

Prevalence of Raised Intracranial Pressure in Cerebral Malaria Detected by Optic Nerve Sheath Ultrasound

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Abstract. We aimed to use optic nerve sheath (ONS) ultrasound to determine the prevalence of raised intracranial pressure (ICP) in African children with cerebral malaria (CM); and if increased ONS diameter is associated with poor outcome. We measured ONS diameter in 101 children with CM and 11 children with malaria and impaired consciousness in Malawi. The prevalence of raised ICP detected by increased ONS diameter was 49%. Case fatality was similar in children with increased ONS diameter on admission (9/55) and those children without increased ONS diameter (11/57). Neurological sequelae were more common in those children with increased ONS diameter (7/46 versus 2/46, $P < 0.05$). Lumbar puncture (LP) opening pressure was elevated in 95% of 46 children who underwent LP. In Malawian children with CM, raised ICP is less commonly detected by ONS ultrasound than LP. This study suggests that raised ICP is not universal in CM and that other mechanisms may account for coma.

INTRODUCTION

Raised intracranial pressure (ICP) is common in cerebral malaria (CM) in children, but its role in the pathogenesis of coma, death, and neurological disability is not known. Almost all children with CM who have lumbar puncture have elevated cerebrospinal fluid (CSF) opening pressure^{1,2} but only 10–15% have papilledema.^{3,4} ICP monitoring in 23 Kenyan children with CM found that all had raised ICP⁵ and that single lumbar puncture pressure measurements did not predict the maximum ICP. Several children in that study developed severe intracranial hypertension, all of whom subsequently died or had neurological sequelae.

The mechanism of raised ICP is not known but is thought to be related to the sequestration of parasitized erythrocytes in the cerebral microvasculature. This mechanism may cause raised ICP in three ways: by compromising the blood–brain barrier, leading to extracellular edema; by hypoxic or cytotoxic injury to cells, leading to intracellular edema (oncosis) and brain swelling; and/or by increasing the intracerebral blood volume through intracranial vasodilatation.

The optic nerve sheath (ONS) is continuous with the brain's dura mater and expands in the presence of raised ICP transmitted from the subarachnoid space along the optic nerve.^{6–8} The distension is maximal 3 mm behind the globe of the eye. Many studies have shown that ultrasound measurement of optic nerve sheath diameter provides accurate, reproducible information on the presence of elevated ICP.⁹ This non-invasive technique has been used successfully in emergency rooms,^{10–12} children with hydrocephalus,¹³ and children with other causes of raised ICP.¹⁴ We have previously established normative values for ONS diameter in Malawian children and showed the use of ONS ultrasound for detecting raised ICP in a resource-poor setting.¹⁵ That study suggested that an ONS diameter of 4.3 mm and above was abnormal and had a sensitivity and specificity of 100%

and 86% for detecting raised ICP, respectively. If an ONS diameter of 4.6 mm or more is taken as an indicator of raised ICP, the sensitivity and specificity were found to be 93% and 100%, respectively.

In the present prospective study, we aimed to use sonographic measurement of the ONS diameter to detect raised ICP in Malawian children with CM or severe malaria with impaired consciousness to increase understanding of the role of intracranial hypertension in severe malaria.

PATIENTS AND METHODS

We conducted the study in the Pediatric Research Ward at Queen Elizabeth Central Hospital, Blantyre, Malawi. We prospectively recruited patients with CM over 14 months. The diagnosis of CM was made in patients with *Plasmodium falciparum* parasitemia and deep coma corresponding to a Blantyre Coma Score (BCS) of two or less maintained for at least 2 hours. Other causes of coma such as meningitis, hypoglycemia, and a postictal state were excluded. Patients with BCS that recovered to three or more within 2 hours were included, but we have termed these patients as severe malaria with impaired consciousness. Parents or guardians were asked in their own language for their consent to the child's participation in the study.

In recruited children, an ultrasound examination of the ONS was undertaken by one observer (N.A.V.B.) on admission. A handheld Sonosite 180 ultrasound machine (Sonosite Inc., Bothell, WA) was used with a 7-MHz curved array transducer (4–7 MHz 11-mm array transducer set to highest resolution frequency of 7 MHz). The scan type was set to neonatal throughout, with maximum scan depth set to 4 cm and the gain control on factory settings. Ultrasound scans were undertaken through the closed eye lid from the temporal side, providing an axial view through the eye and optic nerve longitudinally. The optic disc, together with as long of a section of optic nerve as possible, were included in the freeze frame. The option to toggle through the last 10 seconds of images was often used to obtain the best image, but only one image from a 10-second sequence was used for measurement.

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Measurements of the ONS diameter were made with electronic callipers 3 mm behind the posterior scleral surface of the globe. Care was taken to measure perpendicularly across the optic nerve. The average was taken of three measurements from different scans, with the on-screen measurement masked to the observer until each measurement was finalized.

In patients who had a lumbar puncture (LP) on the research ward, ultrasound of the ONS was performed directly before (within 30 minutes) the LP where possible. The CSF opening pressure was measured by manometer during the performance of the LP. Scans of the ONS were repeated hourly for 12 to 24 hours if the child remained in deep coma. The BCS was recorded at each scan, and the final outcome of the child's illness was recorded as full recovery, neurological sequelae, or death. Patients were examined by direct and indirect ophthalmoscopy through dilated pupils by an ophthalmologist to assess for papilledema and malarial retinopathy.

Ethical approval for the study was obtained from the University of Malawi College of Medicine Research Ethics Committee and the Liverpool School of Tropical Medicine Research Ethics Committee, United Kingdom. Data were analyzed by SPSS (IBM, Armonk, NY).

RESULTS

During the period of the study, there were 171 patients admitted with CM. Seventy CM patients were not included, mainly because of non-availability of study personnel at the time of admission; 11 patients with severe malaria and impaired consciousness were included, resulting in 112 study patients. They had a mean age of 36 months, and 61 (55%) patients were male. ONS diameters ranged from 3.0 to 6.7 mm. Only four patients were under 12 months, and they all had ONS diameter less than 4.0 mm¹³; therefore, these patients were treated as normal and included in the analysis.

The ONS diameter was 4.3 mm or over in 55 patients, giving a prevalence of raised ICP by this method of 49%. ONS diameter was over 4.6 mm in 48 (43%) patients. Results are summarized in Table 1.

The proportion with an ONS diameter of 4.3 mm or more among patients with CM was very similar to the proportion in patients with impaired consciousness: 50 of 101 (49%) and 5 of 11 (45%) patients, respectively. The data were, therefore, treated together.

Papilledema was present in 27 patients, and of these 27 patients, 25 patients had an increased ONS diameter (45% of patients with increased ONS diameter). Two patients with mild papilledema¹⁶ had normal ONS diameter. There were 30 patients with dilated ONS who did not have papilledema on admission. In eight cases, papilledema developed during the course of the illness in the hospital. There were five children with papilledema that resolved after the ONS returned to normal and two children with papilledema that resolved but ONS diameter remained enlarged after 2 and 6 days.

CSF opening pressure values were only available in 46 patients, because LPs were frequently performed in the Accident and Emergency Department, where opening pressure was not measured. In 16 patients, an LP was not done. Of 46 patients with opening pressures, 44 (96%) patients had levels that were elevated (> 90 mmCSF); 27 (59%) of the patients with elevated opening pressure had normal ONS diameters of less than 4.3 mm. The two patients with normal opening pressures also had normal ONS diameters.

In children who had LP, the median opening pressure in the children with ONS diameter less than 4.3 mm was 160 mmCSF (range = 70–290 mmCSF), and in the children with ONS diameter 4.3 mm or greater, it was 220 mmCSF (range = 130–320 [maximum readable] mmCSF). The difference between these two groups was significant ($P = 0.002$, Student t test unequal variance). In 11 patients, it was possible to measure the ONS diameter before and 30 minutes after LP, and there was no difference ($P = 0.91$, Student t test, paired samples).

Case fatality rates were similar in the groups of patients with normal and raised ONS diameter measurements (Table 1). Among survivors, there was a significantly greater prevalence of gross neurological sequelae at discharge in the group with increased admission ONS diameters.

There was no significant difference between the groups in their median admission depth of coma, rate of recovery from coma, prevalence of seizures at the time of admission, or incidence of seizures during the hospital stay (Table 1). There were no significant differences between the two groups in their mean hematocrit, plasma lactate concentration, or human immunodeficiency virus (HIV) status.

Malarial retinopathy was present in 78 (72%) patients (missing data in 4 patients). There were more patients with 20 or more retinal hemorrhages in the enlarged ONS group (10 [19%] versus 3 [6%]; $P = 0.06$, χ^2 for trend). There was

TABLE 1
Comparison of patients with enlarged ONS diameter (≥ 4.3 mm) with patients with normal ONS diameter (< 4.3 mm)

	Enlarged ONS diameter (%)	Normal ONS diameter (%)	<i>P</i> value
All patients ($N = 112$)	55 (49)	57 (51)	
Papilledema present	25 (45)	2 (4)	
Median CSF opening pressure ($N = 46$)	220 mmCSF ($N = 17$)	160 mmCSF ($N = 29$)	0.002*
Deaths	9 (16)	11 (19)	0.9†
Neurological sequelae in survivors	7/46 (15)	2/46 (4)	< 0.05‡
Median BCS on admission	1	2	0.67†
Mean time to BCS three (hours)	39	22	0.07*
Mean time to BCS five (hours)	50	37	0.11*
Fits on admission ($N = 107$)	16 (31)	9 (16)	0.07†
Fits during admission ($N = 107$)	23 (45)	17 (30)	0.11†

*Student t test.

† χ^2 test.

‡Fisher exact test.

Significant P values are in bold.

no difference between the groups in terms of other features of malarial retinopathy.

Fifty-four patients had follow-up scans over 36 hours. Thirty-nine patients had scans repeated at 12 hours, twenty-five patients at 24 hours, and seventeen patients at 36 hours; 41% of patients remained enlarged, 13% of patients returned to normal, 5% of patients started normal, enlarged, and then returned to normal, 15% of patients started normal and later enlarged, and 26% of patients remained normal throughout. All patients started with BCS less than three, and there was no clear relation between the change in ONS diameter and BCS.

DISCUSSION

Ultrasonic measurement of ONS diameter provides an accurate method for the detection of raised ICP.⁹ It has the advantages of being non-invasive and straight-forward to perform on all patients. Using this measure, we have found a prevalence of raised ICP in children with CM of about 50%, and this finding was similar in patients presenting with impaired consciousness but rapidly improving coma. The absence of this sonographic sign of raised ICP in 50% suggests that raised ICP is not required for the initiation of coma.

Raised ICP is an important aspect of cerebral malaria in children but a less prominent feature in adults. The nearest comparable pediatric data come from LP opening pressures, although it is recognized that a single opening pressure measurement is of limited value. A study in 40 Gambian children with CM found an elevated opening pressure in 32 (80%) children. Opening pressure was not related to fatal outcome.² In 26 Kenyan children selected from 61 children with CM, opening pressures were all elevated (between 105 and 360 mmCSF).¹ There are few data on ONS diameter in malaria. A pilot study of several ultrasound techniques in moderate to severe malaria included ONS diameter measurement. It found an enlarged ONS diameter in 5 of 5 patients with CM and 2 of 12 patients with severe malarial anemia.¹⁷

A difficulty in interpreting the data on opening pressure is controversial regarding the upper limit of normal ICP in this age group. Because it is not ethical to invasively measure ICP in normal children, the work by Minns and others¹⁸ used historical published data to define normal ICP as < 5.8 mmHg (79 mmH₂O) in infants and < 6.4 mmHg (87 mmH₂O) in children. We have taken 90 mmCSF as the upper limit of normal in this group with a mean age of 3 years.

There seems to be a difference between the prevalence of elevated opening pressures in CM (80–100%; 95% in this study) and the prevalence of enlarged ONS sheath diameter (50%). Normal opening pressure may be higher in African children than Caucasian children, but this finding would not account for the moderate to highly elevated opening pressures seen commonly in CM. An explanation could be that there is a delay between the ICP being elevated and the ONS dilating, but this data was not found in a study of ONS during intrathecal infusions where it was an immediate response.⁶ It may be because there is selection bias, in that those patients who have opening pressures measured in these studies are more likely to have high ICP than other

patients with CM. The only study using the gold standard of ICP monitoring selected children with CM who were showing abnormal brain stem signs.⁵ Unsurprisingly, all these children had raised ICP. We attempted, in this study, to detect raised ICP in an unselected group of children with CM. We included 60% of those children admitted with CM; reasons for non-inclusion were operational and unrelated to disease severity.

A possible cause of the discrepancy between the ONS enlargement and LP opening pressure is that the CSF is not in free communication but compartmentalized, and CSF pressure may not be equal in different compartments. The composition of CSF sampled from the optic nerve subarachnoid space has been found to be different from spinal CSF, indicating that these two compartments are not in free communication.¹⁹ CSF may be compartmentalized by fluid dynamics and anatomical restrictions, such as the optic canal²⁰ and foramen magnum. This finding may lead to differences in the CSF pressure between the optic nerve and intracranial and spinal compartments. The study by Newton and others⁵ of ICP monitoring took opening pressures from the intracranial monitoring and not LP, and therefore, it offers no comparative data between the cerebral and spinal compartments.

Papilledema takes time to develop, because it results from swelling of ganglion cell axons in which axoplasmic flow has been interrupted. We found papilledema in 45% of those patients with enlarged ONS diameters on admission. In a number of children, the development or resolution of papilledema tracked (with a delay) the observed changes in the ONS diameter.

We found a greater prevalence of neurological sequelae among children whose ONS diameter had been high at the time of admission than among those children with initially normal ONS diameters. It is possible that some of the patients with enlarged ONS had severe intracranial hypertension and that this critically compromised cerebral perfusion led to localized cerebral infarction.⁵

The results of this study suggest that raised ICP is less common in CM than found using opening pressure at LP. Raised ICP is thought to be important in the pathogenesis of CM, but its role remains unclear. Our study suggests that raised ICP is not required for the initiation of coma in all patients, because 50% of comatose children with CM in this study had a normal ONS diameter. However, raised ICP is likely to be important in determining the outcome of a subset. A sufficiently elevated ICP compromises cerebral perfusion and may cause intracranial herniation, thereby contributing to a poor outcome in some patients. There have been no adequate trials of interventions that reduce ICP in CM. Measurement of ONS diameter by ultrasound may have a useful role in identifying a subset of patients in whom such an intervention could be investigated.

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