Onchocerciasis-associated epilepsy: From recent epidemiological and clinical findings to policy implications

*Robert Colebunders, †Alfred K. Njamnshi, ‡Marieke van Oijen, §Deby Mukendi, §Jean Marie Kashama, ¶Michel Mandro, #Nolbert Gumisiriza, **Pierre-Marie Preux, *Patrick Suykerbuyk, and ††‡‡Richard Idro

Epilepsia Open, 2(2):145–152, 2017
doi: 10.1002/epi4.12054

Robert Colebunders

is a professor of infectious diseases at the Global Health Institute of the University of Antwerp.

SUMMARY

A high prevalence of epilepsy is reported in many onchocerciasis-endemic regions. In this paper we discuss recent epidemiological and clinical aspects as well as public health implications of onchocerciasis-associated epilepsy (OAE) and propose a strategy to reduce the burden of disease. OAE probably presents in a variety of clinical manifestations, including the nodding syndrome and the Nakalanga syndrome. The most common clinical presentation, however, is generalized (primarily tonic-clonic) seizures. A characteristic of OAE is the onset of seizures between the ages of 3 and 18 years and clustering in certain families and villages close to rapid-flowing black-fly-infested rivers. A strategy combining active surveillance for epilepsy with early treatment with antiepileptic drugs and prevention of onchocerciasis by increasing the geographical and therapeutic coverage of community-directed treatment with ivermectin (CDTi) may considerably decrease the burden of disease.

KEY WORDS: Epilepsy, Nodding syndrome, Nakalanga syndrome, Ivermectin, Prevalence, Incidence.

An estimated 70 million people in the world are affected by epilepsy, with about 2.4 million people diagnosed each year. Epilepsy prevalence varies largely among continents and countries, with a considerably higher prevalence in populations in low- and middle-income countries. Birth trauma, traumatic brain injury, cerebral vascular disease, brain tumors and bacterial brain infections are well-known causes, but parasitic infections, such as cerebral malaria, neurocysticercosis, echinococcosis, and onchocerciasis, are also known to be associated with epilepsy. In this paper we discuss epidemiological and clinical aspects as well as public health implications of onchocerciasis-associated epilepsy (OAE) and propose a strategy to reduce the burden of disease.

Onchocerciasis, also known as river blindness, is a parasitic disease caused by the filarial worm Onchocerca volvulus (Ov) transmitted by black flies of the genus Simuliidae. Today it is estimated that 37 million people are infected by Ov, of whom 99% live in Africa. In infected persons, the adult female worms form subcutaneous nodules and release thousands of microfilariae daily, leading to itching, dermatitis, blindness (all well-known complications of onchocerciasis), and epilepsy.
Key Points

- Onchocerciasis-associated epilepsy (OAE) occurs clustered in certain families and villages close to rapid-flowing black-fly-infested rivers
- OAE seizures generally start between the ages of 3 and 18 years in previously healthy children
- Clinical presentations of OAE include the nodding syndrome and the Nakalanga syndrome
- Active surveillance for epilepsy in onchocerciasis-endemic regions with early antiepileptic treatment and increasing the coverage of community-directed treatment with ivermectin may considerably decrease the burden of disease

Epidemiological Aspects

The link between epilepsy and onchocerciasis was first reported in 1938 by the Mexican physician Casis Sacre, who described a syndrome characterized by epileptic seizures, stunted growth, and mental retardation in patients with onchocerciasis in Chiapas and Oaxaca, Mexico. In Africa, the association between epilepsy and onchocerciasis was first documented in a population-based epidemiological study by Boussinesq et al. in the Mbam valley in Cameroon in 1991–1992. In this study, the prevalence of epilepsy increased with decreasing distance to the Mbam River, a breeding site for black flies, and with increasing community microfilariae load. Since then, similar associations have been documented in studies from many other African countries. In particular, a huge case-control study conducted in several countries of sub-Saharan Africa found an increased prevalence of epilepsy with onchocerciasis, with an odds ratio of 2.2 (confidence interval [CI] 95%: 1.6–3.2). A meta-analysis of African population-based surveys showed a variation in epilepsy prevalence consistent with onchocerciasis prevalence, with epilepsy prevalence being increased, on average, by 0.4% for each 10% increase in onchocerciasis prevalence. There have also been case-control studies that did not show the association between onchocerciasis and epilepsy, but these studies were performed in areas of low onchocerciasis endemicity or were not able to show an association because cases and controls were matched for ivermectin exposure. Of note is that none of the case-control studies was carried out on incident cases. In all of these studies, cases developed epilepsy many years earlier, and this makes it difficult to identify risk factors preceding the development of epilepsy. Acute symptomatic seizures were not considered as epilepsy in the studies in which the authors of this paper were involved.

In the 1960s a distinctive epilepsy syndrome characterized by head nodding, the nodding syndrome (NS), was first described in an onchocerciasis-endemic region in Tanzania (in children from a few villages in the Mahenge Mountains) by Jilek-Aall. Other characteristics of NS include stunted growth, as in the Nakalanga syndrome, and cognitive decline. Since then, NS- and Nakalanga-like clinical features have been reported in other onchocerciasis-endemic areas in Liberia, West Uganda, Burundi, and possibly the Central African Republic, Ethiopia, Mali, and Cameroon. NS epidemics have been observed in onchocerciasis-endemic regions in South Sudan (onset around 1990) and in northern Uganda (onset around 2002). Case-control studies in the two countries demonstrated a statistically significant higher prevalence of onchocerciasis in individuals with NS than in controls.

Although the association among epilepsy, NS, and Ov infestation seems apparent, the pathophysiological mechanism is not clear. In recent studies Ov DNA was never isolated from cerebrospinal fluid (CSF) in patients with NS/OAE. However, several of the patients enrolled in these studies had taken ivermectin (the antiparasitic drug commonly used to treat onchocerciasis) in the past. In earlier studies, before the use of ivermectin, several investigators had reported the presence of microfilariae in the CSF of patients with onchocerciasis: Hisette in 1932 in Congolese patients with ocular onchocerciasis and Casis Sacre in 1938 in Mexican patients. In 1959 dead and live microfilariae were found by Mazotti in CSF of patients with onchocerciasis treated with diethylcarbamazepine. In 1976 Duke et al. also observed microfilariae in the CSF of heavily infested patients.

Although these findings would suggest a direct effect of microfilariae, another explanation for the association could be the occurrence of an autoinflammatory response induced by antibodies to Ov cross-reacting with neuron proteins. This recent paper seems to support our earlier pilot study that observed antibodies to voltage-gated potassium channels in neurons.

Because Ov may directly or indirectly cause epilepsy, the prevalence and incidence of epilepsy are determined by all the factors that influence the level of the onchocerciasis control endemicity (Fig. 1). Onchocerciasis endemicity is influenced by environmental factors: the presence of fast-flowing rivers with rapids and vegetation at their border; climatological factors: a more constant weekly rate of rainfall may increase the risk for onchocerciasis transmission; the proximity of the village to black fly breeding sites and black fly biting rates: human biting rates in a village may decrease if there is another village closer to the river or if there is a lot of cattle in the village; human behavior: frequent river contact particularly during the daytime when black flies are most active; size of the population at risk: the establishment in northern Uganda of very large internally displaced person camps close to black-fly-infested rivers and population growth in villages close to blackfly breeding sites such as in Mvolo in South Sudan may have played a role in causing NS epidemics;
and degree of immunity among the population: a low cattle:human ratio may lead to increased Ov infestation. Indeed, infection with Onchocerca ochengi, a species prevalent in cattle but transmissible by black flies to humans, may not cause the disease but may cause the creation of antibodies that provide some protective immunity against Ov infestation. Malnutrition and untreated coinfections during episodes of war such as in northern Uganda and South Sudan may have rendered children more vulnerable to heavy infestation with Ov. Exposure to multiple parasites also may increase the prevalence of epilepsy.

Today, onchocerciasis endemicity mainly depends on the quality of the onchocerciasis control program in the area. Between 1995 and 2015, the African Program for Onchocerciasis Control (APOC) coordinated the implementation of community-directed treatment with ivermectin (CDTi) programs in onchocerciasis-endemic areas of 22 African countries. Activities toward the control of onchocerciasis keep expanding in the frame of the World Health Organization (WHO) Expanded Special Project for Elimination of Neglected Tropical Diseases (ESPEN) that was launched in May 2016. By controlling the blackfly by larviciding its breeding sites in fast-flowing rivers, a remarkable reduction of onchocerciasis transmission has been achieved in the past 20 years. However, despite the success and the effectiveness of these targeted intervention programs, certain zones still remain unreached by CDTi, because of local insecurity due to armed conflicts in the endemic region.

It is known that ivermectin rapidly reduces the body’s microfilariae load, thus eliminating the potential trigger that is associated with epilepsy. It therefore appears plausible that high ivermectin therapeutic coverage will decrease the incidence of OAE fairly rapidly. The NS epidemic in northern Uganda started to decrease after 2008 when a limited number of people started ivermectin treatment. In a case-control study in 2009 in the Kitgum-Pader Districts 33% of NS cases and 24% of controls had taken ivermectin. In 2012 the NS epidemic stopped (no new NS cases appeared) within a year after implementing biannual CDTi and larviciding rivers. In 2014, in another case-control study in the Kitgum District 76% of NS cases and 77% of controls had taken ivermectin. In the Democratic Republic of the Congo (DRC), a first small case-control study suggested that ivermectin intake may protect against the development of epilepsy in onchocerciasis-endemic areas, and in a more recent study of 96 cases and 96 controls, matched for village, age, and sex, this finding was confirmed (R. Colebunders, personal communication).

Late introduction of CDTi in onchocerciasis hyperendemic areas, as was the case in certain districts in northern Uganda, has led to high prevalence of OAE. OAE prevalence is also influenced by mortality. Where there is access to adequate health care and antiepileptic treatment, epilepsy-related mortality will be low and therefore the prevalence of epilepsy may only decrease slowly despite an effective CDTi program. In this situation, because children with OAE will become adults and very few new children will develop OAE, the highest prevalence of epilepsy will be observed among the age group between 20 and 30 years and not among the 10- to 20-year age group before the introduction of CDTi. In most places in Africa, epilepsy is
associated with increased mortality because children with epilepsy often die at a young age from drowning, burn injuries, status epilepticus (itself due to lack of access to anti-epileptic treatment), or neglect, malnourishment, or infections.

**Clinical Aspects**

OAE manifests with a variety of seizure types and degrees of severity. In Tanzania, Uganda, and South Sudan, a possibly distinctive form of OAE has been described as NS. NS is a debilitating epileptic disorder developing in children 3–18 years old. NS seizures are characterized by a brief loss of muscle tone in the neck (atonic seizure), leading to repeated head nodding, which gave the disease its name. Cognitive decline and stunted growth in formerly normally developing children are other characteristics of the disease. Repeated seizures are probably the main cause of cognitive decline in persons with OAE. In northern Uganda, since the start of antiepileptic treatment and nutritional and psychosocial support, it has been shown that NS may not be an invariably progressive disease. Several children were able to return to school. This suggests that if timely and adequate treatment and care are provided, cognitive decline can be prevented.

Persons with OAE often present with onchocerciasis-related dermatological manifestations but rarely with blindness. To become blind, most likely a much longer exposure to the Ov infection is required.

The Nakalanga syndrome is another clinical condition observed in onchocerciasis-endemic regions that is associated with epilepsy. The Nakalanga syndrome was first described in 1966 among a population who migrated to the Mabira Forest, Buikwe District, in the central region of Uganda, which was at that time an onchocerciasis-endemic region. The Nakalanga syndrome is characterized by severe stunting and absence or delayed development of external signs of sexual development. Nakalanga features have been described in several other onchocerciasis-endemic regions. During epilepsy prevalence surveys performed between 2014 and 2016, in the DRC several persons with stunted growth, absence of external signs of sexual development, cognitive impairment, and epilepsy were observed in onchocerciasis-endemic areas in the Bas Uélé, Tshopo, and Ituri Provinces. For example, a pronounced form of Nakalanga was observed in a of 26-year-old women in Tshopo Province. She had the appearance of a child (weight 26 kg, height 1.27 m), without any external signs of sexual development. She had developed tonic-clonic seizures at the age of 16, was cognitively impaired, and had only reached third grade of primary school. A Skin snips taken from the left and right italic crests showed the presence of microfilariae (parasite densities of 10 and 33 microfilariae/mg skin, respectively; Fig. 2).
antiepileptic drugs, and certain cofactors, such as malnutrition, may explain the difference in clinical presentation.\cite{50} Children with Nakalanga syndrome are known to be heavily infested with Ov, and the first signs that a child will develop the Nakalanga syndrome are already observed in the second or third year of life.\cite{52} These children were probably infected with Ov at an early age, when their brains were still developing. It is possible that other children, slightly less exposed to Ov and/or exposed later in life, may develop NS (the mean age for developing NS in children in Tumango, in northern Uganda was 7.6 years\cite{24}). Children less exposed to Ov and much later in life may develop epilepsy with minimal or no cognitive impairment and no decrement of growth or sexual development (the mean age of developing tonic-clonic seizures in the DRC was 11 years\cite{3}).

**Case Definitions**

In 2012 a case definition for NS was proposed during a meeting coordinated by the WHO and Ugandan Ministry of Health in Kampala.\cite{51} This case definition was found to be complicated for use in epidemiological surveys.\cite{52} Moreover, there is no case definition for other forms of epilepsy associated with onchocerciasis, including the Nakalanga syndrome. Today, because of the increasing evidence of an association between NS and onchocerciasis, the 2012 WHO case definition of NS may need to be updated. Recently, a simple point-of-care test, the Ov16 rapid antibody test, became available.\cite{50,53} Including a positive Ov16 rapid antibody test in the case definitions of onchocerciasis-associated conditions could be considered.

Proposed clinical case definitions for OAE, NS, and Nakalanga syndrome are as follows:

**OAE (need to meet the following five criteria)**

1. Person with epilepsy living in an onchocerciasis-endemic region
2. Onset of epilepsy between the ages of 3 and 18 years
3. Geographical clustering of persons with epilepsy in the village, or brother or sister with epilepsy
4. No obvious cause for the epilepsy**
5. Normal neurological development before the onset of epilepsy

**Nakalanga syndrome** = OAE + nodding of the head with episodes of decreased responsiveness

**NS** = OAE + nodding of the head with episodes of decreased responsiveness

**Public Health Importance**

The exact burden of disease attributed to OAE is currently unknown but seems to be considerably high because of the number of people at risk. Indeed, if we consider that the onchocerciasis infection is poorly controlled in 30% of the 37 million people infected,\cite{4} and that 1% of those develop epilepsy (equivalent to the approximate excess prevalence of epilepsy over nononchocerciasis areas), the number of OAE cases could be more than 100,000.\cite{50} In Mvolo, a village in South Sudan, one in six children suffer from epilepsy and at least 50% of the families have at least one child with epilepsy.\cite{40} Untreated OAE may lead to further cognitive and physical decline due to uncontrolled seizures and possibly neglect.\cite{44} The psycho-socio-economic importance of OAE in severely affected communities is enormous.\cite{54} Many OAE-affected children have psychiatric problems. Girls with OAE with an intellectual disability are at risk of being sexually abused. Children often die at a young age because they drown in a river or fall in a fire and sustain severe burns. Children with OAE may also be affected by onchocerciasis skin disease that causes intense itching that prevents them from sleeping.\cite{54} Some of the affected children require constant care because they may wander off and get lost.\cite{54} This interferes with the guardians’ day-to-day socio-economic activities reducing the families’ income. When they become children with untreated OAE may not be able to contribute to the family income or take care of older family members.

OAE only occurs in remote rural regions of Africa, where people with epilepsy often have no continuous access to antiepileptic treatment or to basic care for epilepsy-associated complications such as burn wounds. Local health care workers are often not sufficiently trained to treat persons with epilepsy, and there are virtually no neurologists. Moreover, children with epilepsy risk being deprived of education. In many cultures in Africa, there is a belief that persons with epilepsy are possessed by evil spirits and the entire family may suffer from social isolation through stigmatization.\cite{55}

By reducing the disease burden of OAE, the socio-economic status of affected families in Africa will be positively affected, which in turn will ultimately benefit society as a whole. In certain communities in onchocerciasis-endemic regions, ivermectin treatment coverage remains suboptimal. If we can prove that ivermectin can reduce the incidence of epilepsy in onchocerciasis-endemic regions this will

---

**Epilepsia Open, 2(2):145–152, 2017**

doi: 10.1002/epi4.12054
increase the willingness of populations to carefully take the ivermectin every year and will motivate public health officials and funders to strengthen CDTi programs. Ivermectin once a year may not be enough to protect a population against OAE because microfilariae may reappear several months after the intake of the drug. In addition, options of providing treatments of a shorter duration may also be explored. This may ultimately lead to the elimination of onchocerciasis and potentially OAE.

**Policy Implications**

Immediate action is needed because OAE is catastrophic for entire villages in many remote onchocerciasis-endemic regions. OAE policy plans are required and should include the following activities. Of course, these could also be of benefit for other types of epilepsies (Fig. 3).

1. An epilepsy surveillance system using trained community health workers. Such a system is important for public health officials not only for planning interventions and resource needs but also for improving patient care. It could be set up by using the CDTi distributors.

2. When a person with seizures is found in a village, the local CDTi distributor needs to inform and report by text message to a local health care worker who has been trained to diagnose and treat epilepsy. First, an acute cause of seizures (such as encephalitis/meningitis, metabolic disturbances or intoxications) should be excluded, according to the Mental Health GAP guidelines. If there is no reason to suspect an acute cause and the diagnosis of epilepsy is confirmed, common underlying causes such as birth asphyxia and trauma, head injury, history of infection of the brain, and family history of seizures should be explored by taking the patient’s history and doing a complete neurological examination. In remote onchocerciasis-endemic regions, persons often present with seizures of many years without any evidence for a concomitant acute or progressive chronic disease or for a focal neurological deficit. Such an individual could be treated with antiepileptic drugs (AEDs) without performing additional tests. Whether a positive Ov16 antibody test could be useful in the work-up of epilepsy in onchocerciasis-endemic regions to decide whether a person should be transferred to a specialized center to exclude other causes of the epilepsy needs to be investigated.

3. Patients with OAE should receive uninterrupted treatment with good-quality AEDs, and treatment adherence should be monitored. First, the setup of such a system requires the decentralization of epilepsy services. Second, uninterrupted access to AEDs at lower-level health units is needed using a public health approach with simplified low-cost and child-appropriate antiepileptic treatment regimens. Last, this process requires a task shift: the care of patients with OAE, after diagnosis, could be managed by primary health care workers assisted if necessary by medical doctors or neurologists. Training manuals are needed for these health care workers, school teachers need to be taught how to work with children with OAE, and a program to prevent and treat burns in children with OAE needs to be elaborated.

4. There is an obvious need for a program to prevent OAE by strengthening CDTi programs. Health zones with low ivermectin coverage need to be identified and reasons for low coverage need to be investigated. Some individuals are not taking ivermectin because they are not well informed about the drug’s benefits and because they are afraid of the side effects. Therefore, a community
program to raise awareness and address misconceptions is needed to increase the coverage of ivermectin and to fight epilepsy-associated stigma and discrimination. This could be done through health education and a community mobilization program involving persons who suffered from epilepsy in the past but who now are living normal lives thanks to AEDs and onchocerciasis treatment.

Challenges to obtaining optimal coverage by ivermectin include poverty, ignorance, insecurity, and war. Most of the successes with mass drug administration to eliminate onchocerciasis have been observed in countries and communities with higher living standards, such as in South America. Therefore, the eradication of onchocerciasis will require efforts beyond an entirely pharmacologic intervention to include strengthening of the health care system and a comprehensive socioeconomic and political approach.

CONCLUSION

Onchocerca volvulus is a neglected disease that occurs in remote areas in Africa and that affects very poor populations. The incidence of OAE could be significantly reduced by strengthening onchocerciasis control programs. The suffering of individuals with OAE and affected families could be reduced by timely antiepileptic treatment. To implement such a policy, partnerships among scientists, affected communities, advocacy groups, health care workers, Ministries of Health, WHO, nongovernmental organizations, the pharmaceutical industry, the tech industry and funding organizations are needed.

ACKNOWLEDGMENTS

The work of R Colebunders is funded by an ERC grant (No. 671055). R. Idro is supported by a MRC grant reference: MR/M025489/1, which is jointly funded by the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement and is also part of the EDCTP2 program supported by the European Union.

DISCLOSURE

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

REFERENCES

1. Ngugi AK, Kariuki SM, Bottomley C, et al. Incidence of epilepsy: a systematic review and meta-analysis. Neurology 2011;77:1005–1012.
2. Paul A, Adeloye D, George-Carey R, et al. An estimate of the prevalence of epilepsy in sub-Saharan Africa: a systematic analysis. J Glob Health 2012;2:020405.
3. Ngugi AK, Bottomley C, Kleinschmidt I, et al. Prevalence of active convulsive epilepsy in sub-Saharan Africa and associated risk factors: cross-sectional and case-control studies. Lancet Neurol 2013;12:253–263.
4. World Health Organization. Investing to overcome the global impact of neglected tropical diseases. Third WHO report on neglected tropical diseases. 2015. Available at: http://apps.who.int/iris/bitstream/10665/152781/1/9789241564861_eng.pdf?ua=1. Accessed January 8, 2016.
5. Duke BO. Human onchocerciasis—an overview of the disease. Acta Leidens 1990;59:9–24.
6. Njamshii AK, Zoung-Kanyi Bissek A-C, Etya’aale D. Onchocerciasis: neurologic involvement. In: Bentivoglio M, Cavalier EA, Kristensson K, Patel NB (Eds) Nelected tropical diseases and conditions of the nervous system. New York, NY: Springer Science+Business Media; 2014:147–164.
7. Casis Sacre G. El síndrome epileptico y sus reacciones con onchocercosis. Boletin de Salubridad e Higiene 1938;1:11–31.
8. Boussinesq M, Pion SD, Demanga N, et al. Relationship between onchocerciasis and epilepsy: a matched case-control study in the Mbam Valley, Republic of Cameroon. Trans R Soc Trop Med Hyg 2002;96:537–541.
9. Colebunders R, Tepage F, Rood E, et al. Prevalence of river epilepsy in the Orientale Province in the Democratic Republic of the Congo. PLoS Negl Trop Dis 2016;10:e0004478.
10. Kaiser C, Rubaale T, Tukesa E, et al. Association between onchocerciasis and epilepsy in the Itwara hyperendemic focus, West Uganda: controlling for time and intensity of exposure. Am J Trop Med Hyg 2011;85:225–228.
11. Prischich F, De RM, Bruno F, et al. High prevalence of epilepsy in a village in the Littoral Province of Cameroon. Epilepsia Res 2008;82:200–210.
12. Kaiser C, Kipp W, Asaba G, et al. The prevalence of epilepsy follows the distribution of onchocerciasis in a West Ugandan focus. Bull World Health Organ 1996;74:361–367.
13. Pion SD, Kaiser C, Boutrous-Toni F, et al. Epilepsy in onchocerciasis endemic areas: systematic review and meta-analysis of population-based surveys. PLoS Negl Trop Dis 2009;3:e461.
14. Druet-Cabanac M, Boussinesq M, Dongmo L, et al. Review of epidemiological studies searching for a relationship between onchocerciasis and epilepsy. Neuroepidemiology 2004;23:144–149.
15. Druet-Cabanac M, Preux PM, Bouteille B, et al. Onchocerciasis and epilepsy: a matched case-control study in the Central African Republic. Am J Epidemiol 1999;149:565–570.
16. Jilek WG, Jilek-Aall LM. The problem of epilepsy in a rural Tanzanian tribe. Afr J Med Sci 1970;1:305–307.
17. Jeliffe DB, Jones PR, Stroud CE. Nakalanga notes on the endemic dwarfism of Uganda. Trop Geogr Med 1962;14:97–104.
18. Foltz JL, Makumbi I, Sejvar JJ, et al. An epidemiologic investigation of the distribution of onchocerciasis in a west Ugandan focus. Trans R Soc Trop Med Hyg 1998;92:236.
19. Gerrits C. A West African epilepsy focus. Lancet 1983;1:358.
20. Kaiser C, Benninger C, Asaba G, et al. Clinical and electro-clinical classification of epileptic seizure in west Uganda. Bull Soc Pathol Exot 2000;93:255–259.
21. Newell ED, Vyugimana F, Bradley JE. Epilepsy, retarded growth and onchocerciasis, in two areas of different endemicity of onchocerciasis in Burundi. Trans R Soc Trop Med Hyg 1997;91:525–527.
22. Duke BO. Onchocerciasis, epilepsy and hyposexual dwarfism. Trans R Soc Trop Med Hyg 1998;92:236.
23. Tumwine JK, Vandemaële K, Chungong S, et al. Clinical and epidemiologic characteristics of nodding syndrome in Mundri County, southern Sudan. Afr Health Sci 2012;12:242–248.
24. Foltz JL, Makumbi I, Sejvar JJ, et al. An epidemiologic investigation of potential risk factors for nodding syndrome in Kitgum District, Uganda. PLoS ONE 2013;8:e66419.
25. Colebunders R, Mandro M, Mokili JI, et al. Risk factors for epilepsy in Bas-Uele Province, Democratic Republic of the Congo: a case-control study. Int J Infect Dis 2016;49:1–8.
26. Konig R, Narsi S, Meinl M, et al. The role of Onchocerca volvulus in the development of epilepsy in a rural area of Tanzania. Parasitology 2010;137:1559–1568.
27. Hissette J. Memoire sur l’Onchocercose volvulus. Ann Soc Belg Med Trop 1932;12:433–529.
28. Mazotti L. Presenza di microfilari di Onchocerca volvulus nel li-uido cefalorraquideo di enfermos tratados con Hetrazan. Rev Inst Salubr Enferm Trop 1959;9:1–5.
29. Duke BO, Vincellette J, Moore PJ. Microfilariae in the cerebrospinal fluid, and neurological complications, during treatment of onchocerciasis with diethylcarbamazine. *Tropenmed Parasitol* 1976;27:123–132.

30. Johnson TP, Tyagi R, Lee PR, et al. Nodding syndrome may be an autoimmune reaction to the parasitic worm *Onchocerca volvulus*. *Sci Transl Med* 2017;9:eaa6953

31. Idro R, Opak B, Wamala J, et al. Is nodding syndrome an *Onchocerca volvulus*–induced neuroinflammatory disorder? Uganda’s story of research in understanding the disease. *Int J Infect Dis* 2016;45:112–117.

32. O’Hanlon SJ, Slater HC, Cheke RA, et al. Model-based geostatistical mapping of the prevalence of *Onchocerca volvulus* in West Africa. *PLoS Negl Trop Dis* 2016;10:e0004328.

33. Colebunders R, Irani J, Post R. Nodding syndrome—we can now prevent it. *Int J Infect Dis* 2016;44:61–63.

34. Eisenbarth A, Achukwi MD, Renz A. Ongoing transmission of *Onchocerca volvulus* after 25 years of annual ivermectin mass treatments in the Vina du Nord River Valley, in North Cameroon. *PLoS Negl Trop Dis* 2016;10:e0004392.

35. Kamuyu G, Bottomley C, Mageto J, et al. Exposure to multiple parasites is associated with the prevalence of active convulsive epilepsy in sub-Saharan Africa. *PLoS Negl Trop Dis* 2014;8:e2908.

36. Zoure HG, Noma M, Tekle AH, et al. The geographic distribution of onchocerciasis in the 20 participating countries of the African programme for onchocerciasis control: (2) pre-control endemicity levels and estimated number infected. *Parasit Vectors* 2014;7:326.

37. Hopkins AD. Neglected tropical diseases in Africa: a new paradigm. *Int Health* 2016;8(Suppl 1):i28–i33.

38. Spencer PS, Mazumder R, Palmer VS, et al. Environmental, dietary and case-control study of Nodding Syndrom in Uganda: a post-measles brain disorder triggered by malnutrition? *J Neurol Sci* 2016;369:191–203.

39. Kamgno J, Pion SD, Boussinesq M. Demographic impact of epilepsy in Africa: results of a 10-year cohort study in a rural area of Cameroon. *Epilepsia* 2003;44:956–963.

40. Colebunders R, Hendy A, Mokili JL, et al. Nodding syndrome and epilepsy in onchocerciasis endemic regions: comparing preliminary observations from South Sudan and the Democratic Republic of the Congo with data from Uganda. *BMJ Res Notes* 2016;9:182.

41. Wamala JF, Malimbo M, Tepage F, et al. Nodding syndrome may be only the ears of the hippo. *PLoS Negl Trop Dis* 2015;9:e0003880.

42. Dowell SF, Sejvar JJ, Riek L, et al. Nodding syndrome. *Emerg Infect Dis* 2013;19:1374–1384.

43. Sejvar JJ, Kakooza AM, Foltz JL, et al. Clinical, neurological, and electrophysiological features of nodding syndrome in Kitgum, Uganda: an observational case series. *Lancet Neurol* 2013;12:166–174.

44. Idro R, Opoka RO, Anayu HT, et al. Nodding syndrome in Ugandan children—clinical features, brain imaging and complications: a case series. *BMJ Open* 2013;3:e002540.

45. Colebunders R, Titulaer MJ. Nodding syndrome: preventable and treatable. *Sci Transl Med* 2017;9:eaaam532.

46. Marshal AJ, Cherry JK. Endocrine dysfunction in a Nakalanga dwarf. *Trans R Soc Trop Med Hyg* 1961;55:188–191.

47. Raptop AB, Ladkin RG. Endemic dwarfism in Uganda. *East Afr Med J* 1950;27:339–359.

48. Kipp W, Burnham G, Bamuhiga J, et al. The Nakalanga syndrome in Kabalore District, Western Uganda. *Am J Trop Med Hyg* 1996;54:80–83.

49. Oomen AP. Onchocerciasis in Kaffa Province of Ethiopia. *Trop Geogr Med* 1967;19:231–246.

50. Colebunders R, Hendy A, van Oijen M. Nodding syndrome in onchocerciasis endemic areas. *Trends Parasitol* 2016;32:581–583.

51. World Health Organization. International Scientific Meeting on Nodding Syndrome, Kampala, Uganda, 2012. Available at: http://www.who.int/neglected_diseases/diseases/NoddingSyndromeKampala_Report_2012.pdf. Accessed January 8, 2016.

52. Ivengar PJ, Wamala J, Raito J, et al. Prevalence of nodding syndrome—Uganda, 2012–2013. *MMWR Morb Mortal Wkly Rep* 2014;63:603–606.

53. Golden A, Faulx D, Kalnoky M, et al. Analysis of age-dependent trends in Ov16 IgG4 seroprevalence to onchocerciasis. *Parasit Vectors* 2016;9:338.

54. Nakigudde J, Mutamba BB, Bazez Y, et al. An exploration of caregiver burden for children with nodding syndrome (lucluc) in Northern Uganda. *BMC Psychiatry* 2016;16:255.

55. Rafael F, Houinato D, Nubukpo P, et al. Sociocultural and psychological features of perceived stigma reported by people with epilepsy in Benin. *Epilepsia* 2010;51:1061–1068.

56. World Health Organization. mhGAP Intervention Guide. 2016. Available at: http://www.who.int/mental_health/mhgap/en/. Accessed January 8, 2016.

57. Njamnshi AK. Nonphysician management of epilepsy in resource-limited contexts: roles and responsibilities. *Epilepsia* 2009;50:2167–2168.

58. Hopkins A. Beyond providing drugs: the Mectizan donation stimulates new strategies in service delivery and in strengthening health systems. *Curr Pharm Biotechnol* 2012;13:1110–1119.