Cerebral malaria and the eyes: development of appropriate testing protocols for children in the developing world

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Abstract

Aim: To determine the feasibility of a number of tests of visual function and oculomotor control in children tested in Malawi.

Method: Using computerised vision testing software, run on a laptop (Test Chart 2000 Pro), monocular visual acuity (VA) and contrast sensitivity (CS), using Lea symbols, were measured. Binocularity was assessed by the cover test and TNO, with assessment of ocular movements in nine positions of gaze. Visual fields were assessed with a campimeter test run on the laptop. Antisaccade directional error rates were calculated from digital video recordings of eye movements.

Results: Seven subjects with a history of cerebral malaria (CM) and 13 healthy controls were recruited. All the tests were successfully employed in the majority of subjects although the antisaccade task was difficult for children under the age of 6 years. There was a trend to lower VA and CS in the CM subjects compared with controls. There were no cases of strabismus in either group; a slightly higher number of targets were missed on the visual field analysis in the CM subjects. The antisaccade directional error rates were inversely related to age showing the normal developmental trajectory.

Conclusion: The combination of tests used proved a useful and practical means of investigating visual function, binocularity and visuomotor development in children in the developing world.

Key words: Antisaccades, Cerebral malaria, Contrast sensitivity, Visual acuity

Introduction

Malaria remains a serious, and in millions of cases fatal, international health problem. One published estimate put the number of episodes of clinical malaria (P. falciparum) at 515 million for 2007, with around 1 million deaths per year in sub-Saharan Africa alone; the majority of the victims were children. While prevention and treatment continue to be the focus of research efforts, the longer-lasting effects of infection have received far less attention, particularly in the developing world, where resources for rehabilitation are scarce.

Prominent among the features of cerebral malaria (CM) in children are changes in the retina. These are closely related to the brain changes that result from infection, and are useful in diagnosing malaria and also in assessing the likelihood and extent of recovery. Given these retinal changes, it is clearly important to establish whether these lead to long-term consequences for vision and function.

Little is known about the impact of CM on visual function. One report from children in Kenya reported no visual deficits but only assessed visual acuity and only classified a deficit as an acuity of 2 standard deviations below normal. This criterion would miss more subtle acuity losses and other types of visual function deficit. A study from Malawi into the visual outcome following CM reported no deficits. However, as the median age at testing was 3 years and 4 months, for some subjects it was necessary to use tests such as Cardiff Cards, these have been shown to have a low correlation with letter acuity and are therefore insensitive to subtle deficits.

It would be useful to investigate the consequences of both retinal and central damage on a range of visual and visuomotor functions. However, in the developing world (where most cases of malaria occur), this is a challenge. Clinic facilities with attendant skills are usually scarce or absent, and when present are always under pressure. Finding a simple means of testing, preferably using portable equipment, would be ideal. One option is to use easily available laptop computers with recently developed software for vision testing. However, even this might not be straightforward in populations where the technology is unknown, and therefore intimidating from a patient’s perspective.

We recently had the opportunity to conduct a feasibility study in Blantyre, Malawi, on a group of children who had previously suffered CM serious enough to induce coma and require in-patient treatment, and to compare their outcome with healthy controls. In addition to testing a number of aspects of visual function, antisaccades were assessed. In this task, a visual target is flashed; the subject has to suppress the normal eye movement towards the target, and program and execute an eye movement away from it. We have shown that in children born preterm (who suffer from...
diffuse and subtle cortical damage) antisaccade directional error rates are increased compared with appropriate control children.\textsuperscript{11} We therefore wish to investigate whether a similar pattern of results emerges in children who may have diffuse brain lesions due to CM.

The main aim of this initial study was to establish whether computer-based testing of both vision and antisaccades could be used successfully in a population of children who had never encountered computer technology. Similarly, as the experience of attending a hospital environment for testing might affect a child's performance, this study was conducted with a view to investigating the effects of CM on future visits.

Methods

Subjects

Following ethics approval, from the College of Medicine, Blantyre ethics board and informed parental consent, subjects aged 3 years and older were recruited. Subjects with a history of cerebral malaria (CM) and coma were identified from a database of children that had been compiled at the Malawi Liverpool Wellcome Centre in Blantyre. These subjects all had ophthalmic data, including examination of the fundus, recorded from their time in hospital. A group of control subjects with no history of coma were also recruited by a local paediatrician from families recruited for a previous study on development. The visual functions and binocularity assessments were carried out by an orthoptist and took approximately 25 minutes. An oculomotor physiologist assessed the campimetry and antisaccade tasks, which took a further 20 minutes. The parent/guardian and a nurse (acting as a translator) were also present throughout testing. Although English is the official language of Malawi most of the subjects only spoke Chichewa. Therefore much of the communication was via translation, which required the nurse to become familiar with the tests before assessment.

Visual functions

The Test Chart 2000 Pro software (Thompson Software Solutions) was loaded onto a Dell Latitude 505 laptop and operated with a remote control via an infrared receiver plugged into a USB port. For both visual acuity (VA) and contrast sensitivity (CS) measurements the subjects were tested monocularly with the viewing distance set at 6 m for VA and 1 m for CS. The Lea symbols were used for both measurements with a matching card if required. The VA test utilized a line of optotypes with crowded bars surrounding five pictures presented at each level, each optotype had a score of 0.02 logMAR. The CS test also used the Lea symbols but at a fixed low spatial frequency so that all pictures were large, eliminating the potential for any retinal deficit to affect the ability to discriminate the symbols. The CS test was based on the Pelli-Robson test with three symbols presented at each contrast level with the number of pictures identified correctly being recorded (each picture is 0.05 logCS units).

Binocularity

A cover test was used to detect the presence of any ocular misalignment in the primary position. Ocular movements in nine positions of gaze were assessed to determine the presence of an extra-ocular muscle deficit. Stereopsis was measured using the TNO test.

Campimetry

To provide information about visual fields, a computerised multifixation campimetry test (developed by Professor Bertil Damato) was used. The subject sat 40 cm from the laptop screen, which they viewed monocularly with each eye in turn; the order of testing was randomised. The field tested was 28° vertically (i.e. ±14°) and 35° horizontally. Sixty targets were presented either singly or in groups, arrayed in a circular pattern. Before each target appeared (one to four circular spots each subtending 1.4°) a circular fixation target (3.6°) moved across the screen, which the subject was instructed to track and view. The picture of an animal was flashed in this circle synchronously with the field target. The child was required to name the animal (or describe it in the case of younger children, e.g. bird for dove, cat for lion) and report whether they saw anything else and where it was. Particular trials could be repeated if necessary. The result of whether the target was seen or missed was recorded. The illumination in the room was kept constant by closing the blinds and using the room lights.

Antisaccades

Digital video was used to record eye movements. Subjects sat with their heads stabilised by a chin rest, in front of a laptop on which targets were presented. A digital video camera was mounted behind the laptop screen such that the eyes could be clearly seen in the video frame. A mirror was placed below the subject's chin, angled so that the video frame also showed the reflected images of the targets. Each trial consisted of a white fixation square in the centre of the screen, which was displayed for a variable period. When this was extinguished, a red saccade target appeared to either the left or right. The subject was instructed not to look at the red target, but look to the opposite side of fixation, to the mirror image position of the target. After some training trials, each subject was exposed to a total of 60 trials (50% in each direction). The target position was randomised from trial to trial.

Digital video tapes were analysed using Microsoft Windows Moviemaker 1.1. Once each subject's video was imported into the computer, a frame-by-frame analysis was conducted. For each trial the target position and the direction of the first saccade after the extinction of the fixation target was recorded. This was either an erroneous prosaccade (i.e. the eyes moved in the direction of the target) or a correct antisaccade (the first saccade was directed away from the target). For each subject we calculated the directional error rate (the number of erroneous prosaccades divided by the number of valid trials). A small number of trials were discounted, due to blinks or completely missed targets.

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Table 1. Visual function measurements in subjects and controls; differences between the groups were analysed by the Mann-Whitney test

<table>
<thead>
<tr>
<th></th>
<th>VA (logMAR) median (IQR)</th>
<th>CS (CS log units) median (IQR)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subjects (n = 5)</td>
<td>Controls (n = 13)</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>0.12 (0.32)</td>
<td>0.00 (0.14)</td>
<td>0.3</td>
</tr>
<tr>
<td>Left</td>
<td>0.08 (0.33)</td>
<td>0.00 (0.06)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

VA, visual acuity; CS, contrast sensitivity.

Results

In a 1 week period 7 subjects with a history of CM and 13 healthy controls were recruited. The median age of the CM subjects was 5 years (range 3–14 years), which was slightly lower than that of the controls (median 7 years, range 5–11 years) but with no significant difference (Mann-Whitney, p = 0.4). The ages should be interpreted with caution, however, as they were only calculated from the age in whole years. Only 5 (25%) of the children assessed knew their precise date of birth.

Visual functions

Testing of the visual functions was not possible on the two youngest CM subjects aged 3 years, but measurements were successfully recorded for the remaining CM subjects and all the controls (Table 1).

A variety of responses were obtained from different subjects regarding their interpretation of the Lea symbols and this was always ascertained prior to conducting the test. The circle was often referred to as zero, the square as a box or book, and the apple as a flower or pineapple. A correct response was indicated by consistency of whichever name the subject attributed to each symbol.

Binocularity

No child had a manifest deviation and the median level of stereopsis was good for both CM subjects (60° range 60°–240°) and controls (60°, range 30°–120°; p = 0.5).

Campimetry

Most subjects understood the task and the number of missed targets (out of a total of 60 targets presented) was calculated for both subjects and controls (Table 2).

Antisaccade task

It proved possible to record antisaccades in 8 controls (median age 7.5 years, range 5–11 years) and 3 CM subjects (aged 6, 12 and 14 years). For the controls the median (IQR) antisaccade directional error rate was 52% (27.5%; for the 3 CM subjects the rates were 71% (6 years), 33% (12 years) and 55% (14 years). Although the numbers tested were small, we wished to obtain some impression as to how comparable these results were with data obtained from children in the UK. For this purpose we combined the two Malawian groups, and were able to match the combined group with a group of children recruited as controls for a previous study.11 As the minimum age tested in Malawi was much less than the minimum for the UK dataset, it was only possible to compare a group of 8 from Malawi (2 CM subjects and 6 controls, median age 8.5 years) with 8 UK children (9 years). The median (IQR) antisaccade directional error rates were 49.5% (29.5) and 59.2% (24.8) for the Malawi and UK groups, respectively (Fig. 1).

Given the dependence of antisaccade directional error rate on age, the error rates of the 8 Malawian controls and 3 CM subjects were plotted against their age. For the controls’ data, the Spearman correlation coefficient was −0.66 (p = 0.08). The trend is for the error rate to decrease with age. The 2 young CM subjects had error rates which were not distinguishable from the controls; the error rate in the older CM subject was greater than might be expected.

Discussion

Initial data are consistent with a trend towards lower acuity and contrast sensitivity in the CM group, suggesting that visual functions are an important area to evaluate. The difference is rather small between the groups and was not statistically significant. This is probably due to the small number of subjects in this feasibility study, which will have a substantial impact on the statistical power to detect any difference, that is with groups this size only very large differences will be detected, therefore conclusions must be tentative. However, these data are consistent with long-term retinal or neurological deficits persisting in children.

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Table 2. Campimetry results; differences between the groups were analysed by the Mann-Whitney test

<table>
<thead>
<tr>
<th></th>
<th>Number of missed spots, median (IQR)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subjects (n = 4)</td>
<td>Controls (n = 12)</td>
</tr>
<tr>
<td>Right eye</td>
<td>7.5 (8.75)</td>
<td>0.5 (3.25)</td>
</tr>
<tr>
<td>Left eye</td>
<td>4.0 (8.0)</td>
<td>1.0 (4.25)</td>
</tr>
</tbody>
</table>

Fig. 1. Mean ± 95% CI antisaccade directional error rate for age-matched groups of Malawian and UK children.
who have had serious CM. It is intended that further investigation of visual functions will incorporate a measure of hyperacuity, which could help evaluate more subtle deficits.

Using the laptop to generate the Lea symbols for acuity and contrast sensitivity testing proved easy to implement, allowing quick selection of different symbol sizes to keep concentration. One problem identified with testing the visual functions, and in particular contrast sensitivity, was that with a laptop the screen angle can vary and that this has an effect on the visibility of the screen. We have since evaluated this and determined the optimum angle for testing, allowing future testing to be standardised.

No manifest deviation was found on cover test in the small cohort we tested, but this is in keeping with the prevalence of strabismus found in other African countries of 0.5–1.5%,13,15 which is considerably lower than the rate of 3.5–5.6%16–18 found in the developed world. The cover test is still required to differentiate between vision loss due to CM and loss due to amblyopia.

Stereoacuity testing was easier to implement using the TNO test. Given the absence of severe visual defects and strabismus in the CM subject group it was not surprising that stereoacuity levels were not dissimilar to those of the controls.

Visual field assessment using the campimetry technique provided a gross assessment of the visual fields and was managed by most of the children. When interpreting the lack of statistical significance between the groups the small sample size must be remembered, as only very large differences would be detected. Purely recording the number of targets missed is very simplistic and could be misleading, but additional topographical information can be obtained from the plots. When separating the targets missed into central and peripheral there was a greater percentage of targets missed centrally in the CM group compared with the control group (53% and 30%, respectively). However, as the head position was not fixed, these results must be interpreted with caution. Ideally a more robust measure of the visual field, with head movement minimised, would allow comparisons to be made between the field deficits and the areas of retinal damage observed during and after the malaria course.

Antisaccades provide a means of investigating certain aspects of oculomotor control, and more widely the development of a specific aspect of cognitive function, that is the ability to inhibit responses.10 There is a lack of alternative measures of cognitive function as there are no normative data for many tests for the population we were studying; this is particularly the case for language-based tests. Importantly the main dependent measure for antisaccades is the directional error rate and this could easily be calculated from video data. Antisaccade direction error rate also has a marked developmental trajectory, which has been related to the development of frontal cortical structures.16,19 All but the youngest children were able to do the task, and were not particularly distracted by the unfamiliar technology. In general the error rates were similar to those obtained in our oculomotor laboratory in the UK using more sophisticated equipment. Further, the Malawi data exhibited the expected age-related decline in error rate. As we were only able to test 3 CM subjects, we do not have sufficient data to determine whether error rates are affected in CM children. However, it is clear that antisaccades can be recorded and directional error rates calculated using the simpler methods employed here.

Across all the tests employed, we were successful in assessing the majority of CM subjects and controls. However, the need for understanding and co-operation meant that most tests were only feasible from the age of 4 years and above, with the greatest accuracy obtained with the children aged over 6 years. No problems were encountered in using the technology, either in terms of implementing the tests or the children’s responses. The tests used were readily portable and non-culturally dependent and proved a useful means of investigating visual function and binocularity, with an insight into neurological function from the antisaccade task. This battery could be adopted for use in other developing countries, and given its portability might also be used away from a clinic setting. Future visits are planned to Blantyre to implement this battery of tests in a larger cohort of CM subjects.

We are grateful to Professor Simon Harding for his support throughout this project, and the Foundation for the Prevention of Blindness for funding. Mr Nick Beare, staff at the Malawi-Liverpool Wellcome Trust Clinical Research Centre in Blantyre and staff on the Malaria Research Ward also provided assistance in recruiting children. We are also grateful to Professor Bertil Damato for the use of a laptop version of his campimetry test.

References


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