What is onchocerciasis, and what are its effects?

SP: Onchocerciasis, also known as river blindness, is a tropical parasitic disease induced by a filarial worm called Onchocerca volvulus and spread by black flies which tend to live near bodies of water. Apart from eyesight, onchocerciasis also affects the skin, producing incessant and maddening itching. Because transmission is closely linked to infested rivers, it causes wide areas of fertile land to be lost, with enormous negative consequences for the economies of endemic countries.

An association between onchocerciasis and epilepsy was suspected as early as the 1930s in an endemic area of Mexico. In Africa, a number of recognised researchers reported corresponding observations, but no conclusive data were ever presented.

Can you outline the pioneering work performed by Professor Walter Kipp that brought the association of epilepsy and onchocerciasis to your attention? How was your research programme initiated?

CK: In 1992, Professor Walter Kipp, then administrator of a Ugandan-German development project and now Professor Emeritus at University of Alberta, Canada – together with Silver Kasoro-Atwooki, then the Mental Health Coordinator of Kabarole District, Uganda, and Professor Emilio Ovuga, Dean at the Faculty of Medicine, Gulu, Uganda – was the first to publish original data from an African endemic area relating epilepsy to onchocerciasis. Since most of their epilepsy patients were children, Kipp consulted Professor Hans Joachim Bremer, then Head of the University Children’s Hospital Heidelberg (UCHH) and an expert in tropical paediatrics. At this time, I was working as a resident in paediatrics at UCHH and, having some experience in tropical medicine, Professor Bremer suggested that I should carry out a more detailed investigation.

SP: In 2001, during my PhD in Parasitology, I became involved with research into onchocerciasis in Mbam Valley, Cameroon. In the early 1990s, investigators from the Institut de recherche pour le développement (IRD) led by Dr Michel Boussinesq, had been informed by the local population that epilepsy was one of the main health issues in the region. With detailed surveys, we confirmed the prevalence of epilepsy to be one of the highest in the world, and furthermore we demonstrated a close relationship between epilepsy and onchocerciasis in this area.

Are there already effective measures in place to treat onchocerciasis? Do you think the link with epilepsy will give greater urgency to the development of new drugs and distribution to infected individuals?

SP & CK: Two different control strategies have been applied to combat onchocerciasis. The Onchocerciasis Control Program (OCP) was launched in 1974, and it uses vector control with insecticides as its major tool. This resulted in interruption of transmission in large areas of seven West African countries. Since 1987, the African Program for Onchocerciasis Control (APOC) has been in place to cover areas of high risk in countries that are not covered by the OCP. It uses mass treatment with ivermectin – an effective and safe microfilaricidal drug that has been made freely available for this purpose by its manufacturer Merck & Co, USA.

Despite the tremendous success of both programmes, there are still millions of people living in endemic areas without access to treatment and substantial efforts will be needed to consolidate achievements. With respect to the increasing evidence that onchocerciasis is also affecting the brain in addition to the skin and the eye, it certainly appears more urgent than ever to improve and extend onchocerciasis control methods.

In light of their pioneering work on onchocerciasis and epilepsy, Drs Christoph Kaiser and Sébastien Pion discuss the importance of an interdisciplinary approach when it comes to the study of tropical diseases.
What is ‘Head Nodding Syndrome’, and how is it linked with the prevalence of epilepsy?

CK: The term Head Nodding Syndrome (NS) was coined by Professors Louise Jilek-Aall and Andrea Winkler, based on their observations in an area of high epilepsy prevalence in southern Tanzania. Here, patients are suffering from seizures characterised by repetitive head movements, starting between the ages of five and 15 years in previously healthy and normally developed children. NS is a mysterious disease with unclear causation.

17 per cent of the epilepsy patients that we examined in western Uganda had seizures with head nodding. This corroborates the hypothesis that NS, rather than being a distinct disease entity of unknown origin, is a specific seizure type of an epileptic disorder induced by infection with *O. volvulus*. This idea is also supported by recent studies led by the US Center for Disease Control, which found a consistent association between NS and onchocerciasis in northern Uganda and southern Sudan.

Incidentally, I know some parasitologists who possess this open-minded attitude in an exemplary manner.

SP: Originally a biologist with a strong interest in parasitology, I have actually been working as a field epidemiologist for about 15 years. Epidemiology, by essence, is at the crossroads of scientific disciplines – incorporating biology, ecology, geography, medicine, statistics and, increasingly, mathematical modelling. I believe that biological processes often need several eyes and ways of thinking to get close to the full picture.

New insights into an old disease

A cross-disciplinary team has established a conclusive link between river blindness and epilepsy in parts of Africa. Their findings could also help to clarify the cause of an epileptic disorder termed ‘Head Nodding Syndrome’

THE PREVALENCE OF epilepsy, and particularly an epileptic disorder called Head Nodding Syndrome (NS), is an overlooked problem in many parts of Africa. Recently, thousands of patients with NS have been discovered in northern Uganda and southern Sudan. This condition, named for the characteristic repetitive nodding movements of those afflicted, was first observed in Tanzania in the 1960s and then described as a clinical syndrome in 2008.

What is particularly interesting about these epileptic disorders is that they tend to be prevalent in areas where another disease, onchocerciasis, is also common. Onchocerciasis, or river blindness, is a devastating affliction caused by the filarial nematode *Onchocerca volvulus*, and while an association between these two types of illness has long been suspected, no conclusive data have been presented to date to confirm the link. A clearer understanding of the relationship between onchocerciasis, epilepsy and NS could mean prevention of a large proportion of those reported cases of epilepsy.

DISSECTING THE DISORDERS

Researchers, Drs Christoph Kaiser and Sébastien Pion, are working together to understand the relationship between these diseases and further clarify their basic biology. Their work has already confirmed the hypothesis that onchocerciasis and epilepsy are closely related. In addition, they have constructed a detailed description of disease epidemiology in two independent areas of Cameroon and west Uganda, and have produced a clearer clinical picture of epilepsy, NS and onchocerciasis. They found that epilepsy prevalence between the ages of 10-20 reached 10 per cent in some villages, and that epilepsy patients were seven times more likely to die than healthy subjects in the years following their initial study.

Kaiser, Pion and their colleagues employ a range of approaches to tackle several questions relating to the link between onchocerciasis and epilepsy. They hope to elucidate the underlying biological pathology of the condition and the mechanism of epilepsy development following infection. One of the barriers to convincing others of the link between the two diseases results from the heterogeneity of outcomes – why is it that only a proportion of those afflicted with onchocerciasis go on to develop epilepsy? This has led the team to investigate the role of infection intensity; they have systematically reviewed their own results along with all other available studies, as this may help to explain the discrepancies in the emergence of epilepsy. With one approach, they found epilepsy prevalence to be exponentially linked with that of onchocerciasis and therefore with the increase in the number of severe infections in endemic areas. Another source of evidence
INTELLIGENCE

RIVER BLINDNESS AND THE BRAIN: NEW INSIGHTS INTO AN OLD DISEASE

OBJECTIVES
To investigate the link between onchocerciasis (river blindness) and epilepsy in parts of Africa, and having established this link, applying this knowledge to practical solutions that can be implemented to benefit the populations in greatest need.

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DR CHRISTOPH KAISER has spent his career working in both Africa and Europe, training as a doctor at Medizinische Hochschule Hannover, Germany, before undertaking an internship at the University of Gezira, Sudan. He then worked as a resident in paediatrics at St Hedwig Children’s Hospital, Freiburg, Germany, before returning to work in Sudan and initiating his research into onchocerciasis and epilepsy in Uganda. He currently runs a paediatric practice in Baden-Baden, Germany.

DR SÉBASTIEN PION is an epidemiologist with a PhD in Parasitology from University Paris VI, France. He has worked as a research assistant at Imperial College London, UK, UK, and the Institute of Epidemiology and Tropical Neurology, France. He is currently based at the Institut de recherche pour le développement in Cameroon.

is their analysis of case control studies that demonstrated a significant association between epilepsy and a positive *O. volvulus* infection status. They found this association to be even more pronounced in studies which accounted for parasitic infection intensity.

Despite these findings, the mechanism by which *O. volvulus* leads to the development of epilepsy and NS remains elusive. However, there have been promising clues: “Microfilariae have occasionally been found in the cerebrospinal fluid, and it could be speculated that these produce changes in the brain that may even persist after microfilaricidal treatment,” Kaiser explains. “It has also been suggested that immune reactions to the parasite could be involved in epileptogenesis.”

IMPORTANT IMPLICATIONS AND FUTURE WORK

It is hoped that this work will spark a much needed re-evaluation of onchocerciasis and its significance to the populations in which it is endemic. Kaiser describes how their work is profoundly changing previous concepts of onchocerciasis as a disease of the skin and the eyes of elderly people to a brain disease of children and young adults: “This disease has devastating consequences on their development and on their lives. Many die very early”.

Since endemic areas are often poverty-stricken, they lack the resources and facilities to undertake the level of research required to dissect the molecular underpinnings of the conditions. The emphasis is therefore on prevention and control. Kaiser and Pion are hoping that their work will account for this, shifting focus towards practical implications for afflicted regions. For now, their research has made great progress in establishing a link between a parasitic infection and a neurological condition, which at first sight appeared as basically disparate entities. Now, this work needs to be translated into benefits for those who are afflicted by these illnesses.

**ACTION PLAN**

The team behind this pioneering work into onchocerciasis and epilepsy has laid out a plan of how best to advance this project.

1. **STRENGTHEN ONCHOCERCIASIS CONTROL:**
Combating onchocerciasis means combating epilepsy, and as the African Programme for Onchocerciasis Control already has methods in place to prevent disease transmission, this is the appropriate operational organisation to deal with this problem.

2. **COMBINE EPILEPSY RESEARCH WITH EPILEPSY CARE:**
Patients suffering from epilepsy who are subject to research have the right to receive adequate, continuous and long-term treatment.

3. **PROMOTE MULTIDISCIPLINARY RESEARCH**
More intensive cooperation between researchers of different backgrounds will be crucial.

*River blindness*

- Onchocerciasis, or river blindness, is transmitted through bites from *Simulium* black flies, which infect the host organism with parasitic larvae — a filarial worm called *Onchocerca volvulus*.

- When the worms die, endosymbiotic bacteria called *Wolbachia pipientis* are released from inside their bodies and cause a severe immune system inflammatory response in the host. This leads to unbearable itching and can specifically damage optical tissue, often resulting in blindness.

- The parasite affects roughly 37 million people in sub-Saharan Africa and Latin America, over 500,000 of which are blind as a consequence.