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Editorial

Onchocerciasis associated epilepsy—A question of causality

Recently there have been many studies reporting the detection of a high prevalence of epilepsy in areas that are hyperendemic for onchocerciasis. In many of these studies, including the manuscript by Mukendi and colleagues in this issue of *International Journal of Infectious Diseases* a positive association between past or current infection with onchocerciasis has been found. However, not all studies have found such an association. An earlier meta-analysis did not find a statistically significant association (Druet-Cabanac et al., 2004). More recent meta-analyses have generally affirmed the association between onchocerciasis and epilepsy (Kaiser et al., 2013; Pion et al., 2009), but only after pooling data from heterogeneous studies that have used varying methodologies to diagnosis both exposure and outcome. In some cases, including this current study and one of the previously published meta-analyses (Kaiser et al., 2013), the association weakens or disappears when controlling for potential confounders which suggests that confounders may explain part or all of the association. One recent retrospective case-control study found a dose response between a single measurement of microfilarial density in the skin and the development of epilepsy over a period of follow-up of up to 26 years (Chesnais et al., 2018). Unfortunately, the numbers were small, no information about potential confounders was available, and there was potential for misclassification of the outcome as the diagnosis of epilepsy was not confirmed by a neurologist. Although retrospective case-control studies cannot establish causality and no pathophysiologic mechanism has been described which explains how onchocerciasis causes epilepsy, the finding of a potential dose response will keep the debate about causality alive.

Why are confounders important? A confounder is a factor that is associated both with the exposure of interest and the outcome, but that has a causal relationship for the outcome (Rothman and Greenland, 1998). Thus if a confounder explains part or all of an association, it would be more appropriate to target the confounder alone, if there is no causal role for the exposure of interest, or both the confounder and the exposure of interest, if both play a causal role. There are many other causal factors that could be confounding the association between onchocerciasis and epilepsy which could be common in areas that are typically missed by national health programmes due to lack of funds, instability of the area due to conflict, or remoteness of the area. These known causal factors associated with symptomatic seizures include malnutrition, vitamin deficiency, metabolic and electrolyte abnormalities, birth trauma, head trauma, parasitic infections (e.g. neurocysticercosis, cerebral malaria, and toxocariasis) and other infections (e.g. viral and bacterial meningitis and encephalitis), toxins (e.g. heavy metals and hypoglycin in akee fruit), and genetic disorders. Chief among these, and germane to the issue of epilepsy in areas that are hyperendemic for onchocerciasis, are infectious etiologies and head trauma, both very prevalent in sub-Saharan Africa and major causes of symptomatic seizures (Ba-Diop et al., 2014; Bruns and Hauser, 2003; Preux and Druet-Cabanac, 2005). Unfortunately, we know little about the distribution of the factors as well. However, these are often not measured (or cannot be measured) in studies of the association between onchocerciasis and epilepsy in hyperendemic areas or assumptions about their distribution are made based on the limited data currently available. The distribution of focal exposures, such as toxins or infectious agents, really cannot be assumed to be true across large areas. The lack of an association in one site in Cameroon between a positive serological test for neurocysticercosis and epilepsy (Elliott et al., 2013) cannot necessarily be extrapolated to an area in the Democratic Republic of Congo, particularly when cysticercosis is a known cause of epilepsy and studies in Africa have consistently affirmed that relationship (Quet et al., 2010). In focal studies, like the one in this journal, a thorough exploration of confounders is needed. The authors did control for a limited number of potential risk factors for epilepsy (e.g. birth trauma) in a multivariate analysis that failed to find an association between Ov16 positivity (a marker for onchocerciasis) and epilepsy. None of the known causal factors evaluated were found to have an association either. The factors that were associated epilepsy were ivermectin use and body weight.

Nonetheless, this study is important. It has identified an area where the onchocerciasis programme is failing to convince enough of the population to take ivermectin to stop the transmission of onchocerciasis. Survey determined coverage of ivermectin treatment was only 55%, which is below the minimally effective target for interruption of transmission (WHO, 2018). Eight percent of children between the ages of 7 and 10 years had detectable antibodies to Ov16. This clearly demonstrates that active transmission is ongoing. This is an important observation and merits efforts to improve the situation. There are tools available that can be used to rapidly evaluate population adherence to ivermectin MDA and to search for root causes that need to be addressed. They can currently be found on the Neglected Tropical Diseases (NTDs) Support Center website (https://www.ntdsupport.org/resources/supervisors-coverage-tool and https://www.ntdsupport.org/resources/coverage-survey-builder-coverage-

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evaluations, accessed 16 January 2019). The study also identified a population that does not have access to the WHO-recommended package of care for epilepsy (https://www.who.int/mental_health/evidence/mhGAP/en/, accessed 16 January 2019). Less than 10% of people with epilepsy were taking medications to control seizures and more than 40% of people with epilepsy reported never having received such medications. A sound response to the problem with epilepsy in these underserved areas is not insurmountable. Countries have committed to strengthening their systems for epilepsy management in accordance with World Health Assembly resolution 68.20. There are low cost, efficacious treatments available for epilepsy whatever the etiology. A focused approach by ministries of health or supporting partners could help mitigate the problem of symptomatic seizures and have significant positive impact of the lives of the affected people. A better understanding of the distribution and determinants of epilepsy in sub-Saharan Africa might allow for more targeted prevention and treatment strategies, but developing this knowledge should not prevent scale-up of currently available treatment modalities. Neither improving treatment of onchocerciasis nor improving management of seizures requires additional studies or tools; those tools already exist.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the US Centers for Disease Control and Prevention or the World Health Organization.

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