Taking a swipe at Africa's epilepsy

Evidence is fast building that a preventable and treatable parasitic disease, onchocerciasis, underlies a great deal of the extraordinary prevalence of epilepsy in sub-Saharan Africa. Is an end to much suffering in sight? Adrian Burton investigates.

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For more on **the prevalence of epilepsy in sub-Saharan Africa** see *Tanzan J Health Res* 2013; **15**: 102–19

For more on **the prevalence of epilepsy in Cameroon** see **In Context** *Lancet Neurol* 2015; **14**: 980–81

For more on **parasites associated with epilepsy in Africa** see *Epilepsy Curr* 2014; **14**: 29–34

For more on **the first reports of *O volvulus* and epilepsy in Uganda** see *Lancet* 1994; **343:** 183–84

For more on **nodding syndrome** see **In Context** *Lancet Neurol* 2016; **15:** 30–31

For more on **the Ugandan Ministry of Health survey** see *MMWR Recomm Rep* 2014; **63**: 603–06

For more on **the use of ivermectin in *O volvulus* treatment** see *PLoS Negl Trop Dis* 2016; **10**: e0004478.

Paradigm shifts do happen in medicine. The discovery of penicillin, the finding that gastric ulcers are caused by *Helicobacter pylori*, the development of antivirals able to prevent the advance of HIV/AIDS—all changed the lives of millions. There is now growing reason for optimism that a similar breakthrough might be made against epilepsy in sub-Saharan Africa. Research is showing that a good proportion of it might be caused by a parasite that we already know how to control and kill: *Onchocerca volvulus*, the causal agent of river blindness. Should a project now underway to examine the relationship between onchocerciasis and epilepsy confirm researchers' hopes, a radical change in Africa's neurological health could be on the cards.

Epilepsy is often idiopathic, but can also be acquired as the result of an insult to the brain caused by trauma or infection. It is this second kind that appears to be causing misery to many people in Africa. The prevalence of epilepsy in some parts of the continent is extraordinarily high. For instance, in rural Djidja, Benin, a figure of 1·05% has recently been reported. In certain villages in rural Burkina Faso, a prevalence of 4·5% has been documented, and in parts of Cameroon, values of well over 10% have been recorded. Compare this prevalence to 0·71% as estimated for the USA. A genetic component might be involved, but the current best candidate for explaining this difference is parasitic infection. In sub-Saharan Africa, epilepsy has been associated with infection by *Plasmodium falciparum* (a protozoan) and *Schistosoma mansoni* and *Schistosoma haematobium* (trematodes), but far more commonly with the cestode *Taenia solium* (the tapeworm) and the nematode *Onchocerca volvulus*. Neurocysticercosis, a cerebral infection caused by *T solium*, has for years been linked to epilepsy in Latin America and is among the most common of neurological infections in Africa. Some researchers suggest that it may be responsible for 30–50% of all acquired epilepsy south of the Sahara. But that falls well short of explaining it all; indeed, in some areas, researchers report finding no clear association between epilepsy and *T solium* infection at all. Enter *O volvulus*.

Indications that this organism might be associated with epilepsy began to appear in earnest during the mid-1990s. It was first reported from western Uganda that epilepsy was substantially more frequent in villages with the highest levels of endemic *O volvulus*. Similar findings then came in from across central Africa and, in 2002, a relationship was picked up in a case-control study done in Cameroon. In 2009, a meta-analysis involving data from Benin, Nigeria, Cameroon, the Central African Republic, Uganda, Tanzania, and Burundi indicated a clear relationship between the presence of *O volvulus* and the prevalence of epilepsy, or river epilepsy as the authors dubbed it in word association with river blindness, the disease for which *O volvulus* was then best known. "For many years there had been anecdotal evidence from people working in the field about an overlap between the distribution of river blindness and epilepsy, which gradually turned into scientific evidence", says Sébastien Pion (Senior Researcher at the Institut de Recherche pour le Développement, Montpellier, France). "Our meta-analysis began to make people look seriously at the possible relationship, although it did not quite get all the scientific and health community on board." That came later, via nodding syndrome.

"We hypothesised that nodding syndrome, which appears only in areas with endemic *O volvulus*, and with which strong epidemiological and serological links are known, was in fact just 'the ears of the hippo', the severe end of a spectrum of epilepsy linked to *O volvulus* infection", says Robert Colebunders (Professor of Infectious Diseases, Global Health Institute, University of Antwerp, Antwerp, Belgium). "A 2012 survey by the Ugandan Ministry of Health in areas where nodding syndrome was very prevalent revealed there were also many cases of convulsive epilepsy, with one or the other problem sometimes affecting different children in the same household. In effect it showed there was an epidemic of epilepsy right alongside nodding syndrome that no-one had been talking about". Since then, Uganda's use of larvicide in rivers to kill the black fly vector of *O volvulus*, plus the distribution of ivermectin, an effective treatment for *O volvulus* infection, have managed to stop any more cases of nodding syndrome appearing. "We need to find out if the incidence of this parallel epilepsy has also been reduced", says Colebunders, "but in South Sudan, where war has prevented control efforts, an epidemic of both nodding syndrome and epilepsy clearly continues. The question is, if nodding syndrome and other types of epilepsy in onchocerciasis endemic regions are different manifestations of the same problem, might not steps taken to control one also control the others?"

Maybe. In the Imo River Basin of Nigeria, where ivermectin has been used since 1994, most people with epilepsy are 20–29 years old, not well

under 20 years as was seen in northern Uganda before ivermectin was introduced. "Indeed, a characteristic of nodding syndrome and other forms of onchocerciasis-associated epilepsy is that they generally appear at primary school age", says Colebunders. "In all onchocerciasis endemic regions where ivermectin has never been distributed (and if access to anti-epileptic treatment is limited), most people with epilepsy are well below the age of 20. So once ivermectin is introduced we should see an age shift in the epilepsy burden to older age groups."

In 2015, Colebunders received a €2·4 million European Research Council grant to find out. The project aims to verify the epidemiological relationship between epilepsy and *O volvulus* in South Sudan, Uganda, Tanzania, Cameroon, the Democratic Republic of Congo, and Tanzania, as well as confirm the link between the reduced incidence of epilepsy and ivermectin distribution. "We know of places where ivermectin has been used for maybe 15 years, where it has been used for 3 years, and where it has never been used, and we are expecting to see that where its use has been strongest, the incidence of epilepsy will be lowest", says Colebunders. "We will also check [for that] switch to epilepsy among older age groups where ivermectin is used." Trials are also being planned to test whether treatment with ivermectin can reduce the incidence of epilepsy and the number of seizures in patients with *O volvulus*-associated epilepsy, and whether or not using doxycycline to kill the nematode's bacterial symbiant, *Wolbachia* spp., has a similar effect.

Laboratory work will try to establish the elusive pathophysiological link between onchocerciasis and epilepsy. Although constant reinfection seems necessary for epilepsy to appear, no parasitic microfilariae have ever been recovered from patients' brains. Colebunders intends to use state-of-the-art techniques to examine adequately preserved donated brains, while immunological studies will hunt down cross reactions between pathogen (*O volvulus*) and brain proteins that might cause autoimmune-induced epilepsy. Preliminary evidence from other groups suggests that antibodies against *O volvulus* tropomyosin cross react with human leiomodin 1 in patients with nodding syndrome. Clearly neurotoxic, these antibodies can be found in the cerebrospinal fluid and leiomodin 1 detected in the brain.

But knowing the mechanism of disease is not essential for a strategic strike against epilepsy. "If the epidemiological evidence is strong enough, and certainly if the prospective trial reveals a statistically significant reduction in epilepsy incidence with ivermectin use, with an accompanying safe side-effect profile for [the drug], there is good reason to offer this as prevention in endemic areas", says Alexandra Martiniuk (Associate Professor of Epidemiology at the University of Sydney and George Institute for Global Health, Sydney, Australia). "But this would require political support, social and political stability, plus health system strengthening including the organisation of the distribution of ivermectin, health monitoring services, black fly monitoring, and training people to be involved in all this—which in some parts of Africa could be a tall order."

Undeterred, Colebunders is searching for support to reduce the suffering caused by onchocerciasis-associated epilepsy. "We need to get a grand coalition of the WHO, the pharmaceutical industry, non-governmental organisations, private foundations, national health services, local health services, and anyone else who can help to get this off the ground", he says. "Also, we need to work together to emulate the kind of environment that reduced the cost of HIV treatment to people in Africa, and so bring them antiepileptic drugs—even those in remote areas. If we can do all that, then perhaps we could massively reduce the burden of epilepsy."

John Atherton

For more on **WHO onchocerciasis program** see http://www.who.int/blindness/partnerships/onchocerciasis_OCP/en/

In fact, WHO already has a black fly control and ivermectin distribution program for tackling river blindness up and running. In 2014 alone, over 112 million people were treated in 22 African countries, representing 65% of the global coverage against onchocerciasis. "Our findings will hopefully be a stimulus to strengthen and extend this program", says Colebunders. "This is really exciting", remarks Tamara Bugembe, a consultant paediatrician at King's College Hospital, London, UK, who previously worked to develop an epilepsy service in Cameroon. "Finding a pathological and reversible cause for epilepsy will help in reducing the mystery and stigma around the disease. Hopefully this will encourage more research into other causes of epilepsy." Of course, controlling onchocerciasis will not solve everything. Idiopathic epilepsy will remain, and epilepsy caused by tapeworms and other parasites will still need to be dealt with. But if things go to plan, the eradication of a large proportion of Africa's epilepsy burden could suddenly become a possibility. It is worthy of our best efforts to discover whether or not such a paradigm shift is within our reach.

Adrian Burton