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River Epilepsy—A Preventable Form of Epilepsy

Effect of Onchocerciasis Elimination Measures on the Incidence of Epilepsy in Maridi, South Sudan: A 3-Year Longitudinal, Prospective, Population-Based Study.

Jada SR, Amaral LJ, Lakwo T, Carter JY, Rovarini J, Bol YY, Logora MY, Hadermann A, Hopkins A, Fodjo JNS, Colebunders R. *Lancet Glob Health*. 2023;11(8):e1260-e1268. doi:10.1016/S2214-109X(23)00248-6. PMID: 37474232.

Background: High onchocerciasis transmission predisposes endemic communities to a high epilepsy burden. The 4.4% epilepsy prevalence documented in 2018 in Maridi, South Sudan, prompted the strengthening of onchocerciasis elimination measures. Community-directed treatment with ivermectin was implemented annually in 2017, 2018, and 2019, interrupted in 2020, and re-implemented biannually in 2021. We aimed to assess the effect of these interventions, along with slash and clear vector control on the incidence of epilepsy, including nodding syndrome. Methods: In this longitudinal, prospective, population-based study, we did a two-stage house-to-house epilepsy survey before (May 10-30, 2018) and after (March 9-19, 2022) the strengthening of onchocerciasis elimination interventions in South Sudan. Strengthening also included the implementation of a community-based slash and clear vector control method that we initiated in 2019 at the Maridi dam (the main blackfly breeding site). Eight sites were surveyed near the Maridi dam and inclusion required residence in one of these sites. All household residents were first screened by community workers, followed by confirmation of the epilepsy diagnosis by trained clinicians. The primary outcome was epilepsy incidence, including nodding syndrome, which was assessed via self-reported new-onset epilepsy in the previous 4 years of each survey, confirmed by clinician assessment. Findings: The preintervention survey included 17 652 people of whom 736 had epilepsy (315 female and 421 male), and the post-intervention survey included 14 402 people of whom 586 had epilepsy (275 female and 311 male). When biannual community-directed treatment with ivermectin was initiated in 2021, the intervention's coverage rose by 15.7% (95% CI 14.6-16.8); although only 56.6% of the population took ivermectin in 2021. Between 2018 and 2022, epilepsy incidence decreased from 348.8 (307.2-395.8) to 41.7 (22.6-75.0) per 100 000 person-years. Similarly, the incidence of nodding syndrome decreased from 154.7 (127.6-187.3) to 10.4 (2.7-33.2) per 100 000 person-years. The identified risk factors for epilepsy were: living closer to the Maridi dam, being aged between 6 and 40 years, not taking ivermectin, and being male. Interpretation: In onchocerciasis-endemic areas with high epilepsy prevalence, strengthening onchocerciasis elimination interventions can decrease the incidence of epilepsy, including nodding syndrome. Additional efforts are needed to increase community-directed treatment with ivermectin coverage and sustain blackfly control in Maridi.

Commentary

Many readers might not have heard of river epilepsy. We are more familiar with the term river blindness. Both conditions are caused by the human parasitic nematode, *Onchocerca volvulus*.

While responsible for a small percentage of epilepsy cases worldwide, any cause of epilepsy that is preventable is of considerable importance in the context of the goals of the Intersectoral Global Action Plan for epilepsy and neurological disorders (IGAP)—to reduce or prevent the burden of epilepsy and neurological disease worldwide. The Global Burden of Disease Study estimated that in 2017 there were at least 20.9 million people infected worldwide with Onchocerca.[1] There are no clear estimates of Onchocerca-associated epilepsy (OAE). However, the prevalence of epilepsy in Onchocerca endemic areas is up to 7.8%. In one rural city in South Sudan with high Onchocerca exposure rates, up to 50% of families had at least one child with epilepsy.[2]

There is strong epidemiological evidence linking Onchocerca to epilepsy and Nodding syndrome (NS).[3] The phenotype of OAE includes tonic–clonic or focal unaware seizures, electroencephalogram (EEG) with focal or multifocal epileptiform discharges, and magenetic resonance imaging (MRI) with cortical or cerebellar atrophy.[4,5]

NS is an epileptic encephalopathy seen in children of ages 3 to 18 (peak 11-13 years) with generalized tonic–clonic, absence and clusters of atonic seizures ("nodding"), and is seen only in Onchocerciasis.[5] The cause of NS has long been controversial. In a collaboration between the Uganda Ministry of Health and the National Insititutes of Health/Centers for Disease Control and Prevention (NIH/CDC) in 2021, a representative family of 8 of whom 3 had NS, were brought to the NIH and extensively tested for alternative causes with none found, including whole exome screening.[6] NS is now considered to be in the spectrum of OAE.

We may think that OAE is too far away to be relevant in first world countries—however, with increasing human migration due to climate change and war, being familiar with these diseases grows in importance. Adult Onchocerca worms in humans can live for 10 to 15 years and may be present in migrants or visitors from endemic areas. In addition, as humanitarian neurologists, we need to show interest and support for global neurology.

In this prospective population-based study in South Sudan, the authors examined the effect of Onchocerca elimination measures including community-based mass drug administration (MDA) with Ivermectin and vector control "slash and clear" on the incidence of OAE and NS around the Maridi Dam area of South Sudan.[7] In an informative supplementary video, we see that the Maridi Dam area is a verdant agricultural rural area with a high prevalence of OAE. As the population is Muslim, neurocysticercosis was not a competing cause of epilepsy.

To deliver an effective elimination program, we need to understand the life cycle of the parasite. Onchocerciases is endemic in west and central Africa and is also present in Yemen and Latin America. Humans are the sole reservoir and blackflies are the vector. Blackflies are also present in the USA (known as "buffalo knats"), Canada, and Eastern Europe, although in these regions they are associated with transmission of zoonotic rather than human disease. Blackflies breed best near fast flowing rivers where their larvae develop and hatch in river vegetation.

The Blackfly blood meal allows both the uptake and deposition of Onchocerca larvae, to transmit them from human to human. One cannot contract Onchocerca from person-to-person contact. Larvae aggregate into nodules under the skin where they mature over 12 months and have a mean life span of 12 to 15 years. If females are fertilized by males, up to 1500 microfilariae (MF) per day form and can migrate from nodules to other tissues such as skin, eyes, lymphatics, and rarely are thought to cross the blood–brain barrier. While MF have been found in cerebrospinal fluid, they have not been found in brain, so the mechanism of epileptogenesis is poorly understood, and is thought to be immune mediated. People with OAE have high MF densities reflecting higher disease burden. Time from infection to development of clinical symptoms can be 1 to 3 years; a prolonged exposure up to 3 years and many blackfly bites with increasing MF burden is necessary to develop Onchocerca associated disease.

What can be done to prevent OAE? MDA with ivermectin has proven to be effective at reducing the incidence of Onchocerca transmission and reduce the seizure burden in at risk populations. Ivermectin reduced seizure frequency by 74% to 100% in 215 patients, comparing before and 3 to 5 months after ivermectin.[2]

However, ivermectin does not kill adult worms (it decreases worm fertility and kills the MF) so treatment needs to be repeated yearly for 12 years or more (the reproductive life of the worm). Without ivermectin, MF loads increase over time, leading to complications such as epilepsy when the children reach an older age. Ivermectin is safe—we give it to our children for the treatment of scabies, a common parasitic disease endemic in people worldwide including the United States.

The slash and clear vector control (manual removal of vegetation in running water that allows the blackfly larvae to hatch, as shown in the video) was very effective with reduction in blackfly bites of >99%, sustained with 6 monthly repeat. In this study, to ascertain the biting rate in the area, teams of human "catchers" worked from 6 am to 6 pm 4 times a month catching flies that landed on them in a specimen jar, extrapolated to a monthly biting rate.

The authors conducted door to door surveys before and after an Onchocerca elimination program in May 2018 and March 2022. Standardized detailed questionnaires were collected which included epilepsy history and risk factors, age of onset, cognitive impairment, Rankin scale, family history, proximity to the water source, and treatment with ivermectin in the prior year. Characteristics of OAE were available for 1322 patients across the 2 surveys. In the 2022 survey, of 586 people with epilepsy, only 42 had either an alternative or adult-onset epilepsy, or insufficient information for OAE. The primary outcome was the incidence of new epilepsy or NS in the 4 years preceding each survey, by a validated screening tool for epilepsy. Each epilepsy case was verified by a medical professional and fulfilled International League Against Epilepsy (ILAE) criteria.

They found a baseline incidence of epilepsy before intervention of 348.8 per 100 000 person years and 154.7 per 100 000 person years for probable NS. After MDA and slash and clear vector control, there was a marked reduction in epilepsy incidence to 41.7 per 100 000 person years and NS to 10.4 per 100 000. Those who did develop epilepsy had not taken ivermectin, and 11/12 met criteria for OAE. Seroprevalence of the Ov16 antibody for onchocerciasis was reduced and less cognitive impairment or disability was reported. In a multivariate analysis, epilepsy was associated with male gender, age 6 to 40 years, not taking ivermectin, and living close to breeding sites.

It is not possible to separate out the individual effects of the MDA and vector control, but it is likely both were effective. Some confounding factors exist including the difficulty in obtaining accurate epilepsy histories from the rural population due to social stigma and recall bias, competing risks, and loss to follow-up. In addition, they showed that the proportion of those on anti-seizure medications increased by 39.7% between the

two surveys, and seizure free patients might not have been reported as epilepsy. The prevalence of OAE and NS was reduced but did not reach statistical significance; it is likely a longer follow-up would be required to identify this. The observed decrease in NS prevalence over time could reflect higher mortality associated with this disease. However, the authors have shown how a form of severe epilepsy could be prevented or even eliminated with application of understanding of the pathophysiology and population-based public health measures.

Further research is needed to understand epileptogenesis in OAE. The NSETHIO project, funded by the European Research Council, provides a multicountry long-term plan to study OAE and NS. Increased awareness of OAE with initiation and promotion of Onchocerca elimination measures is essential to eradicate this preventable form of epilepsy.

Peter Widdess-Walsh, MB, FRCPI
Neurology Day Unit,
Beaumont Hospital

ORCID iD

Peter Widdess-Walsh http://orcid.org/0000-0003-4217-2575

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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