Ophthalmic pathologist, Dr Valerie White, details the background of her work towards linking symptoms observed in the eye to the prognosis of the severe, and often fatal, cerebral malaria.

Could you begin by explaining your primary research objectives? What drew you to the sub-specialty of ophthalmic pathology?

My primary research objectives are fourfold: firstly, to understand the causation of the funduscopic eye findings seen in living people with cerebral and other forms of malaria; secondly, to use the pathology seen in the eye to correlate the findings observed in the living body with what is going on in the brain, which cannot be directly visualised during life. Thirdly, I hope to better understand some mechanisms of inflammation in the retina; and finally I’d like to use the retinal inflammation model to understand brain pathology in other inflammatory central nervous system diseases.

I was drawn to the subspecialty of ophthalmic pathology because I wanted to know why we had not received any training involving eye diseases during our pathology residency. I took an elective in the subject and was encouraged to continue in this direction.

You obtained your primary medical degree in 1979 and an MHSc in Healthcare and Epidemiology in 2006. What motivated you to obtain the latter qualification and how does it help your current research?

At the time I undertook that degree, our laboratory system was undergoing top-down reorganisation and change, and I thought that a different focus might be useful to me. In the
end, I decided that I am a better pathologist than I would be an epidemiologist, and that I enjoy this type of work too much to give it up. However, the degree does help me to better understand many issues, including statistical considerations, assessment of projects, quality assurance, stakeholders and leadership.

Your original research investigated the genetic causes of intraocular melanoma. What were your key findings in this area, and how did this lead to your interest in malaria?

My original research into intraocular melanoma helped to identify some of the first chromosomal abnormalities in that type of cancer – as virtually nothing was known about this when I started my work. These abnormalities included monosomy 3 (loss of one homologous copy of diploid chromosome 3) and isochromosome 8q (reduplication of the long arm of chromosome 8), and we later found that they held prognostic significance. Patients whose tumours exhibited these changes had a high chance of dying of the disease, whereas those without these specific abnormalities would almost certainly not die. Unfortunately, I was not able to get funding to continue this work and so, when the chance came to be part of the malaria project, I jumped at the opportunity to be involved in understanding a disease of major global significance.

Why was the Blantyre Malaria Project established, and what are its aims and key methodologies?

The Blantyre Malaria Project was established by tropical disease specialists Drs Terrie Taylor and Malcolm Molyneux in 1986 after the Malawi Ministry of Health specifically identified ‘severe malaria in children’ as a research priority. They started the autopsy study in 1996 when they realised, after caring for patients with cerebral malaria, that they could not further their quest to understand pathogenesis without looking at autopsy data. Patients are admitted to a special ward in the Queen Elizabeth Central Hospital in Blantyre where they are examined and treated according to a standard protocol. Shortly after admission, the eyes are examined fully and photographed by a qualified ophthalmologist. In more recent years, infected children have undergone an MRI in an attempt to further understand the disease process. If a patient dies, permission to conduct an autopsy is requested from the parents or guardians. Obtained tissue is stored in multiple modalities for several research projects.

Through this work, you determined that retinal vessel abnormalities are due to the presence of parasitised red blood cells, which have a marked reduction in haemoglobin. Are there any other findings or achievements you wish to highlight?

I think that the major accomplishment is the correlation between the findings in the brain and those in the retina. This allows the retina to be used during life to make an accurate diagnosis of cerebral malaria, to follow the patients as they are being treated for signs of worsening of the disease and to predict those who are most likely to die.

A cerebral solution

Researchers from the Vancouver General Hospital, Canada, are carrying out highly collaborative research to elucidate answers to the many current unknowns regarding the most severe form of malaria.

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 frequent visits to Malawi as a participant in the BMP – an autopsy study based at Queen Elizabeth Hospital in Blantyre under the leadership of Drs Terrie Taylor and 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 with 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...
INTELLIGENCE
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, Kilonjaro 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

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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.

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 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 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 her 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.

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 to develop a new understanding of cerebral malaria – an understanding that will, in time, influence the path towards eradicating this problem for good.