Onchocerciasis and epilepsy: a causal relationship?

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Epilepsy caused by infectious agents is a potentially preventable disease; however, the aetiological relationships between these agents and epilepsy are complex. In the 1930s, Guillermo Casis Sacre observed[1] that many of his patients in rural Mexico who had onchocerciasis also had what appeared to be epilepsy. Therefore, he hypothesised that the *Onchocerca volvulus* parasite also affected the brain and not just the skin and eyes, as previously thought. Since his early hypothesis, many cross-sectional and case-control studies have documented an association between onchocerciasis and epilepsy. However, more definitive longitudinal studies have been scarce.

In *The Lancet Infectious Diseases*, Cédric Chesnais and colleagues[2] report the results of a longitudinal study examining the relationship between onchocerciasis and the development of suspected epilepsy later in life. Their study began in 1991–93, when they measured microfilarial densities (MFDs) by corneoscleral skin punch in children from 25 villages in Cameroon. During follow-up in 2017, in seven of those 25 villages, epilepsy history was ascertained from the individual or a family member for an impressive 85% of the 856 individuals initially surveyed in those villages in the early 1990s. The adjusted incidence ratio for developing epilepsy in individuals with detectable MFDs was 7·07 (p=0·053; 95% CI 0·98–51·26) in individuals with initial MFD of one to five microfilariae per skin snip (mf per snip), 11·26 (2·73–46·43) for six to 20 mf per snip, 12·90 (4·40–37·83) for 21–50 mf per snip, 20·00 (3·71–108·00) for 51–100 mf per snip, 22·58 (3·21–158·56) for 101–200 mf per snip, and 28·50 (p=0·001; 95% CI 3·84–211·27) for more than 200 mf per snip, compared with that of individuals without detectable densities of skin microfilariae.

Not only was a positive skin snip associated with risk of subsequent epilepsy, establishing a temporal order, but there was also a dose-response relationship between individual and community-level microfilarial density and the risk of epilepsy. The authors estimated that if onchocerciasis was eliminated in these communities, more than 90% of suspected cases of epilepsy could also be eliminated.

These are very compelling findings. However, it should be noted, as the authors point out, that the pathophysiological mechanism underlying this relationship is not well understood. For example, epilepsy might possibly result from a direct effect of microfilarial infestation on the CNS or an indirect autoimmune reaction.[3,4]

There are also some methodological issues that should be considered. First, the observational design of the study leaves open the possibility of uncontrolled confounding, which might have led to an overestimation of epilepsy risk. Nevertheless, because of the strong association between onchocerciasis and epilepsy and the dose-response relationship shown in this prospective study, it seems unlikely that unmeasured confounders would completely attenuate the high magnitude risk ratios reported. Second, the use of MRI would have been useful to differentiate epilepsy due to other competing causes, such as neurocysticercosis or non-infectious causes. Other researchers have proposed that neurocysticercosis might be the actual culprit in some cases of what is thought to be onchocerciasis-related epilepsy, because *Taenia solium* is co-endemic with *O volvulus* in much of sub-Saharan Africa.[5] Although this possibility has been controversial,[6] the only way to be more certain is to do a study using imaging.[7] MRI is, unfortunately, not feasible clinically in many low-resource settings, but it might be possible to use in research.

More broadly, the study by Chesnais and colleagues underscores (with less susceptibility to bias) the potential benefits that eliminating onchocerciasis could have on the incidence of epilepsy in endemic areas. The path towards onchocerciasis elimination in sub-Saharan Africa will require improving the effectiveness of mass drug administration and enhancing blackfly control.[8] Additionally, addressing the epilepsy treatment gap in sub-Saharan Africa is crucial. Although there have been major strides in strengthening primary care infrastructure and increasing access to antiretroviral treatment for HIV in many places, access to neurological care in rural sub-Saharan Africa remains minimal or non-existent. There is an urgent need to increase the number of health-care workers who are capable of diagnosing and treating epilepsy and to ensure access to antiepileptic drugs.[9] The epilepsy treatment gap in sub-Saharan Africa is especially complicated by the destructive social stigma associated with the condition,

undermining diagnosis and treatment and negatively affecting nearly every aspect of life for a person living with epilepsy,[10] which must also be addressed.

This study is an important milestone in elucidating the relationship between onchocerciasis and epilepsy, which should attract the attention of policy makers and funders who are able to make onchocerciasis elimination and closing the epilepsy treatment gap a reality in sub-Saharan Africa. As the authors point out, it will be important to replicate these findings in other settings of high endemicity; however, we also hope that such a study will use MRI, which will help to further elucidate the onchocerciasis-epilepsy relationship.

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