Royal College of Ophthalmology: Ethicon Travel Grant Report

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Ophthalmology StR

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Role: Clinical research fellow, Department of eye and visual science, University of Liverpool
Placement: Malawi Liverpool Wellcome Trust, Queen Elizabeth Central Hospital, Blantyre, Malawi.
Supervisor: Professor Simon Harding, Consultant Ophthalmologist, Royal Liverpool University Hospital. Head of department, Eye and Visual science, University of Liverpool.
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Overview
In early 2015 I saw an advert in the Royal College of Ophthalmology news looking for a researcher to take on an exciting position working in Blantyre, Malawi at a well-established and resourced research centre at the Queen Elizabeth Central Hospital (QECH). I was at a stage of my training where I had established a sound knowledge and skill base and was looking for opportunities to both develop myself academically and personally. With this in mind I applied for and successfully secured a clinical research fellowship with the University of Liverpool. After an induction period in Liverpool at the Royal Liverpool University Hospital, I left for Malawi in September 2015 for 10 months.

Introduction
Malawi
The country of Malawi, formally known as Nyasaland was once a British Protectorate which declared independence in 1964. The population of the country is approximately 16 million with the biggest concentration of the population in the Southern Region. Malawi was recently ranked as the poorest country in world based on their Gross Domestic Product (GDP) per capita approximately $494 which has decreased from $857 per capita in 2012. According to the World Health Organisation, spending on healthcare is $93 per capita, 11% of the total GDP, which is similar to surrounding countries ($115 in Zimbabwe, $137 in Tanzania, $79 in Mozambique).

The Southern region (population of 5.8 million) is served by only four Ophthalmic consultants (1: 1,450,000 per head of the population). When compared to my deanery of Yorkshire (population of 5.3 million) which has approximately 124 consultants (1: 42,741 per head of the population), the differences are stark.
The Lions Sight First Eye Hospital (LSFEH) was built as an extension of Queen Elizabeth Central Hospital (QECH) in Blantyre with the financial assistance of the Lions charitable group based in Malawi. LSFEH has designated male and female wards for ophthalmology patients, two ophthalmic theatres and a number of eye clinics running throughout the week (casualty, diabetic, paediatric, private). LSFEH is a regional referral center serving all of the surrounding districts and national referral center for complex cases including all paediatric cases. The eye hospital is often very busy with multiple cases of varying complexity, an ideal environment for teaching and training. The College of Medicine in Blantyre has an Ophthalmology training programme based in LSFEH employing four registrars on a five-year training programme.

The Malawi Liverpool Wellcome Trust (MLW) is a research facility funded by the Wellcome trust and home to a large team of researchers and administrative staff. The centre has a fully equipped laboratory, research offices and a large administrative team to oversee the numerous trials that run in Malawi. The majority of researchers are employed by the University of Liverpool and the Tropical schools based in London and Liverpool.

**Research Projects**

During my time in Malawi I had two main roles. Firstly, the running of the MDRS2 study and diabetic service and secondly, running the OCT in Cerebral Malaria study which was an unanticipated opportunity while stationed in Malawi.

**MDRS2**

The Department of Eye and Visual Science (DEVS) in Liverpool led by Professor Simon Harding has had a long established relationship extending over 20 years with MLW and the LFSEH in Blantyre. DEVS have collaborated on projects mainly focussing on Malarial Retinopathy but more recently, in keeping with the increased burden of non-communicable disease, research has focussed on diabetes and the identification and management of diabetic retinopathy (DR) and ocular surface disease.

Since 2012 there has been an ongoing Malawi Diabetic Research Study (MDRS), an epidemiology study seeking to identify and define the prevalence and severity of DR in Southern Malawi. Through this, many patients with advanced retinopathy were treated with photo-coagulative laser. Following the completion of MRDS a second study was established, ‘MRDS2’ designed to assess the efficacy and cost-effectiveness of retinal laser for the Malawian diabetic population. The results from this study will be compared to benchmark trials from the UK in order to provide evidence for the ongoing use of a retinal laser in LFSEH donated by the World Diabetes Foundation in 2007.

My role for MDRS2 included seeing all study patients for follow up, clinically grading their retinopathy and taking fundus photos. All patients who required laser were treated and follow up offered. In addition to the MDRS2 study, I also ran the diabetic clinic in LFSEH. This included seeing and grading non study patients, identifying, counselling and treating patients with advanced retinopathy and supervising my Malawian colleagues in their grading and decision making. I also delivered teaching to two of the more senior registrars on how to perform retinal laser.
OCT in Cerebral Malaria

While in Malawi I was offered the opportunity to undertake a new project in researching Malarial retinopathy using hand–held Spectral Domain Optical Coherence Tomography (SD-OCT). DEVS has been in an ongoing partnership with the Blantyre Malaria Project (BMP) to study Malarial retinopathy as part of BMP’s ongoing work researching Cerebral Malaria. Over the years this has involved using B-scan ultrasound to describe optic nerve head changes in Cerebral malaria, fundus colour photos to categorise retinal changes and Fluorescein angiography (FA) to document vascular changes. Professor Irene Gottlob from the University of Leicester loaned us a SD-OCT machine in order to further our understanding of the retinal changes in Cerebral Malaria.

Cerebral Malaria occurs in a small proportion of children with Malaria and causes reduced consciousness, often accompanied by seizures and death due to cerebral oedema and brain stem coning. The main aim of Ophthalmic research has been to use the retina as a marker for the CNS, trying to identify diagnostic features and markers of severity on different imaging modalities that can give an indication of prognosis and guide treatment. Malarial retinopathy presents in the eye as a triad of features: retinal haemorrhages, retinal whitening and vessel changes. Often papiloedema is seen but alone is not part of the diagnostic criteria for malarial retinopathy.

The OCT study ran throughout the malaria season (January to June) and all children admitted with cerebral malaria were invited to participate in the study. Once they consented to participate, I examined their eyes clinically for evidence of Malarial retinopathy and then performed OCT of the macular and disc, colour fundus photos and FA. Children were reviewed daily for evolving signs of Malarial retinopathy and if possible had a repeat OCT at 1 month. As this study is novel, with no pre-existing database of normal values for retinal and optic nerve thickness, I was required to undertake a control study to acquire a “normal” database and I therefore collected data from over 100 other children.

Outcomes

MDRS2
The MDRS2 study completed its second year with 145 patients enrolled in the study, having completed a course of retinal laser. Follow up at 1 year was 86% and for these patients the mean change in vision was 0.06 letters with 70.6% of patients achieving stable vision (+/- 4 EDTRS letters) post laser. Follow up was reduced at year two to 44% and at two years the mean change in VA was -4.2 letters with 62.5% maintaining stable vision. These results were encouraging when compared to benchmark studies based in developing countries. Combined with an analysis of cost effectiveness it is likely to show that retinal laser is a cost effective treatment for DR and an essential investment for the Malawian government in the ongoing management of the diabetic population.

During my time managing the diabetic service at LSFEH I also enjoyed the opportunity to see non-study patients, teach colleagues and perform retinal laser. By the end of the placement
I had performed over 100 retinal laser procedures, both macular and PRP. Figure 1 shows one of my colleagues examining a patient in the DR clinic and the severity of disease often presenting to clinic.

Figure 1. Dr Patty (Ophthalmology trainee) examining a patient with diabetic eye disease (photographed)

As part of the process of trying to improve attendance in the diabetic clinic we would often undergo fieldwork in order to find patients who had failed to attend their check-up visits, understand why they couldn’t attend and encourage them to do so. On one occasion we went far out into the countryside to a small village in search of a lady who had ceased to attend the clinic. This was a window into real life for many of the rural Malawians and will stay with me as a unique opportunity to be welcomed into these communities. Communication and transport were two of the key barriers to patients attending clinic. This often resulted in poor diabetic control and associated sequelae, such as this patient who had undergone a recent amputation.
Figure 2. a) Following the local guide and translator to the village b) Finally meeting my patient and discussing her diabetic treatment.

**OCT in Cerebral Malaria**

The OCT study provided a very different challenge to the MDRS2 study both practically and emotionally. All the children who participated in the study were unconscious and severely unwell on admission into the high dependency unit. Much like the diabetic patients the severity of pathology was apparent in all imaging modalities. During the season I enrolled and examined 31 study patients performing daily reviews and scans where possible until their discharge. Children were aged between two months and ten years, presenting with fever and parasitaemia. MRI data showed significant cerebral oedema in 80% on admission. 2 patients (6.5%) died despite treatment due to respiratory failure secondary to cerebral oedema.

The OCT was useful in identifying changes in the retina associated with cerebral malaria. The cause of retinal whitening has been the focus of much debate as it seems to mirror the oedema occurring in the cerebral tissue leading to death. The OCT clearly demonstrated the whitening as hyper-reflective plaques and suggests a relationship with the deep capillary plexus. Detailed analysis of the images will hopefully enable us to further understand the cause of the whitening; ischemic, vaso-congestive or intra vascular swelling. During the analysis we will also be looking for clinical correlation between OCT features and cerebral oedema and outcome.

Below are photos of me working on the Malaria ward. Children are admitted in a coma and following blood tests they have their eyes examined and colour images taken including FA (top left). They are then moved to a bed on the ward and the retinal scan is performed using the hand-held SD-OCT (top right).

Following the retinal photograph these images (bottom left) are used to look for signs of disease. The OCT scan (bottom right) is has less clarity when compared with static scans
often performed in clinic as the scans are average to reduce motion artefact. If examined closely you can see the capillary network (superficial and deep) and some of the diffuse hyper-reflective patches (whitening) and intra-retinal fluid.

Figure 3. Different images modalities as part of the OCT in cerebral malaria study

The control study was invaluable to provide a normal baseline for the data from children with cerebral malaria. For the control study I saw 110 children aged two months to six years old. These children had visual acuity tested by me using Preferential looking cards or Kay pictures. They were refracted, had a occulo-motility exam and dilated for fundoscopy and OCT scanning. This data will hopefully be of use for future work using OCT in Malawi.

Life outside of the Hospital

Working in the hospital was often challenging both practically and emotionally. Thankfully there is an amazing community in Blantyre, both locals and ex-pats who opened their homes and welcomed my wife and I into their lives. This was one of the best things about Blantyre, being thrown into a new community of like-minded people in a beautiful country. We made many friends who we will miss sorely. We managed to use our weekends to travel around the country from the north to the south, camping out of the back of our car. This was an unforgettable way to see the country and provided the adventure I had been dreaming of when stuck in a clinic in rainy Huddersfield! We also became keen members of the Mountain club of Malawi and had some of our happiest times on the mountain. The rugged plateau (figure 5) and challenging peaks provided a physical challenge we came to enjoy. Figure 6 shows a happy pair on a cold windy morning at the top of Sapitwa peak, the highest peak on the Mulanje range at just over 3000m.
Conclusion and Acknowledgements

Being able to spend the last year in Malawi, using my medical training in a resource poor setting, both in the care of patients and the dissemination of skills to local Ophthalmologists has been the highlight of my career to date. I have enjoyed the experience both in its challenges and rewards and am extremely grateful to Ethicon and the College for the support and encouragement to discover this wonderful country. We were blown away by the humility and kindness of the Malawians we met and hope to maintain these characteristics back into our jobs in the UK. My work has been novel and interesting, and the use of the retinal scanner to advance diagnosis and treatment in Cerebral Malaria has been a highlight. I will be presenting some of this work in ARVO in May 2017 in America and look forward to imparting both some interesting science and a glimpse of Malawian life. Both these projects are currently being written up into papers with the aim of publication later this year. I also hope to maintain my connections with DEVS in Liverpool and the Malawian Ophthalmologists and look forward to collaborating on more projects in the future.