

# A Comparison of Brain, Core and Skin Temperature in Children with Complicated and Uncomplicated Malaria

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## Summary

**A prospective study was carried out in which brain, core and skin temperatures were studied in children with cerebral malaria ( $n = 23$ ), uncomplicated malaria ( $n = 12$ ) and normal children ( $n = 9$ ) using the zero heat flow method. Patients with cerebral or uncomplicated malaria were admitted to the paediatric wards (mean age, 6 years 8 months  $\pm$  2 years 8 months). Normal children, children of the investigators, of the same age group, served as controls. Parasitaemia levels were similar in the cerebral and uncomplicated malaria cases. Higher brain than core temperatures would have been expected in cerebral malaria but not in uncomplicated malaria but this was not the case in this study. There was no statistical difference in brain, core and skin temperature between cerebral and uncomplicated malaria patients. However, there was a highly significant difference between normal children and cerebral and uncomplicated malaria patients. Brain temperature was 0.02–0.2°C below core temperature in all the groups with larger differences during the febrile period. Mean differences of brain minus core, brain minus skin and core minus skin between the two groups of patients were not statistically significant. There was no correlation between temperature and the level of coma or parasitaemia for cerebral and uncomplicated malaria patients. There was a positive correlation between brain and core temperature in both groups of patients during the febrile phase. Brain temperature remained lower than core temperature in cerebral and uncomplicated malaria as in normal children. Normal thermoregulation appears to be maintained in cerebral malaria.**

## Introduction

Cerebral malaria is a common complication of malaria with a high mortality especially in developing countries where malaria prevalence is high.<sup>1</sup> It carries a mortality rate of between 15 and 50 per cent with less than 10 per cent having temporary neurological sequelae.<sup>1–4</sup> Malaria prevalence is unknown in Eldoret but hospital data indicate that it is second only to acute respiratory infections in both morbidity and mortality.<sup>4</sup>

Occurrence of malaria in Eldoret is popularly known as highland malaria because 10 years ago

malaria was rare in the highlands of Kenya. Eldoret has an altitude of about 2000 m above sea level and malaria epidemics occur due to the non-immune status of the inhabitants. These epidemics occur during the rainy season of April to October, with cerebral malaria being the most common complication especially in children.

The pathogenesis of cerebral malaria has been the subject of various studies the results of which have been inconsistent and inconclusive. The obstruction of the cerebral microcirculation by parasitized red blood cells (RBC) and their binding to the endothelial cells at the capillary level has been the most plausible postulate. However, it does not explain the absence of permanent neurological sequelae in the majority of the survivors.<sup>5–8</sup> Cytoadherence mediated by *Plasmodium falciparum* erythrocyte membrane protein 1 (pfEMP1) causes anchoring of the parasite to the RBC membrane causing knobs or humps on its surface. These knobs are the points of attachment to vascular endothelium. However, some parasites do not cause these knobs and therefore this theory of pfEMP1 is not universally accepted.<sup>5–7</sup>

The binding of the parasitized red blood cells (pRBCs) to cellular differentiation antigen 36 (CD36) at low pH in the presence of hypocalcaemia has been postulated to be involved in the pathogenesis. CD36 is the sticky protein on the surface of the

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vascular endothelium that binds the parasitized RBC. Intercellular adhesion molecule (ICAM) also binds pRBCs, and tumour necrosis factor (TNF) enhances cytoadherence. ICAM seems to be the main ligand for sequestration in the brain and CD36 for the other tissues.<sup>5-7,9</sup> It has also been found that pRBCs adhere to non-parasitized RBCs thus forming rosettes, whereas all species of *P. falciparum* cyto-adhere, but not all rosettes. Rosetting is associated with cerebral malaria; however, this does not explain fully the pathogenesis of cerebral malaria since rosetting is not demonstrable in all cases. Parasitized RBC deformability has been postulated as responsible for sequestration but it cannot explain the sequestration that occurs in the venules that is observed in cerebral malaria, since deformed RBCs can only cause obstruction at midcapillary level.<sup>5</sup>

Studies on the role of fever in the pathogenesis of febrile diseases are few in the literature, but they indicate that fever is independent of the disease state although they did not involve studies of brain temperature.<sup>10</sup> However in an earlier study by the author there was no statistical difference between measles, cerebral and uncomplicated malaria patients when the core and skin temperatures were compared, but there were significant within-group differences for core and skin temperature comparisons.<sup>10</sup> Studies on temperature changes in the brain among patients with or without cerebral malaria have not been done and this study incorporated monitoring of temperature in the management of these patients using the zero heat flow monitor/thermometer that non-invasively records brain, core, skin and ambient temperatures simultaneously on the same graph.<sup>11,12,18-20</sup> It has been noted in some studies that TNF acts as a mediator in cerebral malaria in which low levels are beneficial in the host parasite interaction and high levels cause hyperpyrexia and other severe functional derangements, which has been corroborated by high TNF levels in some of these patients. This TNF activity is thought to be absent or lower in uncomplicated malaria.<sup>12-17</sup> If this is the case then one would expect to find higher brain than core temperatures in cerebral malaria than in uncomplicated malaria.

The objectives of the study were to compare the brain, core and skin temperature between cerebral and uncomplicated malaria patients, to establish whether brain temperature is higher in cerebral malaria than core temperature and to compare these with those in uncomplicated malaria cases and in normal children.

## Patients and Methods

### Patients

A total of 28 consecutive cerebral malaria cases were recruited of whom three died within 6 h of admission

and two absconded from the study. A total of 23 consecutive cases of cerebral malaria were therefore studied over a 5-month period (May–September 1997). Twelve uncomplicated malaria cases and nine normal children were also recruited. Patients with uncomplicated malaria were selected from amongst those admitted to the paediatric wards. The normal controls were healthy children of the collaborating researchers or participants in the study. All children that met the admission criteria and were included in the study were from Uasin Gishu district in the Rift valley province of Kenya of which Eldoret (340 km north-west of Nairobi) is the headquarters.

### Inclusion criteria

Patients were included based on the following criteria.

All children had to be between 1 and 12 years old.

Demonstration of the asexual forms of plasmodium malaria in the peripheral blood film for both cerebral and uncomplicated malaria cases.

Haemoglobin levels of higher than 5 g/dl for all patients with uncomplicated malaria.

Absence of convulsions, normal mental state, no other signs of other febrile illness, absence of any signs of complicated malaria and good response to anti-malarials for uncomplicated malaria patients.

Coma scores of 3 and below using the Blantyre coma scale with normal cerebrospinal findings for cerebral malaria patients.<sup>6,21</sup>

Normal controls had to be within the same age bracket, with no clinical evidence of malaria and had to be medically fit on physical examination.

### Exclusion criteria

The following patients were excluded from the study.

Patients with unexplained coma, documented bacterial meningitis or mixed infection (malaria and meningitis), i.e., patients with cerebrospinal fluid (CSF) findings of raised protein, increased white blood cell (WBC) counts and low sugar.

Patients with a history of head injury, even if the blood slide was positive because of the similarity of the features with cerebral malaria.

Patients with uncomplicated malaria with severe anaemia (Hb below 5 g/dl) or the presence of altered consciousness.

Children below 1 year and above 12 years.

### Coma scoring

Grading was done using the Blantyre coma scale on admission and then twice a day until a coma scale of 4 was recorded on two consecutive occasions.<sup>21</sup> The grading was done by two independent clinicians who compared their scores and recorded the consensus score. In a few cases there was no agreement and a third clinician was requested to carry out an independent score. Scores of 1–3 were considered coma while scores of 4 and 5 were not.

### *Ethical considerations*

Informed and written consent was obtained from the parents or guardians for all patients before admission into the study. Informed consent was obtained from the guardians of the normal controls.

The study was conducted with the approval of the Institutional Research and Ethics Committee of the Faculty of Health Sciences Moi University.

### *Temperature measurements*

All the three groups had the individual temperatures monitored by the zero heat flow method using the Terumo zero heat flow electronic temperature monitor over a period of 30 min per single observation.<sup>18,19</sup> The monitor has four thermistors that are pasted on the forehead for brain temperature, on the lower trunk near the axilla for core temperature, on the lateral shin for skin temperature, and on the bed for ambient temperature. The four temperatures were recorded simultaneously at 1 min intervals on a graph. The peak temperature was reached within 30 min for all the four types of temperature. Three observations were carried out for the cerebral and uncomplicated malaria patients at 9 am, 3 pm and 9 pm for 5 days and only one reading was taken for the normal children. Day 1 was defined as the first 24 h of admission. The zero heat flow method of temperature measurement is based on the assumption that if heat flow across the skin is reduced to zero, skin surface temperature is equilibrated with tissue temperature thus allowing the latter to be measured at the surface.<sup>19,20</sup> Some of the uncomplicated and cerebral malaria cases were not able to stay for the 5 days as they were well, they absconded, or they were unavailable at times for the regular observations of temperature.

### *Laboratory methods*

Five millilitres of venous blood was drawn from the cerebral and uncomplicated malaria patients on day 1, 3 and 5 for haemoglobin estimation, peripheral blood film, malaria parasites and blood sugar. A lumbar puncture was done on admission for cerebral malaria cases only, for the estimation of CSF sugar and protein, microscopy and culture to exclude bacterial meningitis. A portion of the serum and CSF was immediately frozen at  $-70^{\circ}\text{C}$  for cytokine studies to be reported in a separate article.

No specimens were drawn from the normal controls for ethical reasons.

All the laboratory tests were carried out in the research laboratories of the Departments of Immunology and Child Health and Paediatrics using the standard methods for the respective tests.

### *Treatment*

Patients with cerebral malaria were treated with intravenous quinine 20 mg/kg in 500 ml of 5 per cent dextrose to run over 4 h followed by two doses of

10 mg/kg in 500 ml of 5 per cent dextrose to run over 16 h on the first day and then every 8 h for subsequent days until out of coma. This applied to the uncomplicated malaria patients on the first day and was changed to intramuscular quinine until the fifth day. All were discharged on oral quinine for 3–5 days after the fifth day of parenteral therapy.

### *Statistical methods*

The data was analysed using the SPSS PC+ database program using the *t*-test for equality of means and Levenes test for equality of variances. The mean temperatures for each day were obtained for the individuals for the two patient groups and for the normal controls and these were compared between the groups. For the differences between the temperature types the mean differences were obtained by subtracting the means of the temperatures for the groups to be compared. The average mean differences were obtained and these were then compared.

## **Results**

A total of 23 cerebral malaria cases, 12 uncomplicated malaria cases and nine normal children were studied. The results are summarized in the Tables 1 and 2.

Most of the children were aged below 10 years in all the three groups with most of them being between 5 and 10 years (mean age was 6 years  $\pm$  2 years 8 months, for cerebral malaria cases, 5 years  $\pm$  3 years, for uncomplicated malaria cases, and 6 years for normal children).

Seventy per cent of cerebral malaria cases were male, 50 per cent of uncomplicated malaria patients and 78 per cent of normal children. This male predominancy could be due to the small sample size and for normal children this could be due to selection bias as most of the researchers had more boys than girls.

On admission 13, 56.6 and 30.4 per cent of the cerebral malaria patients were in Blantyre coma scale 1, 2 and 3, respectively. A total of 39.1 per cent of the cases were out of coma in 24 h, 73.9 per cent were out of coma in 48 h, and all the cases were out of coma by 72 h.

No correlation was found between coma, parasitaemia and temperature level in all the days for both cerebral and uncomplicated malaria patients. A positive linear correlation was found between core and brain temperature during the febrile period ( $r = 0.8734$ ,  $p < 0.001$ ) but this correlation disappeared when the children become afebrile.

The haematological parameters (haemoglobin, WBC count etc) were the same in both groups. There was no statistical difference between the parasitaemia levels in cerebral and uncomplicated malaria patients (mean = 214 729  $\pm$  39 930

TABLE 1

*Brain, core and skin temperature comparisons between cerebral and uncomplicated malaria for days 1, 2, 3, 4, and 5*

Day	Temperature type	Cerebral malaria		Uncomplicated malaria		Statistical parameters (two-tail sig)
		<i>n</i>	mean temp (°C)	<i>n</i>	mean temp (°C)	
1	Brain	23	37.7	12	37.3	0.4
	Core	23	37.9	12	37.4	0.39
	Skin	23	31.2	12	32.1	0.41
2	Brain	23	37.7	11	37.2	0.22
	Core	23	37.8	11	37.3	0.22
	Skin	23	36.9	11	36.5	0.37
3	Brain	23	37.1	7	36.8	0.32
	Core	23	37.1	7	36.9	0.37
	Skin	23	32.4	7	32.6	0.68
4	Brain	22	36.4	7	36.2	0.54
	Core	22	36.7	7	36.5	0.47
	Skin	22	32.2	7	31.8	0.59
5	Brain	15	36.6	4	36.8	0.67
	Core	15	36.8	4	36.7	0.75
	Skin	15	32.1	4	31.8	0.84

Key: two-tail sig = two-tailed test of significance; *n* = number of patients.

No significant difference was found between cerebral and uncomplicated malaria for brain, core and skin temperature using the Student *t*-test for equality of means and the Levenes test for equality of variances on a two tailed significance testing ( $p = 0.01$ ). Using the same statistical tests there were significant statistical differences in brain and core temperatures between normal and cerebral malaria patients as expected for the period of fever (days 1, 2 and 3) but this difference was not seen during the afebrile period (days 4 and 5). Similar observations were found when these comparisons were made between normal and uncomplicated malaria children.

TABLE 2

*Comparison of temperature differences between cerebral and uncomplicated malaria patients*

Day	Temperature difference	Cerebral malaria		Uncomplicated malaria			Statistical parameters (two-tail sig)
		<i>n</i>	mean (°C)	<i>n</i>	mean (°C)	mean difference (°C)	
1	B-C	23	-0.2	12	-0.2	0.24	0.94
	B-S	23	6.5	12	5.2	1.19	0.28
	C-S	23	6.7	12	5.3	1.23	0.28
2	B-C	23	-0.2	11	-0.3	0.14	0.25
	B-S	23	5.5	11	6.1	0.62	0.53
	C-S	23	5.6	11	6.4	0.78	0.41
3	B-C	23	-0.01	7	-0.1	0.10	0.73
	B-S	23	4.7	7	4.2	0.50	0.43
	C-S	23	4.7	7	4.3	0.41	0.36
4	B-C	22	-0.4	7	-0.4	0.01	0.99
	B-S	22	4.0	7	4.4	0.36	0.55
	C-S	22	4.4	7	4.8	0.36	0.54
5	B-C	15	-0.2	4	-0.2	0.01	0.99
	B-S	15	4.6	4	4.9	0.30	0.82
	C-S	15	4.7	4	4.9	0.11	0.93

Key: B-C = brain minus core temperature; B-S = brain minus skin temperature; C-S = core minus skin temperature; mean difference = overall mean temperature difference between the two groups; mean = mean temperature difference for the group; two-tail sig = two-tailed test of significance.

No statistical difference was found between the two groups in the mean differences of the three temperature measurements for all 5 days ( $p = 0.01$ ) using the Student *t*-test for equality of means and the Levenes test for equality of variance. Note the decreasing mean difference from day 2 to day 5 for all the types of temperature. Using the same statistical tests above there were no significant differences between the mean temperature differences between normal children and cerebral malaria patients, and between normal and uncomplicated malaria children. Brain temperature was always lower than core temperature in all the three groups (normals not shown).

parasites/ml for cerebral malaria and  $352\,955 \pm 91\,995$  parasites/ml for uncomplicated malaria).

### Discussion

In this study we found that brain temperature is lower than core temperature in cerebral malaria as well as in normal children and in uncomplicated malaria. This seems to agree with the suggestion that brain temperature tends to remain constant in the face of changes in core temperature. It has been thought that one of the differences between cerebral and uncomplicated malaria could be that this type of thermal autoregulation is lost in cerebral malaria thus contributing to the pathogenesis of cerebral malaria.<sup>22</sup> The present study indicates that thermoregulation and brain temperature control is not altered in cerebral malaria. This is an important finding because several studies on cytokines indicate that hyperpyrexia occurs in patients with cerebral malaria due to raised cytokine levels especially TNF.<sup>12-17</sup> Thus it would be expected that brain temperature would rise out of proportion to core temperature and significantly contribute to the occurrence of coma in these patients, but the findings in this study do not support this hypothesis.

These findings agree with our earlier findings in which no differences were found between measles, cerebral and uncomplicated malaria when core and skin temperatures were compared.<sup>10</sup> The fact that there were no differences between cerebral and uncomplicated malaria cases for skin temperature, and for the difference between core and skin temperatures, indicates that these children do not get into a state of shock but rather maintain an equilibrium. This means that they develop a 'fever in convergence' in which the difference between core and skin is less than  $7^{\circ}\text{C}$  in contrast to 'fever in dissociation' found in shock states in which the difference is more than  $7^{\circ}\text{C}$ .<sup>11,23</sup>

Fever is usually due to pyrogens, in this case malaria parasite, and it would be expected that the higher the pyrogen density the higher the temperature, but this was not observed in this study. In unstable malaria low pyrogen densities are necessary to evoke pyrexia. However, at most times these patients present with high pyrogen densities and therefore most of them present with pyrexia while in endemic areas very high pyrogen densities are required to evoke pyrexia. Our study area included patients with the unstable form of malaria and the pyrogen and pyrexia findings were consistent with earlier studies.<sup>24</sup>

The methods used to study temperature in this study were indirect; however, the method used here has been proven accurate in both human and animal studies.<sup>11,19,20</sup> We did not use invasive techniques for temperature monitoring for ethical reasons and for the associated risks, such as transmission of

infections. The temperature recorded by the electronic device on the surface represents the temperature of the underlying tissues. The thermistor on the forehead records brain temperature while that in the axilla records the temperature of the internal organs of the chest cavity (lungs, heart, etc.). The thermistor on the exposed lateral shin records skin temperature and this served as a control. Room temperature was always lower than skin temperature.

The criteria for the diagnosis of cerebral malaria and uncomplicated malaria were those recommended by the World Health Organization (WHO) and the difference between the two was clearly outlined.<sup>2</sup> In this study we did not find a difference in the parasitaemia levels between cerebral and uncomplicated malaria, which is at variance with some studies that have compared them, but the difference has not been universally observed. All consecutive cerebral malaria cases were studied over a 5-month period but the uncomplicated malaria cases were randomly selected. There were fewer of the latter because they were relatively well and therefore were less likely to be admitted and were discharged earlier. These facts explain the reducing number of patients, as seen in the tables above, as we went beyond the third day. This is more evident among the uncomplicated malaria cases than the cerebral malaria cases. This makes the results on days 3, 4 and 5 unreliable as the numbers were too small for reliable statistical analysis.

There were no deaths in this study and thus we were unable to compare the pattern of brain temperature between those who died and the survivors. There is a need to make this comparison as the findings would be interesting in view of current knowledge on cytokines, pyrexia and parasitaemia alluded to in the discussion above. High pyrogen densities, hyperparasitaemia and hyperpyrexia are associated with poor prognosis.<sup>12-17</sup>

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