

Original Article

Noninvasive measures of brain edema predict outcome in pediatric cerebral malaria

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Received: 10 August 17 Accepted: 19 December 17 Published: 01 March 18

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 ≤ 3 mm; cisternal CSF volume ≤ 7.5 ml; SamKam ratio ≥ 6.5 ; and recovery factor ≤ 0.75 .

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10.4103/sni.sni_297_17

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How to cite this article: Kampondeni SD, Birbeck GL, Seydel KB, Beare NA, Glover SJ, Hammond CA, et al. Noninvasive measures of brain edema predict outcome in pediatric cerebral malaria. *Surg Neurol Int* 2018;9:53.

<http://surgicalneurologyint.com/Noninvasive-measures-of-brain-edema-predict-outcome-in-pediatric-cerebral-malaria/>

Conclusion: All noninvasive measures of BV performed well in predicting death and providing a proxy measure for brain volume. Initial MRI assessment may inform future clinical trials for subject selection, risk adjustment, or stratification. Measures of temporal change may be used to stage PCM.

Key Words: Brain herniation, brain volume, intracranial pressure, noninvasive measures, pediatric cerebral malaria, receiver operator characteristic

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.^[1,7,14] 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 prepontine 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;^[2,16] 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 ($RF = \text{Vol. day 2}/\text{Vol. day 1}$). 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 upswing sections of the curve. Some survivors scanned later in the disease for a variety of reasons may only exhibit the upswing 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

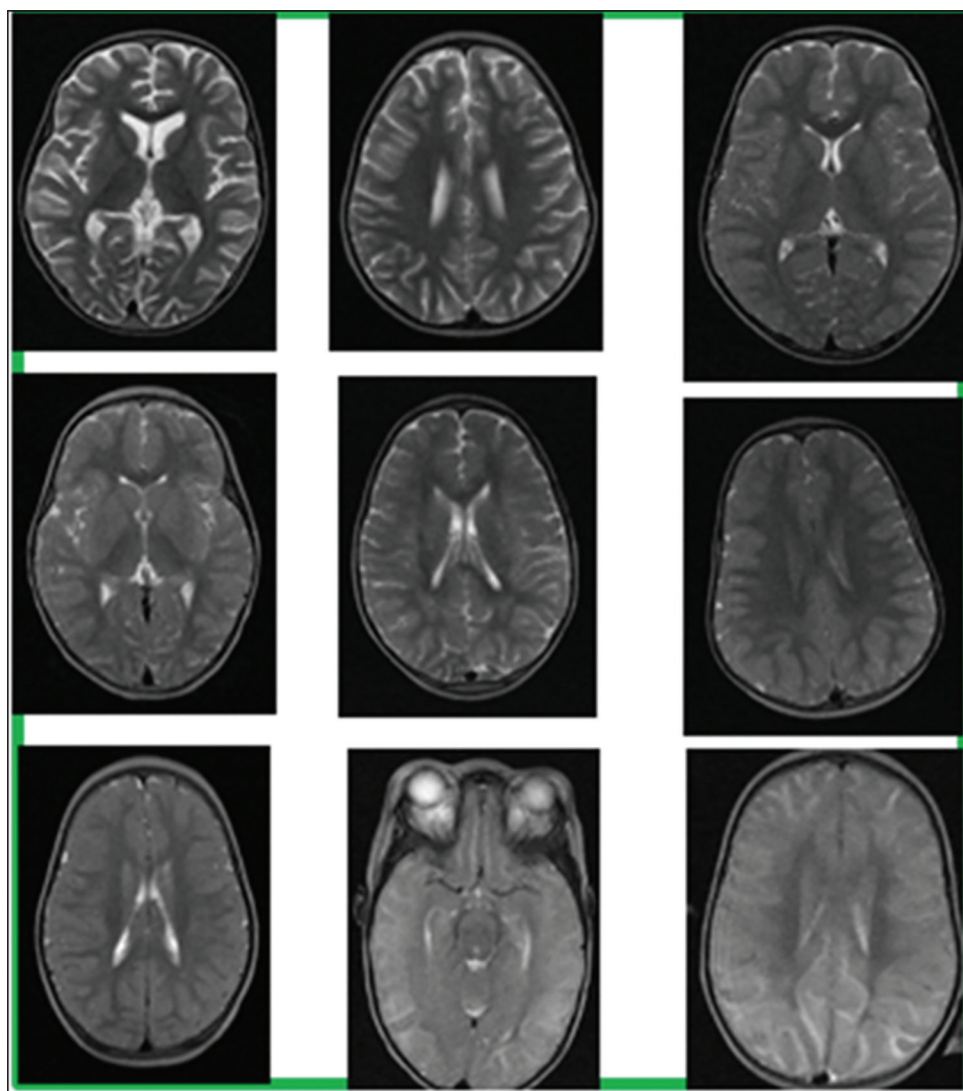


Figure 1: Images for radiologist-derived BV 1-8 score, L-R:Top row (BV 1,2,3), Middle row (BV4,5,6), Bottom row (BV 7,8,8)

Table 1: Grading features for the radiologist-derived score from 1 to 8

Brain volume grade	Axial T2 findings
1	Severe atrophy markedly abnormal for age with diffuse prominence of the cisternal and sulcal markings
2	Mild atrophy – subtle prominence of the markings for age
3	Normal brain volume
4	Mild increased volume but with maintenance of cisternal and sulcal markings
5	Mild swelling – some loss of markings but not diffuse
6	Moderate swelling – diffuse involvement with some loss of markings
7	Severe swelling – loss of all sulcal markings, presence of cisternal effacement, decreased grey/white matter delineation
8	Severe swelling – loss of all sulcal markings, presence of cisternal effacement, presence of uncus herniation, loss of grey/white matter delineation

Table 2: PCM severity grading by RF

Grade	Recovery factor	Survived	Died	% Survival rate
1	0.75-1.0	7	3	70
2	<0.75	2	5	28

(For RF >1, the late recovery phase, 19 children survived out of 20)

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,

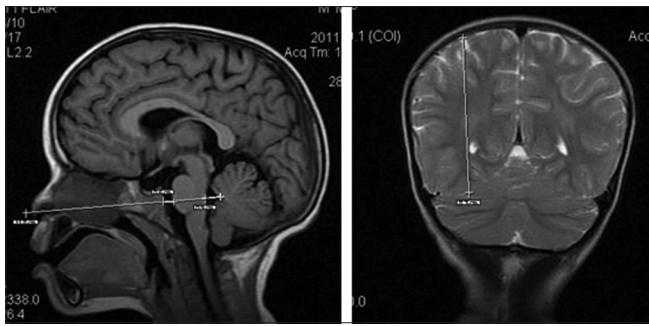


Figure 2: SamKam ratio

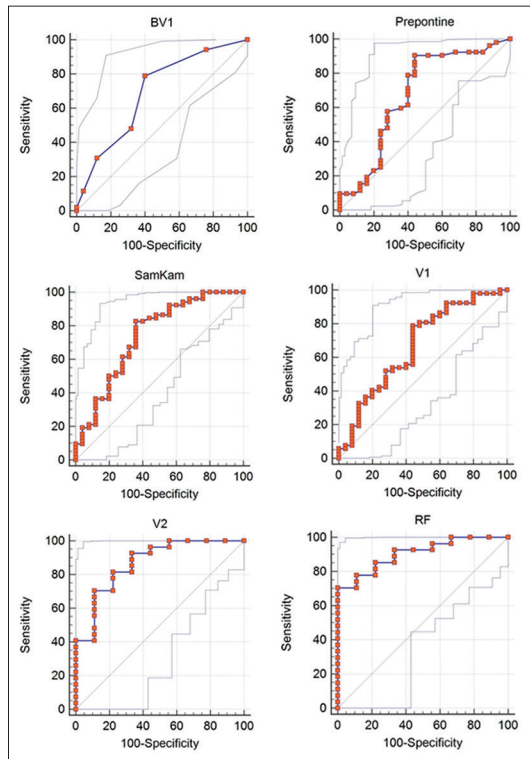


Figure 4: ROCs for all six MRI brain edema evaluation methods

need for highly skilled personnel, and its various complications.^[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.^[4] Many noninvasive methods for estimating ICP have been developed and some of them offer promise for use in clinical practice.^[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%); prepontine

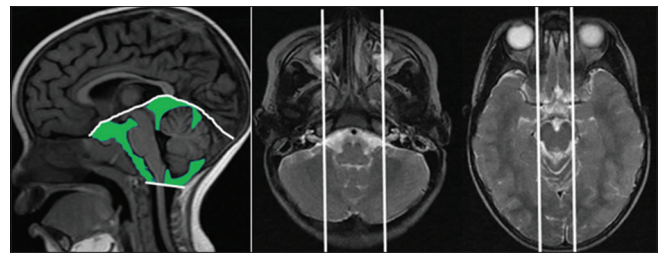


Figure 3: Cranial cisternal CSF quantification method

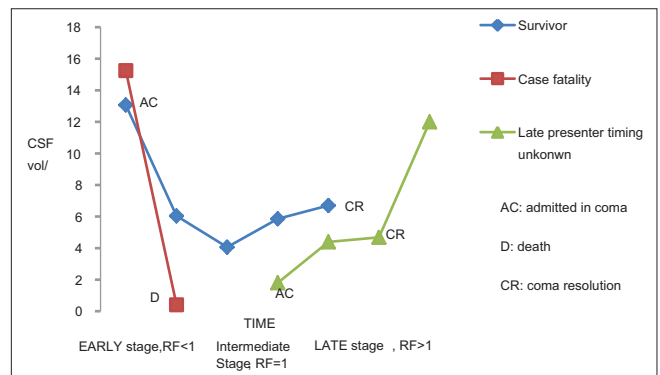


Figure 5: Staging of PCM

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;^[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 prepontine cistern AP dimension are quick and easy methods, requiring no special training. The main setback with these methods is the limitation of scale

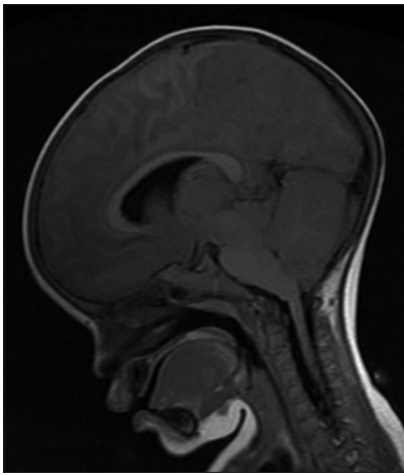


Figure 6: Poor prognosis: Mid-sagittal T1 flair image showing severe brain edema in a child who succumbed to CM: radiologist BV score = 8; prepontine cistern dimension = 0; Cisternal CSF volume = 0.41 ml; SamKam ratio = 35; and RF = 0.026

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

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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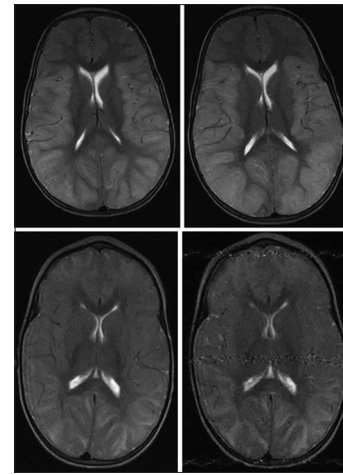
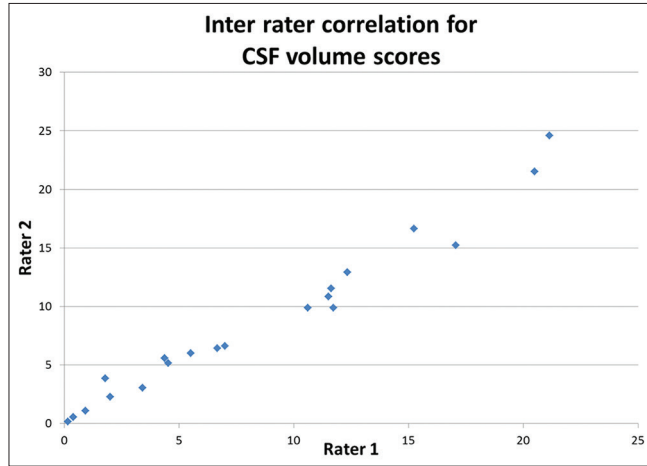


Figure 7: Earlier oedema resolution detection by staging than global image assessment. Axial T2 images done on subsequent days showing severe oedema in two children. Top row: Child died (BV scores 8; 8; RF= 0.026). Bottom row: Child survived (BV scores 8; 8; RF=2.4)

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

Appendix b: Inter rater agreement cranial CSF volume measurements

	Day number	Radiologist CSF vol/cc	MRI technician CSF Vol/cc
MP2810	1	1.8	3.84
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
MP 2723	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