Onchocerciasis-associated epilepsy in Western Equatoria State, South Sudan

Stephen Raimon Jada,[1] Gasim OE Abd-Elfarag,[2,3,4] Luís-Jorge Amaral,[5] Amber Hadermann,[5] and Robert Colebunders[5]

Authors Affiliation:
1. Amref Health Africa, Juba, South Sudan
2. Access for Humanity, Juba, South Sudan
3. School of Public Health, University of Juba, Juba, South Sudan
4. Health and Social Sciences Institute-South Sudan, Juba, South Sudan
5. Global Health Institute, University of Antwerp, Antwerp, Belgium

Correspondence:
Robert Colebunders robert.colebunders@uantwerpen.be

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ABSTRACT

Onchocerciasis-associated epilepsy (OAE) is a neglected public health problem in remote African regions endemic to onchocerciasis with sub-optimal elimination programmes. OAE manifests in previously healthy children aged 3-18 years in the absence of any obvious cause for epilepsy and is marked by a diverse range of seizure types, including head nodding seizures (nodding syndrome). This paper reviews recent studies investigating the association between onchocerciasis and epilepsy in South Sudan. Surveys in Maridi, Mundri West, and Mvolo Counties demonstrated a very high prevalence (3-6%) and incidence of epilepsy, as well as substantial onchocerciasis serological prevalence (12-34%) in young children. However, a longitudinal population-based study conducted in Maridi and Mvolo showed that strengthening onchocerciasis elimination programmes was followed by a significant and consistent reduction in the incidence of epilepsy. Despite this progress, a large epilepsy treatment gap and a high level of misconceptions about epilepsy and epilepsy-related stigma were observed. Treating epilepsy in onchocerciasis-endemic regions is challenging. More advocacy is needed to provide uninterrupted access to free anti-seizure medication and promote community awareness programmes for improving the lives of persons with epilepsy and their families in these impoverished areas.

Keywords: epilepsy, nodding syndrome, onchocerciasis, ivermectin, treatment, vector control

Introduction

The association between onchocerciasis and epilepsy was first observed by Casis-Sacre in Chiapas and Oaxaca, Mexico, in 1938.[1] During the last two decades, various epidemiological studies have shown this association to be responsible for an important disease burden in remote onchocerciasis-endemic foci in sub-Saharan Africa.[2] A meta-analysis of eight population-based studies before 2008 found a significant association between onchocerciasis prevalence and epilepsy with an average epilepsy prevalence increase of 0.4% for every 10% increase in onchocerciasis prevalence.[3,4] Furthermore, results from two cohort studies in Cameroon showed a temporal and microfilarial dose-dependent association

between the level of *Onchocerca volvulus* (OV) infection in early childhood and the development of epilepsy later in life.[4,5] While case-control studies largely corroborated the association,[6-9] some, because of sub-optimal study design and methodological problems, were unable to confirm the association.[10,11] This paper explores the burden of onchocerciasis-associated epilepsy (OAE) in South Sudan and the potential for reducing it through improved onchocerciasis control programmes.

Onchocerciasis-associated epilepsy clinical characteristics

Onchocerciasis-associated epilepsy is a debilitating neurological condition primarily affecting children. In areas where OV transmission remains high, many persons with epilepsy (PWE) meet the OAE criteria.[12] These criteria include seizures appearing in previously healthy children aged 3-18 years who reside in a meso- or hyperendemic regions for onchocerciasis, with no other obvious causes for epilepsy.[12,13] OAE exhibits a wide spectrum of convulsive and non-convulsive seizure types, such as head-nodding seizures (nodding syndrome, NS) and Nakalanga syndrome, which is characterised by stunting, delayed sexual development, cognitive impairment, facial dysmorphism and epilepsy.[14] Both NS and Nakalanga syndrome are debilitating forms of OAE.[15] Different forms of epilepsy often coexist within one family.[16]

OAE case definition

A simple OAE case definition has been proposed to estimate the OAE-related burden of disease.[12,17,18] This definition has proven valuable in identifying epilepsy hotspots where onchocerciasis elimination programmes were working sub-optimally.[19] However, this definition is not intended for individual clinical decision-making. An important criterion of the definition is the exclusion of other obvious causes of epilepsy through a detailed medical history and clinical examination.[12,18] Unfortunately, the absence of neuroimaging, particularly to rule out neurocysticercosis caused by *Taenia solium*, is a limitation of the OAE case definition. However, in the specific context of Western Equatoria State of South Sudan, where pig rearing is uncommon, neurocysticercosis is unlikely to be a substantial cause of epilepsy.[20]

Onchocerciasis in South Sudan

Onchocerciasis was first reported in Sudan as early as 1908,[21] with a case identified in Maridi County, Western Equatoria State. South Sudan is among the highly endemic countries for onchocerciasis in Africa, with the disease endemic in half of the country.[22] The most affected foci are Western Equatoria, Northern and Western Bahr El Ghazal States, and part of the Central Equatoria State.[23] In 2006, around 4.1 million people in South Sudan were considered at risk of onchocerciasis.[22] By 2008, some villages in Western Equatoria, Northern and Western Bahr El Ghazal States had alarming prevalence rates, with over 80% of individuals having palpable onchocerciasis nodules and an overall onchocerciasis prevalence exceeding 12%.[22] As of 2022, estimates suggest over 9 million South Sudanese live in areas requiring community-directed treatment with ivermectin (CDTI).[24] Routine CDTI programmes started in Western Equatoria State in the mid-1990s. However, these programmes faced low coverage and interruptions due to insecurity, resulting in treatment coverage as low as 40.8% in 2017.[20]

Burden of OAE in Western Equatoria State

Already in 1946 it was reported that certain persons with onchocerciasis also presented with epilepsy.[25] In the 1990s, the first cases of NS were recognised,[7] and the WHO subsequently estimated its prevalence to be 4.6% in Western Equatoria in 2001-2002.[7] A preliminary household assessment conducted in Mvolo town in 2013 revealed that a considerable proportion of children, approximately one in six, were affected by epilepsy.[26] Since 2017, several population-based epilepsy prevalence studies have been conducted in different counties of Western Equatoria State. These studies documented a very high prevalence of epilepsy, including NS, a high prevalence of blindness and a high Ov16 seroprevalence among 3-to-9-year-old children, indicating ongoing and substantial OV transmission in the region (Table 1). This high burden of disease is explained by the high level of ongoing OV transmission and the low therapeutic CDTI coverage observed at all study sites.

In May 2018, a house-to house survey in selected villages in Maridi revealed an overall prevalence of epilepsy of 4.4 %, ranging from 3.5% to 11.9%, with the highest prevalence observed in Kazana 2, an area close to the Maridi Dam, the blackfly (*Simulium*) breeding site in the area.[20] Blackflies are the transmission vector of OV. In 2021, despite biannual CDTI, only 56.6% of the population took ivermectin, below the 80% threshold for onchocerciasis elimination.[29]

In 2023, a high number of persons with epilepsy were found to attend the epilepsy clinic of Maridi

Table 1. Population epilepsy prevalence and Ov16 rapid diagnostic test (RDT) seroprevalence among 3-to-9-year-old children observed during house-to-house surveys in onchocerciasis-endemic areas with ongoing Onchocerca volvulus transmission.

Study site	Epilepsy prevalence n/N (%)	PWE meeting OAE criteria n/N (%)	Blindness n/N (%)	Ov16 prevalence in 3–9-year-old children n/N (%)
Maridi, 2018[20]	774/17,652 (4.4%)	414/486 (85.2%)		35/144 (24.3%)[27] 12/24 (50%)*[27]
Mundri East and West, 2021[28]	85/2588 (3.3%)	65/80 (81.3%)	70/2588 (2.7%)	19/74 (25.7%)** 4/150 (2.7%)***
Mvolo, 2020[16]	798/15,699 (5.1%)	566/709+ (78.4%)	445/15,755 (28.2%)	41/150 (27.3%)

*n – number; N – total; + OAE – onchocerciasis-associated epilepsy; * Kazana 2 close to the Maridi Dam ** Amadi, *** Mundri Centre*

hospital. Therefore, as Ibba County is also located in an onchocerciasis-endemic area, a research team of Amref Health Africa visited Ibba in June 2023 and conducted an Ov16 RDT seroprevalence survey among 3–9-year-old children in three villages, Atodigi, Dakiti and Yangu. However, none of the 100 children tested Ov16 RDT positive, suggesting a low level of OV transmission. Therefore, it was hypothesized that OAE would not be a public health problem in Ibba County. Nevertheless, an epilepsy clinic was established at Ibba hospital to reduce travelling distance that persons with epilepsy would otherwise have to make to Maridi to obtain anti-seizure medication (ASM).

A survey in 2021 in Mundri East and West County revealed an epilepsy prevalence of 3.3% with NS affecting 0.9% of the population.[28] The highest epilepsy prevalence was observed in Hai Gabat in Amadi (4.3%) where the Ov16 RDT seroprevalence among children also suggested high OV transmission.[28] A very high prevalence of OAE (13.7%) was also observed in Diko.[30] CDTI coverage in Mundri East and West County was only 47.4% and in Amadi, only 35% of 5–9-year-old children eligible for ivermectin took ivermectin in 2021.[28]

Mvolo County has a long history of high OV transmission. In 1948, entomologist DJ Lewis described in Mvolo an extremely intense blackfly biting with high OV infection rates of blackflies (up to 10% OV larvae in the heads of the blackflies).[31] A 2020 house-to-house study in Mvolo revealed the highest prevalence of epilepsy (5.2%), including NS (2.2%) among the three counties.[16] Mvolo also had a high Ov16 seroprevalence among 3-to-9-year-old children, suggesting ongoing and substantial OV transmission. CDTI therapeutic coverage in Mvolo reached 64.0% in 2019 but decreased to 24.1% in 2021 following a CDTI interruption in 2020 due to COVID-19.[32]

Onchocerciasis-associated epilepsy is preventable

OAE is a preventable condition through the enhancement of onchocerciasis elimination measures. In Maridi, annual CDTI followed by bi-annual CDTI combined with a community vector control intervention involving the removal of vegetation around blackfly breeding sites ("Slash and Clear") significantly reduced the incidence of OAE including NS[29] Similarly, in Mvolo, where only annual CDTI was implemented, a population-based longitudinal study showed that the incidence of epilepsy also decreased[32] (Table 2). Comparable results were obtained in other onchocerciasis-endemic regions. In northern and western Uganda, the incidence of epilepsy, including NS, decreased after the implementation of biannual CDTI and ground larviciding of rivers in the North, as well as after the interruption of OV transmission in western Uganda.[33,34] Similarly, in Tanzania, biannual CDTI with high coverage resulted in a reduction in the incidence of epilepsy, including NS.[35] Also, in the Imo River Basin in Nigeria, two decades of CDTI were followed by a significant decline in the prevalence of epilepsy.[36]

Epilepsy treatment challenges

A substantial epilepsy treatment gap has been observed in all sub-Saharan African countries.[37] Delays in epilepsy diagnosis and initiation of ASM contribute to intellectual and mental decline, adversely affecting individuals with epilepsy. The absence of ASM in healthcare facilities, coupled with the high costs associated with obtaining

Table 2. Studies demonstrating that the implementation and strengthening of onchocerciasis elimination programmes are followed by a reduction in the incidence of epilepsy in onchocerciasis-endemic regions of South Sudan.

	Methodology		Pre-intervention		Post-intervention	
Study site	**Intervention**	**Survey periods**	**Epilepsy cases per 100,000 p-y** (95% CI)	**NS cases per 100,000 p-y** (95% CI)	**Epilepsy cases per 100,000 p-y** (95% CI)	**NS cases per 100,000 p-y** (95% CI)
Maridi, South Sudan[29]	Bi-annual CDTI with sub-optimal coverage + "Slash & Clear" vector control	Pre: 2018 Post: 2022	348.8 (307.2–395·8)	154.7 (127.6-187.3)	41.7 (22.6-75.0)	10.4 (2.7-33.2)
Mvolo, South Sudan[32]	Annual CDTI with sub-optimal coverage	Pre: 2013–2015 Post: 2019–2021	326.5 (266.8–399.1)	151.7 (112.7-203.4)	96.6 (65.5–141.7)	27.0 (12.5-55.5)

p-y=person-years

these medications from private clinics, forces families with a person with epilepsy to allocate a significant part of their limited monthly income to procure ASM, often resulting in irregular or inadequate dosages. These irregularities contribute to poor seizure control, leading to an increased incidence of seizure-related incidents, such as burns and injuries.

In May 2018, in Maridi, only 378 (51.4%) of the 735 diagnosed PWE were taking ASM.[13] Thanks to an epilepsy treatment programme established in May 2020 at Maridi County Hospital by Amref Health Africa in partnership with Doctors with Africa CUAMM, 1,556 persons with epilepsy received free ASM between May 2020 and July 2023. This programme significantly increased ASM intake by PWE in the central Maridi area by 39.7% (95% CI 35.3–44.2%) from 2018 to 2022.[29] It is important that this programme is further decentralised and established in other areas in South Sudan with a high prevalence of epilepsy.

Epilepsy misconceptions and epilepsy-related stigma

Epilepsy, beyond the physical challenges, is often accompanied by stigma and discrimination due to misconceptions about the condition. In 2019, focus group discussions in Maridi with community leaders and PWE and their families revealed many misconceptions about the cause and treatment of epilepsy.[38] Most people, for example, believed epilepsy is caused by bad spirits and is contagious through saliva, air and contact with PWE. The fact that onchocerciasis-endemic areas often have several children with epilepsy in one family strengthens the belief that families are "cursed." Very few participants were aware of the link between onchocerciasis and epilepsy.

These misconceptions translate into social stigma and practical challenges for PWE. Restricted daily activities and limited school attendance are common. Many children with epilepsy do not attend or drop out of school. They may be moved to separate rooms or huts when they develop seizures, forced to use different utensils, and not allowed to play with other children for fear of transmitting the condition. Families of PWE also experience stigmatisation, social exclusion and financial constraints due to the high cost of epilepsy care.[39] Stigma can further limit opportunities for PWE, with denial for adults and educational barriers for children, often resulting in low levels of schooling.[40] Suboptimal seizure control not only amplifies the financial burden but also intensifies stigmatisation, fostering social isolation and depriving PWE of employment opportunities. This underscores the pressing need for concerted efforts in addressing epilepsy comprehensively, including tackling misconceptions and promoting social inclusion.

Conclusion

Robust epidemiological evidence suggests that a significant fraction of epilepsy in onchocerciasis-endemic areas with high past or ongoing OV transmission is OAE. This highlights the urgent need to strengthen onchocerciasis elimination strategies in South Sudan. Increasing CDTI

therapeutic coverage and scaling up vector control interventions, such as "slash and clear", may prevent children from developing OAE. Effective collaboration between onchocerciasis elimination and mental health programmes, for example through joint training and resource allocation, is key to addressing the OAE public health problem.

An epilepsy awareness programme could be implemented to reduce epilepsy misconceptions and stigmatization of the condition. Seizure control through regular treatment with appropriate ASM can significantly improve the quality of life for PWE and contribute to reducing stigma and increasing schooling of children with epilepsy. Additionally, advocacy at national and international levels is needed to provide uninterrupted free access to ASM for PWE to facilitate their educational development and integration into society. See https://youtu.be/-bPTC41NBbE

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Conflict of interest: None

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