Sara Brown | Visit to Uganda | October 2017
Report for Roger Harman African Travelling Fellowship - Winter 2017

Why Uganda?

Uganda means a lot to me. I was born in Mbale in Eastern Uganda whilst my parents were working at a secondary school (Teso College, Figure 1a). We returned to the UK when I was three years old and I grew up wanting to go back to Africa. My first opportunity came in 1989, in my gap year before university. I taught biology in a boarding school near Mbale and during that year I met my future husband who was working at a nearby school. We next visited Uganda together in 1993 when I co-led on an expedition to climb the Rwenzori mountains in Western Uganda, with sponsorship from the Royal Geographical Society to survey glacial retreat.[1] Because of my interest in Africa, I chose parasitology and entomology for my intercalated degree and it has been my long-term aim to return to Uganda with skills and training to contribute in a meaningful way.

Background

The 'Pearl of Africa', as Winston Churchill called Uganda, is a country of diverse and beautiful scenery, an abundance of wildlife (Figure 1) and people who have a culture of welcoming visitors. The political situation has been quite stable over the past two decades allowing substantial economic development in Uganda, despite the high prevalence of HIV infection. The top three causes of mortality currently are HIV/AIDS, pneumonia and stroke[2] but the average life expectancy has risen to 60.3 years for males and 63.3 for females.[2] Skin disease is a substantial burden in Africa and Uganda ranks 12th in the world for mortality associated with dermatological conditions: 9.1 age-standardised deaths per 100,000 of the population compared with 1.7 per 100,000 in the UK.[2]

Atopic disorders are less prevalent in Africa than in northern Europe; within Uganda the prevalence of atopic eczema ranges from <1% in some island populations[3] to >10% in urban areas.[4] African populations studied as part of the International Study of Asthma and Allergies in Childhood (ISAAC) showed a marked increase in 12-month period prevalence of atopic eczema amongst 13 and 14 year-olds, from 11.8% in 1995 to 19.4% in 2002.[5]

Atopic eczema is a complex trait, arising from a combination of multiple genetic and environmental factors. In the white European population and several Asian populations studied to date, loss-of-function mutations in the gene encoding filaggrin *(FLG)* contribute substantially to genetic risk.[6] In contrast, despite careful analyses there does not appear to be a significant contribution made by *FLG* null mutations to eczema risk in the African and African-American populations that have been studied.[7-9] A role for *FLG2* mutations in contributing to eczema persistence has been proposed,[10] but the genetic mechanisms contributing to eczema pathogenesis in Africa remain largely unknown.

Roger Harman Fellowship

I am very grateful to have been awarded a Roger Harman African Travelling Fellowship to support my visit to Uganda. This funding allowed me to spend time in an outpatient dermatology clinic at Kisubi Hospital and to visit a research unit with a Ugandan birth cohort: the Entebbe Mother and Baby Study.

Kisubi Hospital

In Kisubi Hospital (Figure 2a) I joined the medical director Dr Robert Asaba in his weekly dermatology clinic (Figure 2b). Dr Robert received his formal training in dermatology through distance learning provided by the Cardiff diploma course and he has recently established a specialist clinic. We saw a range of cases together including inflammatory and infectious dermatoses. One memorable case was a 3-year-old boy with severe atopic eczema (Figure 2c, photo with parental consent); this little boy's mother had run out of topical steroids. The use of soap to wash children is popular in Uganda, resulting in the same discussion that I have with my patients in the UK, explaining the importance of avoiding soap and detergents because of their irritant effect. I was also impressed to learn that HIV treatment is provided free of charge in Government facilities and this was advertised widely in the clinic (Figure 2d) to promote screening and early intervention.

Entebbe Mother and Baby Study

The Entebbe Mother & Baby Study (EMaBS)[11] is a birth cohort which was initiated as a randomised controlled trial of anthelmintic treatment for pregnant women in Uganda.[12] 2507 women were enrolled and received albendazole or placebo and praziquantel or placebo, with a 2×2 factorial design.[13] Babies were followed up and allergy events recorded prospectively. Maternal albendazole treatment was associated with a significantly increased risk of eczema in the infants (Cox hazard ratio 1.82 (95% confidence interval 1.26-2.64) p=0.002) in this Ugandan population; praziquantel treatment was associated with increased risk among infants of mothers infected with Schistosoma mansoni (Cox HR 2.65 (1.16-6.08) p=0.02).[13] EMaBS has continued to collect detailed phenotype information as well as DNA samples for genetic studies and the children are now aged 11-13 years.

Opportunities for collaboration

I was awarded a senior fellowship from the Wellcome Trust in 2015, to continue my research into the molecular and genetic mechanisms in atopic skin. I was delighted to make contact with Professor Alison Elliott, another Wellcome senior research fellow; Alison is based at the Medical Research Council / Uganda Virus Research Institute Unit in Entebbe and she leads the EMaBS study. Alison's team would like to use the clinical data and DNA samples from EMaBS to address the gap in knowledge about genetic risk mechanisms for atopic eczema. They have welcomed my offer of collaboration to provide dermatology and eczema genetic expertise.

In my visit to the research institute in Entebbe I gave a seminar entitled '*Molecular and genetic mechanisms in eczema: why do these matter for our patients?*' I explained my work and gave an overview of recent research into genetic mechanisms in eczema, contrasting what is known from studies in the white European population with the limited findings of genetic risk mechanisms in African populations. During my visit I was able to meet with staff working in the maternity and child health clinics (Figures 2e and 2f) as well as research staff and students from Alison's team in Entebbe (Figure 2g). We discussed the opportunities to investigate genetic risk for eczema in Uganda, including genome-wide analysis and candidate gene approaches for eczema and other atopic diseases. The genome-wide analysis is now underway. Alison and her team are also keen to apply longitudinal latent class analysis to investigate sub-phenotypes of eczema, an approach that I have participated in using successfully in UK and Dutch population cohorts.[14]

Conclusion

On a personal level, the hospital and research visits formed part of a 2-week-long road trip around Uganda with my husband and our teenage son and daughter. It was very rewarding to be able to introduce our children for the first time to our Ugandan friends and some of our favourite places. This experience has confirmed again my love for Uganda. I am excited about the potential to contribute through research collaboration and the hope of further visits in the not-too-distant future.

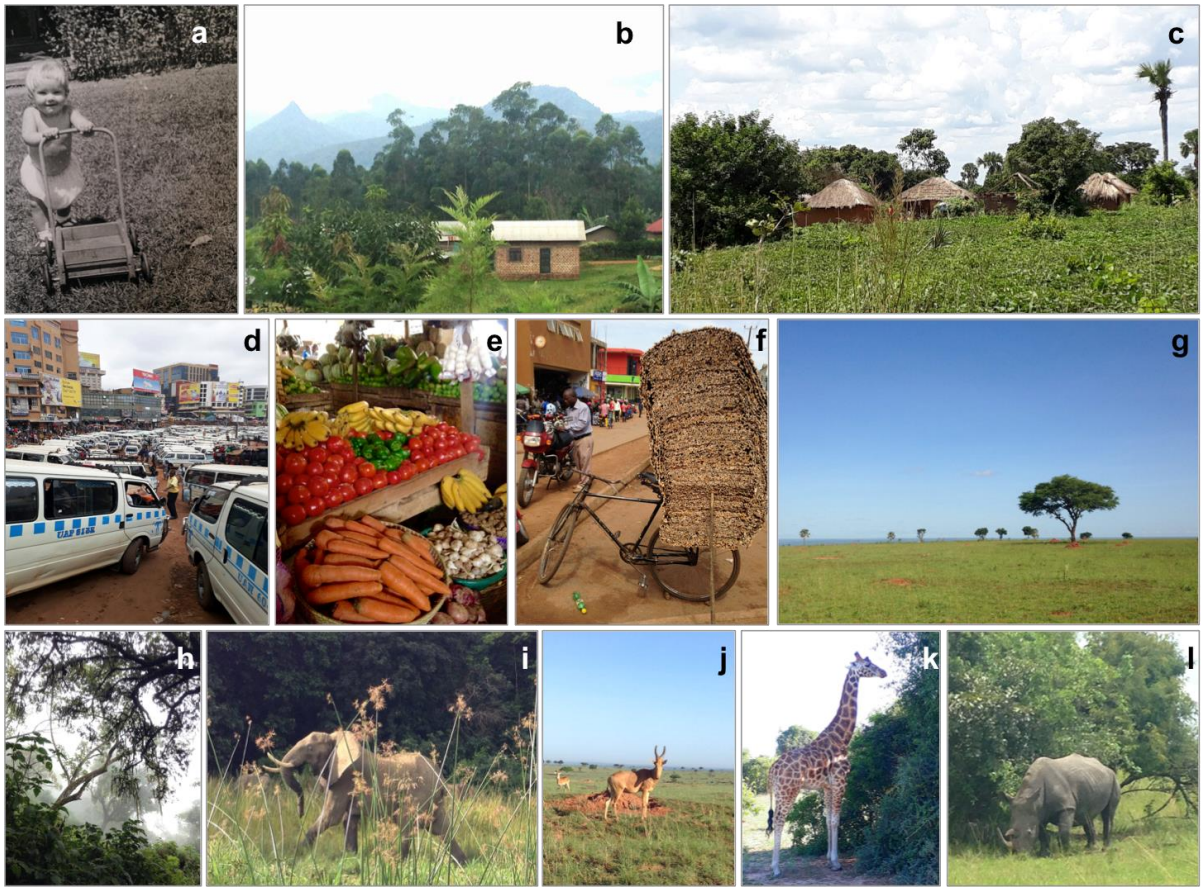

Figure 1.

(a) Sara in Soroti, 1971 (b) Village scene in Eastern Uganda (c) Village near Soroti (d) Kampala taxi park (e) Mbale market stall (f) Loaded bicycle (g) Murchison Falls national park (h) Rain forest on Mount Elgon (i) Young African elephant (j) Jackson's hartebeest (k) Nubian giraffe (l) White rhino.

Figure 2.
(a) Kisubi Hospital, main entrance (b) Out patient department, Kisubi Hospital (c) 3 year-old boy with widespread atopic eczema (d) Poster advertising free HIV testing and treatment (e) EMaBS clinic desk (f) EMaBs clinic, Entebbe (g) Collaborators' meeting at the Medical Research Council/Uganda Virus Research Institute Unit in Entebbe.

References

1 Talks A. East African Hot Ice 1993, Royal Geographical Society internal report, Sir Roger Manwood's School, Kent, UK. 1993.

2 World Health Review: data from WHO, World Bank, UNESCO, CIA and individual country databases for global health and causes of death. http://www.worldlifeexpectancy.com/world-health-review/uganda-vs-united-kingdom. In. 2017.

3 Nampijja M, Webb EL, Kaweesa J *et al.* The Lake Victoria Island Intervention Study on Worms and Allergy-related diseases (LaVIISWA): study protocol for a randomised controlled trial. *Trials* 2015; **16**: 187.

4 Elliott AM, Ndibazza J, Mpairwe H *et al.* Treatment with anthelminthics during pregnancy: what gains and what risks for the mother and child? *Parasitology* 2011; **138**: 1499-507.

5 Zar HJ, Ehrlich RI, Workman L *et al.* The changing prevalence of asthma, allergic rhinitis and atopic eczema in African adolescents from 1995 to 2002. *Pediatr Allergy Immunol* 2007; **18**: 560-5.

6 Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. *N Engl J Med* 2011; **365**: 1315-27.

7 Thawer-Esmail F, Jakasa I, Todd G *et al.* South African amaXhosa patients with atopic dermatitis have decreased levels of filaggrin breakdown products but no loss-of-function mutations in filaggrin. *J Allergy Clin Immunol* 2014; **133**: 280-2 e1-2.

8 Taylan F, Nilsson D, Asad S *et al.* Whole-exome sequencing of Ethiopian patients with ichthyosis vulgaris and atopic dermatitis. *The Journal of allergy and clinical immunology* 2015; **136**: 507-9 e19.

9 Margolis DJ, Gupta J, Apter AJ *et al.* Exome sequencing of filaggrin and related genes in African-American children with atopic dermatitis. *J Invest Dermatol* 2014; **134**: 2272-4.

10 Margolis DJ, Gupta J, Apter AJ *et al.* Filaggrin-2 variation is associated with more persistent atopic dermatitis in African American subjects. *The Journal of allergy and clinical immunology* 2014; **133**: 784-9.

11 Entebbe Mother and Baby Study (EMaBS) http://emabs.lshtm.ac.uk/. In. 2017.

12 Webb EL, Mawa PA, Ndibazza J *et al.* Effect of single-dose anthelmintic treatment during pregnancy on an infant's response to immunisation and on susceptibility to infectious diseases in infancy: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011; **377**: 52-62.

13 Mpairwe H, Webb EL, Muhangi L *et al.* Anthelminthic treatment during pregnancy is associated with increased risk of infantile eczema: randomised-controlled trial results. *Pediatr Allergy Immunol* 2011; **22**: 305-12.

14 Paternoster L, Savenije OEM, Heron J, Evans DM, Vonk JM, Brunekreef B, Wijga AH, Henderson JA, Koppelman GH, Brown SJ. Identification of atopic dermatitis subgroups in children from two longitudinal birth cohorts. *J Allergy Clin Immunol, accepted 2017.*