Retinal clues reveal malaria risk

CHILDREN suffering from cerebral malaria are much more likely to die or suffer prolonged coma if they have severe retinopathy, according to a new study.

"The retinal effects of malaria have not been well studied and they are proving to be important. What’s happening pathophysologically in the brain is like the Holy Grail of cerebral malaria research and our study offers a promising research lead," said Nicholas Beare FRCoPhth, lead author of the study, which appeared in the August issue of the Archives of Ophthalmology.

The researchers sought to relate retinal findings in children treated for severe malaria to disease outcome by tracking changes in the fundus. This prospective study followed children admitted to the Malaria Research Project in Malawi with cerebral malaria and severe malarial anaemia during two malaria seasons. Indirect and direct ophthalmoscopy were performed on admission and daily, subject to the patient’s cooperation.

The study recruited 325 [this is actually an error on the abstract] patients with complicated malaria. Cerebral malaria existed in 278 patients and of these, 61% had some degree of retinopathy. Of the 47 children with severe malarial anaemia, 53% had retinopathy. In cerebral malaria, retinopathy was associated with subsequent death, with a relative risk of 3.7. Papilloedema was associated with the highest mortality rate, with a relative risk of 4.5.

Increasing severity of retinal signs was related significantly to increasing risk of a fatal outcome, independent of papilloedema. In survivors, retinal signs were significantly associated with prolonged time to recover consciousness. Patients with severe malarial anaemia had better outcomes and less severe retinopathy than those with cerebral malaria.

The investigators also reviewed fundus exams taken in patients with cerebral malaria during the course of the disease. They noted that a large increase in retinal haemorrhages was associated with death. Other retinal signs resolved over one to four weeks after recovery without retinal sequelae.

The authors concluded that in childhood cerebral malaria, severity of retinopathy is related to prolonged coma and death. The results support the hypothesis that retinal signs in cerebral malaria are related to cerebral pathophysiology.

Dr. Beare believes the fact that the retinal signs are specific to severe malaria and have prognostic significance, have important implications for clinicians treating children with severe malaria. In a related post-mortem study, retinopathy has been shown to be the only clinical sign which can confirm that malaria is actually the cause of coma in this setting (Nature Medicine Feb 2004; 10(2):143-5). He also notes that the research offers an even more promising avenue of study into the cerebral pathophysiology of malaria.

"The unique feature of cerebral malaria is that the infected red blood cells stick to the endothelium of blood vessels in the brain and also the retina. This causes coma and death, but exactly how is not known.

"Parasites stimulate the release of mediators such as cytokines, tumour necrosis factor and nitric oxide, which in such high concentrations may be damaging. They also release their own toxins. However our research suggests that a relative hypoxia or lack of metabolites causes whitening of the retina."

He noted that the retina is a very metabolically demanding tissue, and that parasites may “steal” the available metabolites from inside the affected blood vessels, putting retinal cells under metabolic stress. As a result they swell and become opacified or white. Retinal cells can recover function from this once the disease is under control.

He hypothesised that similar processes may also be happening in the brain. If so, it would account for some patients having a rapid and full recovery, whilst others die from the knock-on effects of metabolic derangement and brain swelling.

The team will investigate retinal blood flow next year through fundus fluorescein angiography.

“We’re supposing that what’s going on in the retina is what is going on in the brain, and if we can demonstrate that vessel whitening is associated with decreased blood flow in the retina, then it is like to be happening in the brain as well.”

The researchers also plan to investigate the use of ultrasound of the optic nerve sheath, because that becomes distended when there is raised intracranial pressure.

“That’s important in cerebral malaria as well, but no one knows how it affects coma and the process that makes cerebral malaria fatal. We hope to find out more about that, and develop a non-invasive test for clinicians to detect and monitor raised intracranial pressure,” said Dr. Beare.

During the retinopathy study, which took place between 1999 and 2000, the team developed a chart for recording retinopathy (Annals of Tropical Medicine, January 2002. 96:1; 105-108), using the principal criteria of haemorrhage number, vessel whitening and retinal whitening, as well as the presence or absence of papilloedema.

Dr. Beare got involved in the Malawi project through contacts at the Liverpool School of Tropical Medicine, and at Liverpool’s University Hospital. Local paediatricians and nurses look after the children clinically in Malawi, and are also involved in research.

“When we go next time we want to get a budding Malawian ophthalmologist involved, who will work with us, and have six months of general ophthalmology, as a precursor to post-graduate training. There’s a desperate shortage of ophthalmologists in Malawi,” said Dr. Beare.

For more information, see Beare et al, Arch Ophthalmol. (August, 2006;122:1141-1147).

nbeare@btinternet.com