Onchocerciasis (river blindness) also induces river epilepsy (onchocerciasis-associated epilepsy)

Colebunders Robert, Amber Hadermann

Global Health Institute, University of Antwerp

Abstract:

Onchocerciasis, commonly known as river blindness, has historically been identified as a skin and eye disease; however, recent epidemiological investigations suggest a potential direct or indirect association with epilepsy. Onchocerciasis-Associated Epilepsy (OAE) (river epilepsy) is a neglected public health problem in many remote onchocerciasis endemic areas in Africa with sub-optimal onchocerciasis elimination programs. OAE manifests in previously healthy children aged 3 to 18 years old in the absence of any obvious cause for epilepsy and is marked by a diverse range of convulsive and non-convulsive seizure types including head nodding seizures (nodding syndrome). Various pathophysiological mechanisms have been proposed to explain OAE, yet conclusive evidence supporting any particular hypothesis is currently lacking. Recent studies showed that strengthening onchocerciasis elimination programs significantly reduced the incidence of OAE. Treating epilepsy in onchocerciasis endemic regions is challenging. More advocacy is needed to provide uninterrupted free access to anti-seizure medication to persons with epilepsy in these remote impoverished areas.

Abstract: Onchocerciasis (rivierblindheid) is gekend als een huid en oogziekte. Recent epidemiologisch onderzoek suggereert dat onchocerciasis ook direct of indirect epilepsie zou kunnen veroorzaken: Onchocerciasis-Associated Epilepsy (OAE) (rivierepilepsie) is een verwaarloosd volksgezondheidsprobleem in vele afgelegen onchocerciasis-endemische gebieden in Afrika met suboptimale onchocerciasis eliminatie programma's. OAE komt voor bij tevoren gezonde kinderen van 3 tot 18 jaar oud in afwezigheid van een duidelijke oorzaak voor epilepsie, en wordt gekenmerkt door een breed spectrum aan convulsieve en niet-convulsieve epilepsie aanvallen, waaronder hoofdknikaanvallen (nodding syndroom). Verschillende OAE pathofysiologische mechanismen werden voorgesteld, maar er is er nog geen enkel ervan bewezen. Recente studies hebben aangetoond dat het versterken van onchocerciasis eliminatie programmas de incidentie van OAE aanzienlijk deed verminderen. Het behandelen van epilepsie in onchocerciasis-endemische regio's is moeilijk. Er is meer pleitbezorging nodig om ononderbroken gratis toegang tot anti-epileptica te bieden aan mensen met epilepsie in deze afgelegen, verarmde gebieden.

1. Introduction

Onchocerciasis commonly known as river blindness is a neglected tropical disease caused by the filarial worm *Onchocerca volvulus* and is transmitted to humans through repeated bites of infected female black flies of the genius *Simulium* (1). Black flies lay their eggs in fast flowing rivers and streams, putting people living and farming near these rivers at risk of acquiring the infection. Their larvae develop on supports present in the water (stones/branches/leaves for *Simulium damnosum s.l.* and crabs for *Simulium naevei*). After the bite of the infected black fly, *O. volvulus* larvae invade the skin and develop into the adult female and male worms in the subcutaneous tissue. Adult worms reside in fibrous nodules in the subcutaneous tissue where they can live for approximately 10 to 15 years (1). During this period the female worm produces

millions of microfilariae, which migrate from the nodules to the skin, and eyes. Globally, 20.9 million people are infected with 99% of people living in sub Saharan Africa (1). Onchocerciasis is known as a disease of skin and eye but recent epidemiological studies also suggest that onchocerciasis directly or indirectly is able to induce epilepsy (2, 3). The standard treatment of onchocerciasis is ivermectin. However, because ivermectin only kills the microfilaria and not the adult worms, ivermectin needs to be distributed for 10 to 15 years, the average lifespan of the adult worms (1).

Onchocerciasis was initially controlled using insecticides (1). The Onchocerciasis Control Programme (OCP) was implemented in West Africa in 1974 and conducted vector control in 11 countries (1). By the time the program ended in 2002, onchocerciasis was effectively controlled in the covered areas (4). The African Programme for Onchocerciasis Control (APOC) was launched to extend the control efforts to other parts of Africa not covered by OCP, focusing on 19 countries where onchocerciasis was still endemic (5). The cornerstone of the APOC's strategy was mass distribution of ivermectin (Mectizan®) using a Community-Directed Treatment with Ivermectin (CDTI) approach (1, 6). However, to eliminate onchocerciasis, ivermectin needs to be distributed annually and preferentially bi-annually (six monthly) with a coverage of at least 80% (7).

2. Onchocerciasis-associated epilepsy.

2.1. History

The association between onchocerciasis and epilepsy was already observed by Casis-Sacre in Chiapas and Oaxaca, in Mexico, in 1938 (8). In 1960, Louise Jilek-Aall found a high prevalence of epilepsy in the Mahenge mountains, an onchocerciasis-endemic area in Tanzania (9). She suspected a link between onchocerciasis and epilepsy but her hypothesis was initially rejected by the international scientific community considering that the filarial nematode *O. volvulus* worm could not cross the blood-brain barrier (10).

In October 2015, with funding from the European Research Council, the NSETHIO consortium initiated a trans-disciplinary, multi-country research project to study the link between onchocerciasis and epilepsy (11).

In October 2017, a 1st International workshop on Onchocerciasis-Associated Epilepsy (OAE) took place in Antwerp, Belgium (12). Subsequently, numerous studies have investigated the connection between onchocerciasis and epilepsy (2). In December 2023, the 2nd International workshop on OAE was held in Antwerp to review the research progress since 2017 and to determine priority actions for research and interventions (3).

2.2. Clinical presentation
The characteristic feature of OAE are seizures appearing in previously healthy children aged 3 to 18 years old, in the absence of any other obvious cause for epilepsy, residing in an onchocerciasis meso- or hyper-endemic region (13, 14). Persons with OAE exhibit a wide spectrum of convulsive and non-convulsive seizure types including head nodding seizures (nodding syndrome) and Nakalanga syndrome. Nakalanga syndrome is marked by emaciation, stunting, delayed sexual development, cognitive impairment, facial dysmorphism and epilepsy (15). Nodding syndrome and Nakalanga syndrome represent the more severe forms of OAE (16). Different forms of epilepsy may coexist within one family (17).

2.3. The evidence for the association between onchocerciasis and epilepsy

Various epidemiological studies with different designs suggest that *O. volvulus* directly or indirectly may induce epilepsy (18).

1. **Case control studies**: A study in the Mbam valley, an onchocerciasis-endemic region in Cameroon, revealed more intense infections with *O. volvulus* in persons with epilepsy than in non-epileptic controls (19). There was a strong positive association between community microfilaria load and epilepsy prevalence (19). Additionally, an inverse relationship between villages' distance from the river (breeding site for blackfly vectors) and epilepsy prevalence was found (19). Similarly, in South Sudan, the highest epilepsy prevalence was observed among households living close to blackfly breeding sites, and these households families often had several children with OAE (17, 20). Only case control studies with methodological issues failed to confirm the associasion between onchocerciasis and epilepsy (21, 22).

2. **Population-based studies**: Surveys in onchocerciasis-endemic areas showed a positive association between *O. volvulus* prevalence and the prevalence of epilepsy (23). Epidemics of epilepsy emerged in onchocerciasis-endemic areas with no or little ivermectin distribution or where the onchocerciasis elimination programme had been interrupted (15, 18, 22). A meta-analysis of eight population-based studies before 2008 indicated that the epilepsy prevalence increased, on average, by 0.4% for each 10% increase in onchocerciasis prevalence (23, 24).

It was long considered that in West Africa there has never had been a high prevalence of epilepsy in onchocerciasis endemic areas. However, a meta-analysis of epilepsy prevalence in West-Africa conducted in 2020, showed a high prevalence of epilepsy in two onchocerciasis endemic villages in Ivory Coast of 5.8% in Akoungou and 4.1% in M'Brou with OAE features (73.7% and 83.3%, respectively). Both villages were located in a forest area where OCP was never implemented. A higher pre-control endemicity and a shorter duration of onchocerciasis control were both associated with increased epilepsy prevalence (25). This study suggested that before and during the early years of implementing onchocerciasis control in West Africa, high onchocerciasis endemicity resulted in a high prevalence of OAE and that subsequent control efforts significantly reduced the prevalence of OAE.

Before we started our research on onchocerciasis and epilepsy (NSETHIO project (11) in the Democratic Republic of Congo (DRC), this association was not known in this country. This project showed that OAE is a major public health problem in all investigated onchocerciasis endemic areas (11, 26-29). We believe, similar to the DRC, in West Africa OAE was not recognized in the pre-OCP area because the focus was on blindness. Therefore, the high prevalence of epilepsy, mainly among children and adolescents, was not noticed because of the absence of neurologists and researchers in remote onchocerciasis-endemic areas. Thanks to OCP, onchocerciasis was more rapidly controlled in West Africa than in Central and East Africa. Consequently, no OAE public health problem was observed in areas where OCP was implemented.

3. **Cohort studies**: Two cohort studies in Cameroon identified a temporal and microfilaria dose-dependent association was observed between the level of *O. volvulus* infection in early childhood and the development of epilepsy later in life (30).

4. **Laboratory studies**: Microfilaria have been observed in the cerebrospinal fluid (CSF) of persons with *O. volvulus* infection in studies conducted prior to introduction of CDTI (31, 32).

6. **Intervention studies**: Successful onchocerciasis elimination strategies, such as in northern and western Uganda, Mahenge, and Maridi, reduced the incidence of epilepsy, including nodding syndrome, in onchocerciasis-endemic regions. OAE ceased to appear once onchocerciasis was eliminated (Table 1).

Table 1. Studies demonstrating the ability of strengthening an onchocerciasis elimination program to reduce the incidence of epilepsy in onchocerciasis-endemic regions.

Study site	Intervention	Survey periods	Pre-intervention Epilepsy cases per 100,000 person-year	Post-intervention Epilepsy cases per 100,000 person-year
Northern Uganda [4]	Annual CDTi + vector control	2012 - 2017	1165 (95% CI: 621-2117)	130 (95% CI: 15-630)
Western Uganda (33)	CDTI + vector control	1994 - 2018	418 (95% CI: 265-626)	73 (95% CI: 32-114)
Mahenge, Tanzania [14]	Bi-annual CDTi high coverage	2017/2018 -2021	177.6 (121.2-258.5)	45.5 (22.2-89.7)
Maridi, South Sudan [15]	Bi-annual CDTi low coverage + "Slash & Clear" vector control	2018-2022	348.8 (95%CI: 307.2-395·8)	41.7 (95% CI:22.6-75.0)

CDTI = community directed treatment with ivermectin

2.4. OAE case definition
A simple, OAE case definition was proposed for epidemiological studies and to determine the OAE related burden of disease (14, 34, 35). This definition has proven useful in identifying epilepsy hotspots where onchocerciasis elimination programs are sub-optimal (36). However, due to limited specificity the definition should not be used for clinical decisions. An important criterion is excluding other obvious causes through history taking and clinical examination (14, 35). In the absence of neuroimaging, generally unavailable in onchocerciasis-endemic settings, certain other causes of epilepsy cannot be ruled out. For instance, in *Taenia solium*-endemic areas, using the OAE definition is problematic because neurocysticercosis cannot be excluded. Nevertheless, this definition can be valuable in onchocerciasis-endemic areas in South Sudan, where neurocysticercosis is unlikely as a cause of epilepsy due to the absence of pigs in most areas (20).

Box 1: Diagnostic criteria for OAE from onchocerciasis-endemic regions [48]

1.	History of two or more unprovoked seizures, at least 24 hours apart (ILAE* definition of epilepsy)
2.	Onset of epilepsy between 3 and 18 years of age
3.	Normal psychomotor development prior to epilepsy onset
4.	No obvious cause of epilepsy identified in the individual during the 5 years preceding seizure onset, such as perinatal brain insult, head trauma, or previous infection of the central nervous system
5.	At least 3 years of residence in an onchocerciasis-endemic village with high epilepsy prevalence** and frequent household clustering of persons with epilepsy

All five criteria must be met. Additional arguments in favour of OAE include a positive skin snip for *Onchocerca volvulus* microfilariae or seropositivity to Ov16 antigen confirming exposure to *O. volvulus*, head-nodding seizures and/or severe unexplained stunting with delayed or absence of external signs of sexual development, or presence of persons with such features in the village.

* ILAE: https://www.ilae.org/.

** An epilepsy prevalence threshold is not included because determining whether the point prevalence of epilepsy is above such a threshold would require conducting an epilepsy prevalence study, which can be complicated and costly or beyond what is feasible and may therefore lead to underreporting of OAE. However, if the epilepsy prevalence is known, a prevalence >2% should be considered as a high prevalence, given that the median epilepsy prevalence in sub-Saharan Africa is 1.4% [24].

Abbreviations: ILAE, International League Against Epilepsy; OAE, onchocerciasis-associated epilepsy.

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Nodding syndrome is a more characteristic clinical presentation of OAE. However, relying solely on a nodding syndrome case definition in epidemiological studies would significantly underestimate the burden of OAE, particularly in regions where CDTI has been implemented for several years. Therefore, for determining the onchocerciasis-related burden of disease and making programmatic decisions, an OAE case definition is more useful. Despite the need for such a definition, obtaining WHO support to adopt the proposed OAE case definition is currently challenging. However, in the past, WHO adopted other case definitions for major public health problems in the absence of biomarkers for confirmation. Examples include AIDS (37), Ebola (38), and, recently, the post-COVID syndrome (39).

2.5. OAE burden of disease

Since 2015, the NSETHI consortium has conducted numerous house-to-house epilepsy surveys in onchocerciasis areas with high ongoing *O. volvulus* transmission (11). These surveys showed an epilepsy prevalence between 2.6- 8.4% (Table 2). This is significantly higher than the median epilepsy prevalence in sub-Saharan Africa of 1.4% (40).

Table 2 Population epilepsy prevalence and OV16 RDT seroprevalence among 7-year-old children observed during house-to-house surveys in onchocerciasis-endemic areas with high ongoing *O. volvulus* transmission.

Study site	Population epilepsy prevalence (%)	Ov16 prevalence in 7 year old children (%)
Sanaga valley, Bilomo, Cameroon, 2018 (41)	61/1321 (4.6%)	31/52 (53.7%)
Sanaga Valley, Keleng, Cameroon, 2017 (41)	16/204 (7.8%)	3/6 (50%)
Mbam valley, Nyamongo, Cameroon, 2017 (42)	42/1151 (3.7%)	17/32 (44.4%)
Mbam valley, Bayomen, Cameroon, 2017 (42)	14/582 (2.6%)	25/39 (64.1%)
Mbam valley, Ngongol, Cameroon, 2017 (42)	24/553 (4.3%)	16/36 (44.4%)
Mahenge rural villages, Tanzania, 2018 (36)	88/2499 (3.5%)	19/52 (36.5%)
Draju, Logo health zone, DRC, 2016 (26, 28)	64/1389 (4.6%)	4/39 (10.3)

Wela, Aketi health zone, DRC, 2016 (26, 27)	39/570 (6.8%)	46/60 (76.6%)
Makoko, Aketi health zone, DRC, 2016 (26, 27)	31/367 (8.4%)	19/43 (44%)
Maridi, South Sudan, 2018 (20)	774/17,652 (4.4%)	16/48 (33.3%) *
Amadi, South Sudan, 2021 (43)	14/317 (4.4%)	1/11 (9.1%)
Mvolo, South Sudan, 2020 (17)	798/15,699 (5.8%)	7/15 (46.7%)

*7-9-year-old

High Ov16 seroprevalence among 7-year-old children indicated high recent *O. volvulus* transmission in the study areas. In 2017, it was estimated that more than 300,000 people could be affected by OAE (3). Epilepsy in onchocerciasis-endemic areas is associated with significant psycho-social and economic consequences not only for persons with epilepsy but also for their families (44-47). It is a highly stigmatizing condition, leading to discrimination against persons with epilepsy because communities may believe epilepsy is contagious (46, 48, 49).

2.6. The pathogenesis of OAE
Several OAE pathophysiological mechanisms have been proposed, but none has been proven yet (2). It has been suggested that OAE could be an autoimmune disorder induced by neurotoxic leiomodin-1 antibodies cross-reacting with *O. volvulus* (50). This hypothesis was later rejected (51-53) but it may still be that OAE results from an autoimmune reaction to multiple proteins (54). In a recent clinical trial evaluating the treatment of doxycycline in children with nodding syndrome in northern Uganda, 232 (96.7%) of them presented *O. volvulus* antibodies, and 157 (65.4%) had auto-antibodies to host neural proteins (HNPs) (43). However, the results of this study are difficult to interpret, as HNP antibody tests were not performed in local controls without epilepsy, and these antibodies could also be the consequence of the disease instead of a causal factor (55). Another possibility could be that these autoimmune reactions could be co-factors, as inflammation tends to increase blood-brain barrier (BBB) permeability, potentially allowing entry of the causal entity.

It has been suggested that nodding syndrome is a degenerative tauopathy because tau deposits were detected in the brains of persons with nodding syndrome during post-mortem studies (56, 57). However, tau deposits were not found in all persons with OAE who died (58). Therefore, these deposits may be the consequence of the disease induced by repetitive untreated seizures and/or the consequence of a neuro-inflammatory process (59).

Studies conducted before the introduction of mass drug administration with ivermectin detected *O. volvulus* microfilariae in the CSF of persons with onchocerciasis but without OAE (31, 32). Moreover, the number of microfilariae increased in the CSF after treatment with Diethylcarbamazine (DEC) (31). The inflammation induced by DEC might have increased BBB permeability, allowing the entry of microfilariae, supporting the hypothesis of inflammation as a potential co-factor. However, recent studies using sensitive molecular techniques failed to detect *O. volvulus* DNA in CSF (60, 61), possibly because these studies recruited persons with OAE many years after the onset of seizures, suggesting that the microfilaria causing the initial brain damage had already been cleared by central nervous system immune cells (2). A post-mortem study of nine persons with OAE showed signs of ventriculitis in eight of them, suggesting a pathological mechanism involving the choroid plexus (58). The choroid plexus, known for its weaker BBB/blood-CSF barrier function, creates an ideal environment for (micro)organisms to enter the brain.

Parasitic tolerance in children exposed in utero to filarial infections is also considered a potential co-factor (62). An 18-year follow-up study in West Africa found that children born to

O. volvulus-infected mothers had a four-fold higher odds of becoming *O. volvulus* infected and developed high microfilaria loads earlier in life (52). Children born to infected mothers are thus at risk of developing high-level *O. volvulus* infection at a young age, increasing the risk of OAE if not treated with ivermectin.

Uncovering the pathogenesis of OAE is crucial for convincing policymakers to implement appropriate preventive and therapeutic measures in at-risk communities. The way forward is to increase our knowledge about the basic biology of *O. volvulus* and its interactions with the human host. The recent discovery of a virome in nematodes provides a new research avenue to investigate OAE pathogenesis (63).

2.7. Onchocerciasis-associated epilepsy prevention

Although the pathogenesis of OAE requires further elucidation, taking measures to prevent OAE is crucial (3, 55, 64, 65). Recent population-based studies, both retrospective and prospective, demonstrate that strengthening onchocerciasis elimination programmes decreases the incidence of OAE (9, 73). Retrospective studies in Cameroon suggest that even with suboptimal coverage, annual CDTI can reduce OAE incidence (41). In western Uganda, OAE ceased when onchocerciasis was eliminated through vector control and annual CDTI (19). In northern Uganda, nodding syndrome incidence decreased with the introduction of mass drug administration with ivermectin, and further decline occurred with biannual CDTI and river larviciding (40) (Table 1).

In Mahenge, an onchocerciasis-endemic area in Tanzania, biannual CDTI led to a decrease in epilepsy incidence from 177.6 per 100,000 person-years in 2017/8 to 45.5 per 100,000 person-years in 2021 (45). Finally, in Maridi in South Sudan, biannual CDTI and a "Slash & Clear" community-based vector control dramatically decreased the incidence of epilepsy from 348.8 per 100,000 person-years in 2016 to 41.7 per 100,000 person-years in 2022 (74). This decrease was observed despite that only 56.6% of the population took ivermectin in 2021 (74).

In some of these studies, CDTI was combined with vector control methods, but the rapid impact on the incidence of OAE is attributed to ivermectin. This is achieved by reducing the microfilaria load in infected children below the required threshold for developing OAE, as also demonstrated in a modelling study (66). Vector control methods will only influence the incidence of OAE over a more extended period, by decreasing transmission of *O. volvulus* (66).

Community awareness of OAE is crucial for preventing its occurrence. The distribution of ivermectin, especially among children, is pivotal. To prevent children from developing OAE, high ivermectin coverage among children aged 5-15 years is critical (67). Therefore, considering an additional round of ivermectin distribution in schools is advisable if six-monthly community-based ivermectin treatment is not feasible (67). This school-based distribution of ivermectin is low cost and could be combined with the already existing children deworming programs.

2.8. Epilepsy treatment and management

Onchocerciasis elimination is not imminent. Consequently, a substantial number of individuals with OAE will continue to impose a heavy burden on families and communities (46, 68).

In onchocerciasis-endemic areas, ensuring an uninterrupted supply of anti-seizure medication (ASM) is particularly challenging due to a lack of health infrastructure, trained healthcare workers, and financial resources in these remote, impoverished, and sometimes insecure areas. Stockouts of ASM in health facilities are common, and ASM of questionable quality is often found on the black market at exorbitant costs. Intermittent ASM treatment can lead to severe rebound seizures and high mortality (69).

Therefore, increased advocacy is necessary for the uninterrupted, free access to ASM for all individuals with epilepsy in onchocerciasis-endemic areas. An efficient supply chain for ASM, integrated into the regular health system supplies for essential medicines, needs to be established. Epilepsy diagnostic and treatment services should be decentralized and integrated into primary healthcare services in onchocerciasis-endemic areas (68, 70). This will require organizing training programs for primary healthcare workers about epilepsy in OAE-affected areas. Finally, evidence-based information about OAE needs to be provided to affected communities to reduce misconceptions, stigma, and discrimination (21).

3. Conclusion

There is currently robust epidemiological evidence that a significant fraction of epilepsy in endemic areas of onchocerciasis with high past or ongoing *O. volvulus* transmission is caused by OAE. While awaiting a biomarker or test for definitive OAE diagnosis, it is crucial to develop policies for the prevention and treatment of OAE. Collaboration between onchocerciasis elimination and mental health programs is key to addressing the OAE public health problem.

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