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Onchocerciasis-associated epilepsy

In the context of the ongoing debate about the degree of responsibility of *Onchocerca volvulus* in human cases of epilepsy, Cédric Chesnais and colleagues support a relationship between *O volvulus* microfilariae and the development of epilepsy.[1] Regarding the causes that could trigger onchocerciasis-associated epilepsy, three mechanisms have been proposed: microfilariae present in the central nervous system, the human immune response, and sleep deprivation due to intense itching.[2] Different pathogenic capabilities of *O volvulus* strains, general concomitant viral, bacterial, or parasitic infections, genetic variation in how the body produces antibodies, and measles infection followed by malnutrition have also been considered as possible causes of onchocerciasis-associated epilepsy.[1–3]

Surprisingly, the major cause of pathogenicity associated with onchocerciasis, *Wolbachia* spp, the endosymbiont bacteria of *O volvulus*, has not been considered as a potential trigger of onchocerciasis-associated epilepsy. The worm might not be the direct culprit of the neurological disorders, but only the accomplice for harbouring the bacteria that, when released, could be a potential triggering factor for epilepsy. If onchocerciasis-associated epilepsy is mainly caused by the *Wolbachia* spp, then the virulence could be related to the different wolbachia supergroups or to bacterial burdens present in different *O volvulus* populations,[4] similar to what occurs in blindness caused by *O volvulus*, which depends on the wolbachia burden.

The hallmark of filarial pathogenesis is the inflammatory response of the host, provoked by the death of the parasite and the subsequent release of wolbachia. Extracts from *Brugia malayi* and *O volvulus* infected with *Wolbachia* spp induce inflammation, whereas extracts of rodent filariasis devoid of *Wolbachia* spp did not induce inflammation in rodent models.[5] In humans and in murine models, the release of bacteria has been shown to be associated to the upregulation of proinflammatory cytokines, such as tumour necrosis factor, and neutrophil recruitment.[6] Indeed, the immune system and its associated inflammatory reactions seem to have an important role in epileptogenesis.[7]

PCR tests done in cerebrospinal fluid (CSF) samples of patients with onchocerciasis-associated epilepsy did not identify *O volvulus* DNA so far. Considering that *Wolbachia* spp have a somatic tissue tropism able to invade the CNS (intracellularly and extracellularly),[8] the presence of *Wolbachia* spp DNA should be investigated in the CSF of patients with epilepsy.

There are contradictory results regarding the effectiveness of ivermectin in the decrease of onchocerciasis-associated epilepsy in other study areas.[9] If *Wolbachia* spp were indeed an epileptogenetic factor, larger loads of bacteria released after treatments were done during an onchocerciasis control programme could explain the unknown reason why epilepsy suddenly appeared in a region where onchocerciasis is likely to have been common for centuries.[3]

To confirm the role of *Wolbachia* spp in onchocerciasis-associated epilepsy, anti-wolbachia treatment should be administered in affected areas, therefore preventing the release of bacteria and the subsequent consequences that might ensue after treatment with anti-microfilarial drugs in microfilaria populations with high wolbachia burden.

A first step to ascertain the role of *Wolbachia* spp in onchocerciasis-associated epilepsy is being taken in Uganda by a study being done in 2016–19.[4] Therefore, unless the results of this study confirm otherwise, it seems opportune to consider *Wolbachia* spp as a potential cause of onchocerciasis-associated epilepsy.

I declare no competing interests.

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Authors' reply

We thank M Teresa Galán-Puchades for her interesting comments. In our study,[1] we considered the worms as a whole to be the relevant entity, because the cutaneous and ocular manifestations of onchocerciasis result from a combination of immune reactions against *Wolbachia* spp (mobilisation of neutrophils), and filarial antigens (mobilisation of eosinophils).[2] Consequently, it seemed artificial to consider the partners of this symbiotic relationship separately.

Galán-Puchades hypothesises that *Wolbachia* spp released during the natural death of *O volvulus* (adults or microfilariae) induce inflammatory processes that trigger epilepsy, which would indeed justify distinguishing wolbachia from the worm in our study. Should this hypothesis be true, the release of *Wolbachia* spp into the blood after treatment with diethylcarbamazine or ivermectin (a demonstrated occurrence)[3] would, as Galán-Puchades suggests, induce an epidemic of seizures after mass treatment with these drugs. However, such an event has never been reported with either drug, even in populations with extremely high microfilarial densities (eg, the Vina valley in northern Cameroon). On the contrary, a decrease in seizure frequency was reported after the first ivermectin distribution in the Kabarole focus, Uganda.[4] Furthermore, the nodding syndrome epidemic in northern Uganda, which Galán-Puchades refers to, started in 2000, whereas war in that region delayed mass ivermectin treatment until 2009. Some factors have been proposed[5] to explain the epidemic pattern of nodding syndrome in Uganda and South Sudan, but these hypotheses are difficult to test.

Galán-Puchades suggests that the inter-foci variability in prevalence and severity of onchocercal ocular manifestations is due to some parasite populations harbouring higher wolbachia burdens. A study[6] published in 2017, in different foci in four west-African countries, showed indeed that this burden can vary considerably between and within foci; however, this variability does not correlate with the ecotype of the focus, even though savanna onchocerciasis causes more blindness than forest onchocerciasis. These results certainly deserve to be complemented by analysis of parasites from areas where a strong association between onchocerciasis and epilepsy has been shown.

As mentioned by Galán-Puchades, a study is ongoing to determine whether doxycyline treatment leads to reduction in symptoms and perhaps reversal of the course of nodding syndrome in affected children. However, doxycycline mass treatment to prevent onchocerciasis-associated epilepsy or nodding syndrome, as Galán-Puchades recommends, does not appear feasible because this requires compliance with daily dosing for 5 weeks to achieve macrofilaricidal effects. Importantly, doxycycline is contra-indicated in children younger than 8 years, and the physio-pathogenic mechanisms that put children with high *O volvulus* microfilaridermia at higher risk of developing epilepsy probably appear before this age.

We declare no competing interests.

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Cefiderocol for treatment of complicated urinary tract infections

Co-trimoxazole, fluoroquinolones, and cephalosporins have been used to treat almost all kinds of complicated urinary tract infections, but this golden age has come to an end. Worldwide, an increase in resistant uropathogens, including those resistant to carbapenems, has been observed.[1,2]

Several new drugs or drug combinations are in development or have been made available, such as new or old cephalosporins or carbapenems combined with new or old β-lactamase inhibitors (ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam), new aminoglycosides (plazomicin), and new fluoroquinolones (finafloxacin).

Another new drug is cefiderocol, the first siderophore-antibiotic conjugate to reach late stage clinical testing, which was developed for treatment of complicated urinary tract infections.[3] Siderophore antibiotics bind to free iron and use the bacterial active iron transport channels to cross the outer membrane of Gram-negative bacteria and reach the periplasmic space. In