A Cerebral Solution

Highly collaborative research being carried out by researchers from the Vancouver General Hospital, Canada, is trying to elucidate the answers to the many current unknowns regarding the most severe form of malaria

DR. VALERIE WHITE

The most severe neurological complication of infection with Plasmodium falciparum – one of the four species of malaria parasite to infect humans – is cerebral malaria, a disease characterised by the onset of coma after malarial infection. It is most common in populations with no immunity to malaria, and usually affects children under the age of five in sub-Saharan Africa, or adult travellers visiting the continent without appropriate malaria prophylaxis. Cerebral malaria occurs in a relatively small subset of malaria cases but it is often fatal; many patients die due to a lack of treatment, but some succumb to the disease despite the provision of appropriate therapy. Mortality rates are high and long-term neurocognitive impairments are often sustained amongst survivors. There are a number of problems with effectively treating cerebral malaria, one of the greatest of which is that the precise mechanism by which the disease causes coma and death is still unknown. It seems likely that parasite-infested red blood cells are playing a role as they flood the brain and block smaller blood vessels. However, some scientists contend that inflammatory mediators, metabolic factors, or a combination of these, may be responsible for the impairment of consciousness. Concurrently, the clinical definition of cerebral malaria is vague and prescribes only that a patient should present with both malaria and coma; in sub-Saharan Africa, where malaria is common, this can often lead to misdiagnosis. Significantly, the work of the Blantyre Malaria Project (BMP) has demonstrated that 28 per cent of the autopsied patients were wrongly classified as dying from cerebral malaria; the future course of research into this disease, will no doubt be influenced by this outcome.

MALARIA IN MALAWI

In order to effectively palliate the death toll of cerebral malaria every malaria season, measures are needed to more efficiently and accurately diagnose this life threatening condition. An improved understanding of the pathological mechanisms at work in the brain could also offer potential insights; some children are able to emerge from deep malarial coma apparently unharmed, and an understanding of this obscure occurrence could suggest further therapeutic options. One route towards these goals is through the eye; the retina and the brain share a very close relationship, perhaps because both are derived from the neural tube during embryogenesis, and the study of the eye may therefore be useful for identifying, and more fully comprehending, the action of cerebral malaria in the human body.

Dr. Valerie White is an ophthalmic pathologist based at Vancouver General Hospital's Department of Pathology and Laboratory Medicine. Over the last few years she has made four visits to Malawi as a participant in the BMP – an autopsy study based at Queen Elizabeth Hospital in Blantyre under the leadership of Dr Terrie Taylor and Professor Malcolm Molyneux. Since its founding, 28 years ago, the Project has been responsible for producing a definitive rating scale for comas known as the Blantyre coma score, as well as setting up the Severe Malaria in African Children network. White's research objectives as part of the BMP focus on linking the observable pathology of the eye to the presence of malaria and the action of the parasite within the brain. In time, these findings could also have implications for other diseases of the central nervous system.

EYE-OPENING WORK

The methodology employed by White and the BMP team involves evaluating the fundus of the eyes of patients admitted to the research ward using indirect ophthalmoscopy after dilation. Then, if a patient later dies, permission to perform an autopsy is sought and, if granted, a standard autopsy is performed. As part of this process the eyes are removed and undergo gross examination before being processed and stained for histopathological analysis.

Investigations carried out to date have found that the eyes of children dying of non-malaria causes were usually normal – whereas the eyes of children with cerebral malaria often showed signs of haemorrhages, retinal whitening, and/or abnormally coloured blood vessels. "This combination of findings in African children, in areas where malaria is endemic, is very specific for cerebral malaria," states White. Gross examination of the eyes of affected individuals revealed predominantly white-centred haemorrhages and, on some occasions, white or orange vessels – although the formalin fixation process can interfere with the observation of these after the clinical stage. On microscopic examination, fibrin thrombi and perivascular haemorrhages were also commonly found in addition to the heavily parasitised red blood cells within the small retinal blood vessels; none of these findings were demonstrated in patients who died of other causes.

Perhaps most importantly, the team found that many of the changes that they studied in the retina correlated with those in the brain. The histological hallmark of patients dying from cerebral malaria is the presence of parasitised

RETINAL PATHOLOGY OF PAEDIATRIC CEREBRAL MALARIA IN MALAWI

OBJECTIVES

To understand how retinal pathologic findings can be used to diagnose and characterise the presence of severe cerebral malaria in children in sub-Saharan Africa. The study uses blood tests, retinal observations and autopsy studies to inform ophthalmologists and other clinicians of how retinal pathology can be used to understand the pathogenesis of this life threatening form of malaria.

KEY COLLABORATORS

Dr. Valentina Barerra; Dr. Nick Beare; Dr. Simon Harding, University of Liverpool, UK
Dr. Katerina Dorovini-Zis, University of British Columbia, Canada
Dr. Susan Lewallen, Kilimanjaro Community Centre for Ophthalmology, South Africa
Dr. Malcolm Molyneux, Malawi/Liverpool/ Wellcome Trust Clinical Research Programme, Malawi
Dr. Terrie Taylor, Michigan State University and Blantyre Malaria Project, University of Malawi College of Medicine, Malawi

CONTACT

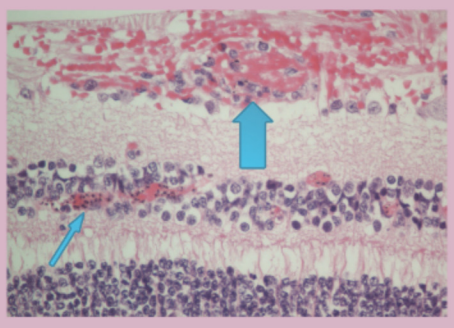
Dr. Valerie A White
Vancouver General Hospital
Department of Pathology and Laboratory Medicine
910 West 10th Avenue, Vancouver
British Columbia V5Z 4E3 Canada
T +1 604 875 4111 x 63975
T +1 604 240 5892
E val.white@vch.ca

DR. VALERIE A WHITE is Professor in the departments of Pathology and Laboratory Medicine, and Ophthalmology and Visual Sciences at the University of British Columbia. She obtained an MD from Memorial University of Newfoundland before moving to work at the University of British Columbia. White joined Vancouver General Hospital in 1988 as an assistant pathologist and is now a consultant pathologist and professor. She teaches ophthalmic pathology to residents, conducts research projects on numerous pathological facets of eye disease and has contributed chapters on orbital pathology for several well-known and widely read ophthalmology textbooks.

red blood cells in the brain and retina. In almost all cases the retina was found to be a very accurate and accessible proxy for the brain – a revelation that may have clinical significance in the future.

FURTHER COLLABORATION

White's interest in malaria extends beyond her role in the BMP; for many years, she has worked with Drs. Simon Harding and Nick Beare from the University of Liverpool, UK, and Dr. Susan Lewallen, currently in South Africa. These ophthalmologists have been instrumental in understanding and delineating retinal findings in hundreds of cerebral malaria patients, as well as introducing new methods of fundus photography and fluorescein angiography that more accurately pinpoint areas of interest for post-mortem study. In 2012, White began a collaboration with Dr. Valentina Barerra, a postdoctoral researcher in their lab, focusing on relating the degree of parasitisation of the blood vessels to the severity of the eye findings and better understanding the mechanisms of haemorrhage.



Photomicrograph of retina in cerebral malaria. Thick arrow indicates a vessel in the ganglion cell layer containing a thrombus and surrounded by hemorrhage. Thin arrow indicates a capillary in the inner nuclear layer with numerous red blood cells containing late stage malaria parasites. Haematoxylin and eosin x400.

CELEBRAL MALARIA

Cerebral malaria is the most serious and life threatening form of malaria caused by the parasite Plasmodium falparum, affecting around 575,000 children in Africa every year.

The condition is defined by the World Health Organization as a clinical syndrome characterised by coma at least one hour after termination of a seizure or correction of hypoglycaemia, co-existing with asexual forms of P. falciparum parasites on peripheral blood smears with no other cause to explain the coma.

Haemorrhages are an important feature of cerebral malaria, as the BMP found, but they also cause damage to tissue. As part of this relatively new collaboration, White and Barerra are trying to understand what promotes the formation of the fibrin-platelet clot that is at the centre of many haemorrhages, and what additional damage this causes. Recent fluorescein angiography of the blood vessels in the eye has shown areas of non-perfusion, and the pair is also trying to elucidate the causes and consequences of this phenomenon.

A BRIGHTER FUTURE

Cerebral malaria is a form of this problematic disease that particularly affects the most vulnerable patients; it is unpredictable, deadly, and capable of causing lasting damage that lingers for far longer than the parasites that cause it. White's work, both independently and in collaboration with the BMP and other researchers, has helped medicine to develop a new understanding of cerebral malaria – an understanding that will, in time, influence the path towards eradicating this problem for good. ■