SHORT REPORT

Changes in optic nerve head blood flow in children with cerebral malaria and acute papilloedema

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Objective: To investigate capillary blood flow in the optic nerve head (ONH) of children with cerebral malaria.

Methods: Malawian children with cerebral malaria admitted to a paediatric research ward were examined by direct and indirect ophthalmoscopy. ONH blood flow was measured using laser Doppler flowmetry (LDF) in suitable patients. Mean blood volume and velocity were obtained from 30 to 60 s recordings from the temporal ONH and used to calculate blood flow. These were compared with admission variables, funduscopic findings and disease outcomes.

Results: 45 children with cerebral malaria had LDF recordings; 6 subsequently died and 5 survivors had neurological sequelae. 12 (27%) had papilloedema. The mean microvascular blood volume was higher in patients with papilloedema (3.28 v 2.54 arbitrary units, $p=0.002$). The blood velocity correlated directly with haematocrit ($r=0.46$, $p=0.001$) and inversely with blood glucose ($r=-0.49$, $p=0.001$).

Conclusion: The increase in ONH microvascular blood volume in papilloedema measured by LDF is consistent with current theories of pathogenesis of papilloedema. LDF has potential as a tool to distinguish papilloedema from pseudopapilloedematous disc swellings. The relationship between blood velocity and haematocrit may relate to levels of sequestration in cerebral malaria.

Cerebral malaria, caused by *Plasmodium falciparum*, primarily affects children in sub-Saharan Africa with mortality ranging from 15% to 50%. The characteristic histological feature of malaria caused by *P. falciparum* is sequestration of parasitised erythrocytes within the microvasculature by cytoadherence. This occurs in the brain^{1–3} and other organs, including the retina.⁴ Sequestration in small vessels is implicated in the pathogenesis of coma in cerebral malaria, although the mechanism remains unclear.⁵

Papilloedema occurs in 10–15% of patients with cerebral malaria, increasing the risk of death by 4.5-fold.^{6–7} Other ocular fundus features associated with cerebral malaria are retinal whitening, orange or white vessels, and retinal haemorrhage.^{6–9} As in other neurological conditions, papilloedema is associated with raised intracranial pressure.⁵ The pathogenesis of papilloedema is associated with increased pressure within the optic nerve sheath, a compartment in contact with the subarachnoid space. This leads to interruption of axoplasmic flow in the optic nerve fibres, resulting in swelling of their prelaminar portion.^{10–11} The exact mechanism of this restriction and the importance of vascular changes remain unclear.¹²

The optic nerve head (ONH) is an accessible element of the central nervous system (CNS), and measuring blood flow in the ONH could illuminate the pathogenic mechanisms in cerebral malaria. Laser Doppler flowmetry (LDF) is a non-invasive method of measuring blood flow in the ONH using the Doppler

shift in laser light scattered by moving erythrocytes. By directing the laser away from visible blood vessels the microcirculation can be sampled. The mean relative blood velocity and volume are computed from the spectrum of Doppler frequency shifts. The volume is derived from the width of the Doppler shift spectrum, and the velocity from the magnitude of Doppler shifts. LDF has proved useful in physiological studies of ONH blood flow^{13–16} and of glaucoma.¹⁷ A feasibility study of LDF in cerebral malaria produced promising results.¹⁸

We report a study of ONH microcirculation in children with cerebral malaria in relation to clinical parameters, particularly papilloedema.

METHODS

Patients

We studied consecutive patients with cerebral malaria admitted to the paediatric research ward, Queen Elizabeth Central Hospital, Blantyre, Malawi, during one malaria season. Patients with parasitaemia and coma, in whom hypoglycaemia, meningitis and postictal state had been excluded, (Blantyre Coma Score ≤ 2) were diagnosed as having cerebral malaria.^{19–20}

Data collection

After the clinical condition of patients was stabilised, direct and indirect ophthalmoscopy was performed after pupil dilation with tropicamide 1% and phenylephrine 2.5% eyedrops.

NAVVB carried out LDF of the ONH in patients within 12 h of admission. Patients unsuitable for LDF included those in a critical condition, with ongoing convulsions, rapid coma resolution or involuntary eye movements. The laser Doppler flowmeter was mounted on a Kowa Genesis hand-held fundus camera. The laser was positioned on the temporal ONH rim avoiding visible vessels, and recordings were taken for 30–120 s. The cardiac cycle was measured by infrared plethysmometry to calculate pulsatility.

Data analysis

LDF tracings were analysed by a blinded observer (CER) who obtained velocity, volume and flow measurements from 30 to 60 s sections with stable direct current. Spikes from blinking and eye movements were removed before analysis.

Statistical analysis of LDF parameters against clinical parameters (coma score, blood pressure, blood glucose, temperature, parasite count and haematocrit), outcome (died, survived with sequelae and full recovery) and fundus findings was carried out using Spearman's rank correlation matrix and Student's *t* test.

RESULTS

A total of 106 patients with cerebral malaria were admitted, and LDF recordings were carried out on 47 consecutive, suitable

Abbreviations: CNS, central nervous system; LDF, laser Doppler flowmetry; ONH, optic nerve head

patients. The median time from admission to LDF recording was 1 h. Two patients had poor tracings which could not be used, and hence 45 patients were included in the analysis. No statistical difference was observed in admission parameters between the studied and excluded patients. There was a difference in the mortality between those included in the study and those excluded (13% *v* 21%) but this was not significant ($p = 0.29$).

Table 1 shows the clinical features of the patients studied. Six patients died and five had neurological sequelae at discharge. There were 12 (27%) patients with papilloedema.

LDF parameters in papilloedema

The mean volume was higher in patients with papilloedema than in those without ($3.28 \text{ v } 2.54$, t test $p = 0.002$). The mean volume pulsatility was higher in patients with papilloedema, but this difference was not significant ($0.24 \text{ v } 0.18$, t test $p = 0.12$). There was no difference in velocity, flow or their pulsilities between patients with and without papilloedema (table 1).

LDF parameters and clinical variables

Velocity correlated directly with haematocrit ($r = 0.46$, $p = 0.001$) and inversely with blood glucose ($r = -0.49$, $p = 0.001$). These correlations remained the same in analysis of the group without papilloedema. On using multiple linear regression to adjust for haematocrit and glucose, the difference in velocity between children with papilloedema and those without remained not significant ($p = 0.11$).

There were no other associations between velocity, volume or flow and clinical variables listed in table 1.

LDF parameters, retinal signs and outcome

There were no correlations between LDF parameters and retinal findings (haemorrhages, macular whitening, peripheral whitening and vessel changes) using Spearman's rank correlation.

No difference was seen in LDF parameters between patients with adverse outcome (death or neurological sequelae) and those with a full recovery.

DISCUSSION

This study shows an increase in the LDF measure of microvascular blood volume in the ONH tissue of children with acute papilloedema and cerebral malaria. This is consistent with the presence of dilated ONH capillaries. This may be due to venous impedance or autoregulatory dilatation of tissue capillaries in the ONH in response to hypoxia. If this finding is replicated in other conditions

causing increased intracranial pressure and papilloedema, then LDF may be a useful tool in discriminating papilloedema from pseudopapilloedematous disc swellings.

The increase in volume measured by LDF may alternatively be an artefact produced by changes in tissue architecture secondary to papilloedema or to the difference in age between the two groups. However, we also found a non-significant ($p = 0.12$) elevation of volume pulsatility in papilloedema. A change in the volume dynamic, as well as level, suggests that a vascular change is responsible. It should be noted that the depth at which LDF obtains readings is uncertain.^{13 21 22}

The relationship between haematocrit and the measured blood velocity was unexpected. It could be due to a cardiovascular response or a disease effect on small vessels. A possible explanation is that more anaemic children have more sequestration and a higher proportion of uninfected red cells with reduced deformability,²³ the combination of these effects leading to impedance in small vessels and decreased flow velocities.

Newton *et al.*,²⁴ using transcranial ultrasound, found normal blood velocities in the middle cerebral artery in children with cerebral malaria. They rose to abnormally high levels in some patients with seizures.²⁴ However, sequestration occurs in small vessels whose blood flow has not been studied previously in the CNS. Knowledge of the effect of sequestration on cerebral blood flow at a microvascular level would enable greater understanding of the pathogenesis of coma and death in cerebral malaria.

We investigated microvascular blood flow in the ONH because it is an accessible part of the CNS. The ONH has similar levels of sequestration to other parts of the CNS (fig 1), and sequestration close to its surface shows that it is a valid object of study when investigating the effect of sequestration on CNS blood flow. Notwithstanding the relationship we found between velocity and haematocrit, how sequestration affects microvascular blood flow in the brain remains unknown. Histologically, sequestration is heterogeneous, with affected vessels next to unaffected (fig 1). The effect of this has been visualised in rectal mucosa using orthogonal polarising spectral imaging, which showed adjacent hypoperfused and hyperperfused areas.²⁵ Tissues sampled by LDF may have included underperfused and overperfused areas, or areas underperfused in one patient and overperfused in another. This may explain why we found no relationship between blood flow and disease outcome.

The use of LDF in ophthalmological studies is extending from static, directed lasers to scanning LDF in which the laser

Table 1 Demographic, clinical and laser Doppler flowmetry parameters of 45 patients with cerebral malaria, comparing those with papilloedema with those without

Admission clinical variables (units)	All patients	Patients with papilloedema	Patients without papilloedema
Age (months)	39 (21.4)	52 (23.4)	34 (18.8)*
Sex (% female)	53	67	45
Coma score	1 (0.76)	1 (0.85)	1 (0.73)
Haematocrit (%)	23 (8.1)	23 (8.1)	23 (8.2)
Blood glucose (mmol/l)	5.7 (2.6)	5.5 (2.3)	5.8 (2.8)
Systolic BP (mm Hg)	106 (17)	108 (19)	106 (17)
Malarial parasites (/ml)	107 500 (158 100)	66 300 (91 200)	122 500 (175 100)
Temperature (°C)	38.3 (1.2)	38.1 (1.2)	38.4 (1.2)
LDF parameters			
Volume (AU)	2.74 (0.72)	3.28 (0.75)	2.54 (0.60)**
Volume pulsatility	0.20 (0.10)	0.24 (0.15)	0.18 (0.06)
Velocity (kHz)	0.48 (0.12)	0.45 (0.09)	0.49 (0.13)
Velocity pulsatility	0.28 (0.10)	0.32 (0.14)	0.26 (0.07)
Flow (AU)	112 (26.4)	114 (30.9)	111 (25.0)
Flow pulsatility	0.28 (0.10)	0.33 (0.10)	0.26 (0.10)

AU, arbitrary units; BP, blood pressure; LDF, laser Doppler flowmetry.

Values are mean (SD), except for sex which is a proportion.

* $p < 0.05$.

** $p < 0.005$.

Figure 1 Photomicrograph of optic nerve head showing sequestration of parasitised erythrocytes in a blood vessel (arrow; haematoxylin and eosin, $\times 20$). Inset: same optic nerve head, $\times 4$.

scans the whole ONH. This could overcome problems with positioning and spatially variable blood flow; however, a sampling protocol is still required for quantitative measurement. This technique is not available in a hand-held unit suitable for patients in coma.

Our study is limited by the lack of a control group. There is no suitable group of unconscious children whose ONH blood flow would not have been potentially altered by anaesthetic agents or cerebral pathology. We hypothesised that differences in severity and outcome of cerebral malaria would be manifested by differences in ONH blood flow. This proved not to be the case, but it remains possible that cerebral malaria alters ONH blood flow, particularly as no normative data exist for children. Notably, LDF was feasible only in 44% of patients with cerebral malaria; this is a possible source of selection bias, although statistical differences between groups were not detected.

This is the first report of blood flow measurements by LDF in patients with papilloedema. Further research is required to see if the increased microvascular volume is replicated in other conditions and age groups. This may prove valuable in conditions in which chronic papilloedema can result in visual loss, such as idiopathic intracranial hypertension, and in differentiating acute papilloedema from other disc swellings.

Sequestration of parasitised erythrocytes within the ONH microvasculature shows that the ONH is a valid object of study to understand the effect of sequestration on blood flow in the CNS. However, the effects of papilloedema on ONH blood flow will need to be taken into account.

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