to have a scan on day 2 had brain edema assessed through two approaches—CSF volumes on day 2 and a Recovery Factor (RF) calculation comparing the change in CSF volumes between day 1 and day 2.

Global CSF Volume Day 2
On the second day, the cisternal CSF volume around the brainstem was manually quantified as detailed above for CSF volume day 1.

Recovery factor
The “recovery factor” (RF) variable is the ratio of the global CSF assessments on day 2 and day 1 (RF = Vol. day 2/Vol. day 1). RF indirectly shows the rate of BV change; this is especially significant around the brainstem as compression of vital structures here is directly related to death, both in PCM[15] and traumatic brain injury.[19] The relevance of the RF is supported by the observation that deaths in PCM occur rapidly after admission.

RESULTS

Study population
The study population was n = 78, age range 5 months to 13 years (mean 4 years) with 44.8% males.

ROC curves for predicting outcome (death vs. survival)
The areas under the ROC curves (AUCs) for the six methods were generated using MedCalc software (http://medcalc.com/) [Figure 4]. The results were as follows: the radiologist-derived score was 0.69 (0.58–0.79; P = 0.0037); prepontine cistern AP dimension 0.70 (0.56–0.78; P = 0.0133); SamKam ratio: 0.74 (0.63–0.83; P = 0.0002); and global CSF space 0.67 (0.55–0.77; P = 0.0137). For subsequent MRIs, the day 2 global CSF space was 0.87 (0.71–0.96; P < 0.001) and the RF was 0.91 (0.76–0.98; P < 0.0001).

Cranial cisternal CSF volume–time curve; Staging of PCM [Figure 5]
The typical volume–time curve of CSF around the brainstem in survivors of PCM reveals a U-shaped curve. The changing RF values allow staging of PCM into early, intermediate, and late stages. Case fatalities exhibit a sharp decline of CSF volume and their graphs often lack the turn and upsweep sections of the curve. Some survivors scanned later in the disease for a variety of reasons may only exhibit the upsweep part of the curve.

Grading of PCM severity using RF
The severity of PCM can be graded using the RF. The grading is shown in Table 2, using figures from the study cohort.

Inter-rater agreement on use of the CSF quantification method
A radiologist and an MRI technician assessed a subset of 10 cases to determine the inter-rater agreement for the CSF quantification method. The Pearson coefficient for the two observers was 0.98, suggesting that the method can be reliably used by various observers [Appendices a and b].

DISCUSSION
PCM remains a leading killer of African children under the age of five.[21] Although artesunate is widely used as part
of standard care, mortality rate from the disease remains high, at 15–25%. Brainstem compression from herniation in severe brain edema is associated with death; effective adjuvant anti-edema therapies are needed and valid, noninvasive measures of quantifying brain edema could substantially improve and inform the design and conduct of clinical trials of edema reduction interventions in PCM.

The development of effective brain edema therapies involves monitoring the intracranial space which may be achieved by different methods. In developing countries where malaria is endemic, invasive catheter monitoring cannot be sustained due to high cost.
need for highly skilled personnel, and its various complications.\cite{4,6} Assessment by imaging and clinical examination is as effective as invasive catheter monitoring. In a large clinical trial that compared management of traumatic brain injury guided by catheter monitoring of ICP vs. care guided by brain edema assessment by imaging (plus clinical assessment), mortality was not different between the two groups.\cite{4} Many noninvasive methods for estimating ICP have been developed and some of them offer promise for use in clinical practice.\cite{6} Methods involving brain imaging offer an added advantage of detecting other pathological processes that may complicate CM including infarcts, bleeds, fluid collections, sinusitis, and otomastoiditis.

MRI methods described here accurately predict outcome in PCM. The mortality rates for the various methods are: radiologist BV score of ≥7 (94%); preponintine cistern dimension ≤3 mm (92%); cisternal CSF volume ≥7.5 ml (78 and 80% on day 1 and 2, respectively); and SamKam ratio ≥6.5 (92%). Patients with RF >1 are in the recovery phase, with only 5% mortality from nonedema causes. The mortality rate of those in the early phase is 72% for a RF of ≤0.75 [Figure 6].

Initial MRI assessment may inform clinical trials on patient selection, stratification, and risk adjustment. Serial imaging can stage and grade PCM. Staging PCM has particular relevance in clinical trials because an effective edema therapy needs to alter the slope of the early phase or prolong the intermediate phase. In resource-poor settings, staging may help identify intensive care patients that are recovering from coma earlier than can be determined by global image assessment by radiologists [Figure 7]; thus enabling better allocation of resources. Disease grading enables further patient stratification in clinical trials. Staging by RF may have utility in traumatic brain injury and other infective encephalopathies whose pathophysiology’s are dominated by brain edema;\cite{19} however, specific studies are needed to establish this.

The advantages and disadvantages of the methods described here deserve mention [Table 3]. The radiologist method is quick and accurate at selecting cases with severe edema. Its main setbacks are the need for an experienced radiologist and its semi-quantitative nature. The SamKam ratio and the preponintine cistern AP dimension are quick and easy methods, requiring no special training. The main setback with these methods is the limitation of scale.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{SamKam ratio}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{ROC for all six MRI brain edema evaluation methods}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Cranial cisternal CSF quantification method}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{ROCs for all six MRI brain edema evaluation methods}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Staging of PCM}
\end{figure}
by the enclosed cranial cavity: the right parietal lobe
does not have enough room for endless enlargement
and the prepontine cistern gets totally effaced in
cases of severe edema. CSF quantification provides
an endless scale and best approximates the actual
biologic process in PCM: reduction of cranial CSF
volume by its extrusion into the spinal theca by a
swelling brain. CSF quantification can be reliably
performed by clinicians of different cadres; however, it
is limited by the human factor; and studies have been
planned to produce a computer automated program
that can speed up the assessment.

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Conflicts of interest
There are no conflicts of interest.

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by including malaria retinopathy. Future Microbiol 2011;6:349-55.

Table 3: Comparative overview of the brain edema
assessment measures

| Method             | Advantages                              | Disadvantages                                |
|--------------------|-----------------------------------------|----------------------------------------------|
| Radiologist-derived edema score | Fast                                   | Requires experienced radiologist, some level of subjectivity |
| Prepontine cistern AP measure   | Fast, limited expertise needed          | Scale limited by enclosed cranial cavity     |
| SamKam              | Fast, limited expertise needed          | Scale limited by enclosed cranial cavity     |
| Global CSF volume   | Best approximation of biologic outcome  | Manual approach time consuming. Automation could improve this |

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Appendix b: Inter rater agreement cranial CSF volume measurements

| Day number | Radiologist CSF vol/cc | MRI technician CSF Vol/cc |
|------------|-------------------------|----------------------------|
| MP2810     | 1                       | 1.8                        | 3.48                       |
| MP2810     | 2                       | 4.39                       | 5.6                        |
| MP2718     | 1                       | 21.14                      | 24.6                       |
| MP2718     | 2                       | 20.5                       | 21.52                      |
| MP2744     | 1                       | 0.169                      | 0.16                       |
| MP2744     | 2                       | 0.932                      | 1.1                        |
| MP2820     | 1                       | 7.017                      | 6.6                        |
| MP2820     | 2                       | 11.734                     | 9.9                        |
| MP2746     | 1                       | 12.35                      | 12.9                       |
| MP2746     | 2                       | 17.06                      | 15.24                      |
| MP2723     | 1                       | 15.25                      | 16.65                      |
| MP2723     | 2                       | 0.41                       | 0.55                       |
| MP2752     | 1                       | 4.53                       | 5.17                       |
| MP2752     | 2                       | 3.42                       | 3.04                       |
| MP2783     | 1                       | 10.62                      | 9.87                       |
| MP2783     | 2                       | 5.52                       | 6.01                       |
| MP2885     | 1                       | 6.67                       | 6.42                       |
| MP2885     | 2                       | 2.01                       | 2.27                       |
| MP3047     | 1                       | 11.52                      | 10.84                      |
| MP3047     | 2                       | 11.63                      | 11.53                      |

Appendix a: Inter rater agreement for CSF quantification method. Rater 1: Radiologist. Rater 2: MRI technologist