Institution:
UNIVERSITY OF LIVERPOOL and LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Unit of Assessment:
UOA1 - Clinical Medicine

Title of case study:
Malarial Retinopathy has Redefined the Diagnosis of Cerebral Malaria and Improved the Management of Coma in African Children

1. Summary of the impact

Since 1997 University of Liverpool (UoL) investigators have led global research into malarial retinopathy, the fundus features associated with severe malaria. The work has propelled this phenomenon from little-known curiosity to an essential component in the diagnosis of cerebral malaria (CM) and has altered understanding of how CM causes coma and kills. It has changed medical practice of those diagnosing one of the commonest fatal diseases in tropical countries. Malarial retinopathy is now considered an essential clinical feature of CM aiding the appropriate management of coma in infants. This change in practice has expanded from African research settings to clinical practice required by WHO guidelines and disseminated in major clinical textbooks from 2008.

2. Underpinning research

Malaria kills an estimated 655,000 people a year, 86% of whom are children under five in Africa. Most die of CM, a complication characterised by sudden and profound coma, convulsions and death in 10-20%. It is not understood how malaria causes coma and death, but adherence of infected red cells to the microvascular lining (sequestration) is thought to be critical [4]. However, malaria is a common infection and a child may present in coma due to another cause and be misdiagnosed with CM because of a coincidental malaria infection. This is surprisingly common occurring in 25-50% of cases.

The key problems that this research addresses are

1. Can malarial retinopathy detection improve the diagnosis of severe malaria?
2. Can malarial retinopathy improve understanding of disease processes in severe malaria which in turn improve care and treatment?

The research to address these questions was conducted by UOL researchers starting in 1997 at the Malawi field site and Liverpool in collaboration with the Liverpool School of Tropical Medicine (LSTM), Malawi-Liverpool-Wellcome Clinical Research Unit (MLW), Malawi College of Medicine and Blantyre Malaria Project (BMP), Michigan State University, but the ophthalmic input is almost entirely from UOL. No other research group has had significant output to address these questions, so the impact claimed is wholly from UoL research. The principal investigator for this research is Beare (1999-present, now Hon Snr Lecturer) with Harding (2003-present, Professor of Clinical Ophthalmology) and Molyneux (Prof until 2009, now Emeritus Prof).

The research has shown that the detection of malarial retinopathy is the only reliable diagnostic sign or test for CM [1]. About 25% of Malawian children who appeared to die of CM had another cause of death at autopsy, whilst co-infected with malaria. The presence of malarial retinopathy was the only clinical or laboratory feature which was able to distinguish malarial coma from other causes. Molyneux initiated, co-directed and funded this ten year autopsy study, and Beare's analysis, supervised by Harding, established the specificity (100%) and sensitivity (95%) of malarial retinopathy.

Studies led by Beare and supervised by Harding and Molyneux, conducted in collaboration with LSTM, MLW and BMP found that (i) the severity malarial of retinopathy predicts risk of death better than any other clinical or laboratory variable in CM [2] and (ii) that patients fulfilling the traditional case definition of CM without malarial retinopathy have lower mortality, shorter coma, and are more likely to have a pre-existing predisposition to epilepsy [2,5]. These insights allow greater prognostic, as well as diagnostic, accuracy enabling clinicians to focus resources.

In 2006 Beare *et al* commenced a study of retinal perfusion in CM using a fundus camera with

capacity for retinal angiography. The retina is central nervous tissue with a similar embryology and structure to the brain, and with comparable malaria parasite sequestration. The study found that there are retinal perfusion abnormalities in the majority of patients with CM [3]. The commonest are multiple zones of ischaemia from microvascular occlusion. There is also breakdown of the blood-retina barrier in association with ischaemia; and in a much more profound way prior to death. This study demonstrated CNS perfusion abnormalities *in vivo* in CM for the first time, and altered theories of CM pathogenesis as it is likely that these abnormalities are also mirrored in the brain [6]. Understanding of CM pathogenesis has turned towards ischaemia and blood-tissue breakdown; and away from the previous hypothesis of the effect of a cytokine and neurotransmitter 'storm'. Now substantiated by MRI studies in children with CM, the next generation of clinical trials are assessing supportive therapies in cerebral malaria, in particular therapies to reduce intra-cranial pressure and hypoxic injury.

3. References to the research

1. **Beare NAV**, Taylor TE, **Harding SP**, Lewallen S, **Molyneux ME**. Malarial retinopathy: a newly established diagnostic sign in severe malaria. Am J Trop Med Hyg. 2006;75(5):790-797. http://www.ajtmh.org/content/75/5/790.long Citations: 103 Impact factor: 2.59

2. **Beare NA**, Southern C, Chalira C, Taylor TE, **Molyneux ME**, **Harding SP**. Prognostic significance and course of retinopathy in children with severe malaria. Arch Ophthalmol. 2004;122:1141-1147.doi:10.1001/archopht.122.8.1141 Citations: 51 Impact factor: 3.71

3. **Beare NAV**, **Harding SP**, Taylor TE, Lewallen S, **Molyneux M**. Perfusion abnormalities in children with cerebral malaria and malarial retinopathy. J Inf Dis. 2009;199:263–271. doi:10.1086/595735 Citations: 49 Impact factor: 5.848

4. White VA, Lewallen S, **Beare NAV**, **Molyneux ME**, Taylor TE. Retinal Pathology of Pediatric Cerebral Malaria in Malawi. 2009. PLoS ONE 4(1): e4317. doi:10.1371/journal.pone.0004317 Citations: 38 Impact factor: 3.730

5. Lewallen S, **Beare NAV**, Bronzan R, **Molyneux M**, Taylor T. Using malarial retinopathy to classify children with clinically defined cerebral malaria. Trans Roy Soc Trop Med Hyg. 2008;102(11): 1089-1094 doi:10.1016/j.trstmh.2008.06.014 Citations: Impact factor: 2.16

6. Maude RJ, Dondorp AM, Sayeed AA, Day NPJ, White NJ, **Beare NAV**. The Eye in Cerebral Malaria: What Can it Teach Us? Trans Roy Soc Trop Med Hyg. 2009; 103(7):661-664. doi:10.1016/j.trstmh.2008.11.003 Citations: 14 Impact factor: 2.16

.

Key grants

2005 – 2008. **The Wellcome Trust** (Ref 075125/Z/04/Z). The eye in life-threatening malaria: a clinical and clinicopathological study, £93,239, **ME Molyneux**, **NAV Beare**, **SP Harding**.

2011 – 2014. **Wellcome Trust** programme grant. Retinal microvasculature in cerebral malaria, £600k, **SP Harding**, RS Heyderman, AG Craig, PS Hiscott, **ME Molyneux**, TE Taylor, S Kampondeni, NAV Beare, P Knox, Y Zheng.

4. Details of the impact

Very few research programmes take a clinical sign from obscurity to the standard textbook description of a disease. This is exactly what research by the Department of Eye and Vision Science has done with malarial retinopathy, and it is all the more remarkable because malaria is a common and frequently fatal disease.

There are approximately 10 million episodes of cerebral malaria in Africa a year and examination for malarial retinopathy has the potential to improve the care of all of these cases. It is plausible

that half these cases, since 2008, have some sort of funduscopy as a consequence of this UoL research, improving the assessment of prognosis in 5 million and uncovering misdiagnosis in 1.25million. Patients benefit from improved diagnosis and better directed treatment. This research has "revealed the importance of the ocular funduscopic examination in distinguishing "true" cerebral malaria from "faux" cerebral malaria" [15].

Note the characteristic patchy retinal whitening around the fovea (~3 disc diameters to the right of the optic disc) and also some white-centred haemorrhages.

Malarial retinopathy is now included in the description of malaria in standard medical textbooks which is a key indicator of the impact of this research. Since 2008, retinal photographs taken by Beare and colleagues such as that presented here) appear in four standard text books - Harrison's Principles of Internal Medicine [7], Davidson's Principles and Practice of Medicine [8], Lecture Notes: Tropical Medicine [9] and Manson's Tropical Diseases[10], as well as multiple reviews on severe malaria and its pathogenesis. These are major reference works used by clinician's worldwide to guide clinical practice. Malarial retinopathy (with the UoL figure) and the importance of funduscopy is now included in the 2013 WHO guidelines on severe malaria [11], particularly used by clinicians and policy makers in malaria-endemic countries to determine best practice, and also regional guidelines eg South-East Asian Regional Guidelines for the Management of Severe Malaria in Large Hospitals 2006 [12].

The reasons that the authors of these authoritative texts have included malarial retinopathy in the description of malaria for the first time are the quality of the UOL research and the importance of its findings. This includes the startling retinal photographs and results of retinal angiography which demonstrated graphically the information on CM pathogenesis that can be gleaned from the retina. The high quality colour images allowed the features of malarial retinopathy to be demonstrated to non-ophthalmologists, and to teach them to recognise malarial retinopathy for themselves. The research has been disseminated by peer-review publication and conference presentation to key opinion leaders initially before wider dissemination in textbooks and guidelines. Publications 1 and 2 were featured by the American Academy of Ophthalmology in its EyeNet magazine and on its Homepage respectively, as well as reported by medical media and Voice of America radio.

The discovery that malarial retinopathy alone can reliably distinguish malarial coma from co-infection in a comatose child was of particular importance, and has literally redefined the disease of cerebral malaria. Now malarial retinopathy is required to be present in order to diagnose CM with specificity. This is established practice in Malawi and has been taken up by other research units in endemic areas; as well as clinical practice in endemic and non-endemic areas to the benefit of critically-ill children in coma. This is now confirmed in a popular website, www.malariasite.com [13].

The Department of Eye and Vision Science has worked with its collaborators who have set up the Paediatric Research Ward in Malawi and have provided for patients with severe malaria and other comas from 1990 to present. Since 2008 this has cared for more than 1,500 patients who have had funduscopy. The malarial retinopathy programme is led by the Department of Eye and Vision Science, whilst collaborators provide expertise in malaria.

Improved specificity in the diagnosis of CM by using malarial retinopathy has reduced spurious results in other CM research which previously included misdiagnosed patients. It has allowed parallel research programmes to use patients without retinopathy as controls or comparators, and to focus on retinopathy-positive CM. Eliminating misdiagnosed patients from studies of severe malaria improves their power to demonstrate the benefit of the investigation or treatment they are studying. As a result of UoL research on malarial retinopathy more studies on severe malaria can be conducted with fewer patients with quicker results. “Without the “eye findings”, our clinical case definition would be far less precise, and the work would have proceeded at a much slower rate.” [15]

This case study of malarial retinopathy demonstrates impacts on health and welfare, by advancing care of children in coma; public policy and services through WHO guidelines on severe malaria; practitioners and services through improving medical texts and knowledge [14-17]. A clinical diagnostic paradigm has been changed with new criteria adopted into clinical practice. The treatment of a major global health issue has been improved with the reduction of potential harm. New research findings have been applied into clinical practice and an improvement in international quality of life and welfare has occurred.

5. Sources to corroborate the impact

Each source listed below provides evidence for the corresponding numbered claim made in section 4 (details of the impact).

7. Harrison's Principles of Internal Medicine. 17th Ed 2008, figure 203; 18th Ed 2012 figure 210. ISBN-13: 978-0071748896

8. Davidson’s Principles and Practice of Medicine. 21st Ed 2010, figure 13.31. ISBN-13: 978-0702030857

9. Lecture Notes: Tropical Medicine. 6th Ed 2009, figure 9.2. ISBN-13: 978-1405180481

10. Manson’s Tropical Diseases 23rd Ed 2013. ISBN-13: 978-1416044703

11. Management of severe malaria: a practical handbook, WHO, 3rd Edition (2013), pages 15, 43 and figure 3. ISBN: 978 92 4 154852 6 http://www.who.int/entity/malaria/publications/atoz/9789241548526/en/index.html

12. South-East Asian Regional Guidelines for the Management of Severe Malaria in Large Hospitals 2006. “Ocular Manifestations” page 16.

13. http://www.malariasite.com/malaria/Complications3.htm

14. Childhood acute non-traumatic coma: aetiology and challenges in management in resource-poor countries of Africa and Asia. Gwer S, Chacha C, Newton CR, Idro R. Paediatr Int Child Health. 2013;33(3):129-38. doi: 10.1179/2046905513Y.0000000068.

Referees

The following individuals are leading experts on malaria, and can corroborate the impact of malarial retinopathy on clinical practice and research.

15. Letter: University Distinguished Professor in the College of Osteopathic Medicine at Michigan State University and Director of the Blantyre Malaria Project, Malawi.

16. Professor of Tropical Medicine, Nuffield Department of Medicine, Director of the Wellcome-KEMRI-Oxford Collaborative Research Programme

17. Locum consultant, Heart of England NHS Trust; Research Fellow, University of Oxford.