

ORIGINAL RESEARCH

The Spectrum of Ocular Diseases in the Onchocerciasis-Endemic Focus of Raga in South Sudan

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Introduction: Raga County is an onchocerciasis-endemic area in the Western Bahr El Ghazal state of South Sudan, known to have a high prevalence of blindness. The objective of this study was to determine the causes of eye disease and blindness in Raga County as well as to assess the relationship of eye diseases with other prevalent conditions like onchocerciasis and epilepsy.

Methods: We reviewed unpublished pre-community directed treatment with ivermectin (CDTI) data about eye disease and onchocerciasis in Western Bahr El Ghazal including Raga. In addition, a cross-sectional study was conducted from 21st March to 2nd April 2023 in 11 villages in Raga County. Participants were persons with blindness or other eye/vision problems, recruited via a community-based approach. Two senior ophthalmic clinical officers, supervised by an experienced ophthalmologist, performed the following assessments on participants: visual acuity measurement with Snellen Charts, anterior chamber examination with a loupe, and fundoscopy to assess the posterior segment with direct and indirect ophthalmoscopes.

Results: Pre-CDTI data showed that the most severe vision problems in villages with a high prevalence of *O. volvulus* infection were caused by onchocerciasis eye disease. During the 2023 survey, in total, 1559 persons (3,118 eyes) were examined (mean age: 47 ± 19.2 years, 58.4% male). The most frequent eye diagnosis was allergic conjunctivitis, observed in 1453 (46.6%) eyes of the participants. The main causes of blindness were onchocerciasis-related blindness (22.6%, caused by onchocerciasis chorioretinitis (9.4%), sclerosing keratitis, punctate keratitis (5.6%), and onchocerciasis optic neuropathy (7.6%)), and cataract (9.3%). A significantly higher proportion of persons with epilepsy presented with clinical signs of onchocerciasis including blindness (53.2%), compared to persons without epilepsy (32.5%) (p = 0.0007).

Conclusion: Despite years of CDTI, the main causes of blindness in Raga County remain onchocerciasis-related blindness observed in 22.6% and cataract observed in 9.3% of the study participants. The study confirmed an epidemiological association between onchocerciasis and epilepsy.

Keywords: Onchocerciasis, ocular disease, blindness, epilepsy, nodding syndrome, ivermectin

Introduction

Onchocerciasis (also known as river blindness) is a neglected tropical disease caused by the filarial worm, *Onchocerca volvulus*, which is transmitted by blackflies of the genus *Simulium*.¹ The disease is transmitted through daytime biting female blackflies. Black flies pass through four stages in their development - egg, larva, pupa to reach the last stage of an adult fly. Eggs are deposited by female flies onto submerged plants or rocks, and the developing fly moves through the

stages to emerge as adult 9–20 days later depending largely on environmental circumstances. These vectors live from 3–4 weeks.²

The causative nematode, *Onchocerca volvulus*, passes through five stages in its development; three stages are in the vector black fly. In taking a blood meal, the black acquires the first stage, the L1 (microfilariae) stage, which develops in the body of the fly to become an infective larva (L3 stage in the head of the fly ready for passage back into humans on the next blood meal the fly takes. This intra-vector development takes some 7–9 days (1).

Following the infecting fly bite, the L3 stage will, over the next 6–12 months, pass through the L4 stage to reach the adult form as either a male or female worm; the adult stages can be found in fibro-vascular granulomas palpable on boney prominences such as the dermal tissues over the iliac crest and the rib cage. Fertilized female worms produce millions of microfilariae and these migrate from the nodules to the skin and eyes. The adult *O volvulus* worms can live for up to 12 years.²

Ivermectin is currently the only readily available microfilaricidal drug that kills microfilariae but does not kill the female adult worm producing the microfilaria. It only and temporarily sterilises female adult worms. Therefore, the ivermectin mass drug administration needs to be given to a population for at least 15 years, the lifespan of the microfilariae. Moreover, to eliminate onchocerciasis, during each community directed treatment with ivermectin (CDTI) a therapeutic coverage of at least 80% is needed.²

South Sudan is among the African countries that are most affected by onchocerciasis, with the disease being endemic in around half (49%) of the country.³ By 2022, over nine million South Sudanese were estimated to live in areas requiring preventive chemotherapy for the disease through CDTI.⁴ The highly endemic foci of onchocerciasis in South Sudan are found in Western Equatoria, Northern and Western Bahr El Ghazal areas, and part of Central Equatoria.⁵ A CDTI program was initiated in Western Bahr El Ghazal in 2005.⁶ However, the programs faced low coverage and interruptions due to insecurity.

Onchocerciasis is mostly known as a skin and eye disease but there is increasing epidemiological evidence for an association between onchocerciasis and epilepsy, particularly in areas with sub-optimal onchocerciasis elimination programmes.⁷ A high epilepsy prevalence was already reported in Western Equatoria as early as 1946.⁸ In the 1990s the first cases of nodding syndrome were recognized.⁹ Door-to-door surveys conducted in Western Equatoria between 2018 and 2021 revealed an epilepsy prevalence of 4.4% in Maridi, ¹⁰ 5.8% in Mvolo, ¹¹ and 3.3% in Mundri. ¹² A high prevalence of blindness was also documented in these sites, notably 2.8% in Mvolo ¹¹ and 2.7% in Mundri. ¹²

Severe ocular onchocerciasis is well known in the north western corner of South Sudan, as was demonstrated in various epidemiological surveys¹³ and major therapeutic studies^{14,15} carried out in Bahr El Ghazal in the late 1970s and the early 1980s.

According to observations by the Ophthalmological Association of South Sudan, it was estimated that 80 to 85% of the eye patients from Raga County suffer from blindness due to complications of onchocerciasis. However, this was never investigated in a scientific study. In 2021, the Health Department of the Catholic Diocese of Wau conducted a health assessment in all parishes within the Catholic Dioceses of Wau. Parishes in Raga County reported high numbers of blind people and people with epilepsy. The objectives of this study were to document in detail the ocular pathologies encountered in Raga County, to determine the causes of eye disease and blindness in these sites, and to assess the relationship between onchocerciasis and epilepsy. We also reviewed historical unpublished data about onchocerciasis eye lesions observed in Western Bahr El Ghazal.

Methodology

Ophthalmological Data Pre-CDTI in Western Bahr El Ghazal

We reviewed unpublished ophthalmological data collected during a survey in six villages in Western Bahr El Ghazal and in hospitals in Raga (in 1985) and Wau (in 1981–84). Village surveys were carried out using standard procedures as previously described (Figure 1).

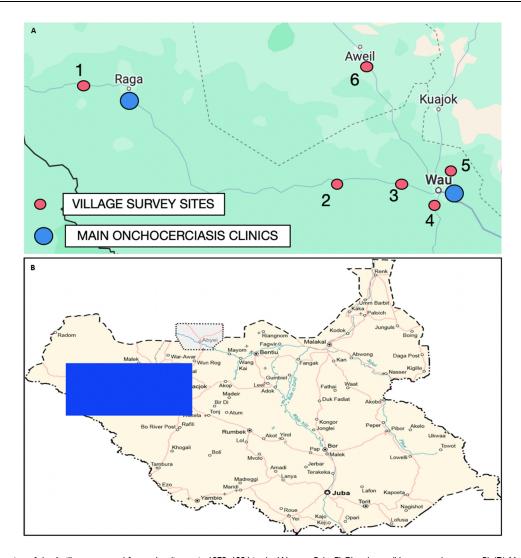


Figure 1 (A) Location of the 6 villages surveyed for ocular disease in 1979–1984 in the Western Bahr El Ghazal area (blue rectangle on map B) (B) Map of South Sudan.

Individuals were assessed by skin snip, and visual acuity (Tumbling "E" Chart system). Those with a visual acuity worse than 20/60 were further examined at the hospital of Raga and Wau for confirmatory visual acuity assessment, assessment of onchocercal corneal lesions, and presence of mf in the anterior chamber.

Eye Survey

Study Design and Period

We conducted a community-based, cross-sectional study from 21st March to 2nd April 2023.

Study Setting

The study was conducted in the Raga County, Western Bahr El Ghazal State, South Sudan. Raga County has six fast-flowing rivers and many seasonal streams which serve as breeding sites for the blackflies. The main river is the Jur River. In Raga, onchocerciasis is known as Jur River Blindness transmitted by the blackflies belonging to the genus *Simulium damnosum*. Demographically, the population of Raga was estimated at 59,638 individuals in 2022. Most residents are engaged in farming (groundnut, cassava, sesame, sorghum, maize, vegetables, millet, and tobacco), animal rearing (goats and poultry), and fishing.

Study Villages and Participants

Within the parishes of Raga County, villages with a prayer center/church and a catechist in charge of the congregation were selected. This facilitated the mobilization of community members, as we used the churches as recruitment sites in these villages. Selected villages were: Abulu, Boro Madina, Deim Zubeir, Ferika and Timsah, Kata, Kuru, Magayat, Raga, Sira-Malaga, and Sopo. Residents in the study villages who were blind or were having an eye problem were eligible to participate in the study, regardless of their ages and sex.

Study Procedure

Community mobilizers were trained by the research team on how to mobilize the community and refer eligible individuals to the church/prayer center for enrolment in the study. Consenting study participants were interviewed and examined by the research team, comprised one experienced ophthalmologist (KLLS) as team leader and two senior ophthalmic clinical officers (DM, ML). Data were collected using a standardized questionnaire which included questions about demographic characteristics, eye symptoms, history of itching, history of epilepsy and family history of epilepsy. The data collection tool also had a section to document findings from the clinical and ophthalmological examination of participants as described below.

Examinations of the participants included visual acuity measurement with Snellen Charts, anterior chamber examination with a loupe, and fundoscopy to assess the posterior segment with direct and indirect ophthalmoscopes. Persons with poor vision without anterior pathology along the visual axis (corneal scar, corneal dystrophies, and cataract) qualified for fundoscopy after dilation with 5% tropicamide drops. Persons with cup and disc ratio >0.5 were classified as having glaucoma. Patients diagnosed with treatable conditions were given medications and counseling. Meanwhile, those with permanent untreatable conditions were counseled and advised accordingly about the prognosis of their conditions. Surgical conditions were referred to Wau Teaching Hospital for free eye surgery.

A person was considered to have onchocerciasis if he/she presented characteristic clinical manifestations such as onchocerciasis skin lesions (hypopigmented areas, nodules), itching, and eye lesions (keratitis, chorioretinitis, optic neuropathy, etc). No skin snip nor O. volvulus antibody test was performed.

A person was considered to present blindness caused by onchocerciasis if he/she had a visual acuity of zero and also presented one of the following conditions: sclerosing keratitis, punctate keratitis, maculopathy, and optic neuropathy.

A person was considered to have epilepsy if he/she or a family member reported that the person presented epileptic seizures, in accordance with Question 5 of the validated epilepsy screening questionnaire of Diagana et al. 18

Data Analysis

The collected data were entered into an Excel spreadsheet and later transferred to SPSS version 21. Descriptive statistics were conducted, with categorical variables presented as counts and percentages. Comparisons across groups were done using the Pearson's Chi-squared test or Fisher's exact test as appropriate, with a significance threshold of 0.05.

Ethics Statement

Ethical approval was obtained from the ethics committee of the Ministry of Health of South Sudan (January 2018, MOH/ ERB50/2019) and from the ethics committee of the Antwerp University Hospital, Belgium (April 2019, B300201940004). All research procedures followed the Good Clinical Practices and the Declaration of Helsinki. Prior to conducting the study, local village representatives were consulted, and approval for the study was obtained. Verbal informed consent, in the presence of a witness, was obtained from all participants including from the parents/guardians of participating children and all data treated confidentially. Approval for verbal informed consent from the participants was obtained from the ethics committees.

Results

Ophthalmological Data Pre-CDTI in Western Bahr EL Ghazal

A very high prevalence of O. volvulus infection was observed in selected villages in the central Western Bahr El Ghazal area (Table 1). Moreover, most of the persons with a visual acuity worse than 20/50 presented onchocerciasis ocular

Table I Prevalence of O. volvulus Infection Observed During Eye Surveys in Selected Villages in the Central Western Bahr El Ghazal Area

	Location	No examined	O. volvulus infection ^c			Number reporting residing in Raga county*
Village surveys ^a						
	Bisellia	97	95 (97.9%)			2
	Pongo	101	99 (98.1%)			9
	Busserri	123	103 (83.7%)			0
	Jallab	81	75 (92.6%)			76
	Nynakok	76	70 (92.1%)			0
	Aweil	43	33 (75.0%)			8
Hospital-based ophthalmologic assessments ^b	Examination site			Mf in anterior chamber	Onchocercal corneal lesions	
	Raga	37	37	37	37	37
	Wau	156	156	143	148	14

Notes: ^aConducted using standard procedures previously reported ¹³ ^bThose with visual acuity worse than 20/50 were examined in eye facilities in hospitals ^cMicrofilaria present in skin snips and or in the anterior chamber or in the cornea *Individuals mentioning Raga as their home location. However, most likely many more were from Raga but did not accurately reported their home location (was not the purpose of the study). **Abbrevations**: MF, microfilaria.

disease. Of the 35 persons examined at Raga hospital, all presented onchocerciasis cornea lesions and microfilaria in the anterior eye chamber and of 156 persons examined at Wau hospital 143 (91.6%) presented onchocerciasis cornea lesions and 148 (94.8%) with microfilaria in the anterior eye chamber, 21 of these had >50 microfilaria in the anterior chamber.

2030 Survey

In total 1,559 persons (3,118 eyes) were examined, 58.4% (911) males and 41.6% (648) females with a mean age of 47.8 ± 19.2 years. The most represented age group was 40–49-year, accounting for 21.2% (331) of the study population. Overall, 635 (40.7%) participants were residents of Raga town (Table 2).

Table 2 Demographic Characteristics of 1,559 Persons with Eye Problems in Raga County, 2023

Variable	Frequency (n)	Percentage (%)			
Gender					
Male	911	58.4			
Female	648	41.6			
Age group (years)					
0–9	53	3.4			
10–19	61	3.9			
20–29	138	8.9			

(Continued)

Table 2 (Continued).

Variable	Frequency (n)	Percentage (%)
30–39	239	15.3
40–49	331	21.2
50–59	262	16.8
60–69	244	15.7
70 or more	231	14.9
Residence		
Abulu	64	4.1
Boro Madina	116	7.4
Deim Zubeir	291	18.7
Ferika and Timsah	108	6.9
Kata	43	2.8
Kuru	68	4.4
Mangayat	95	6.1
Raga	635	40.7
Sira-Malaga	74	7.9
Sopo	29	1.9

The most frequent eye diagnosis was allergic conjunctivitis observed in 1,453 (46.6%) of the eyes of participants (Table 3). The main causes of blindness were onchocerciasis-related blindness (22.6%) (onchocerciasis chorioretinitis (9.4%), corneal scar/dystrophies (5.6%), and onchocerciasis optic neuropathy (7.6%)). Other ocular blindness is due to cataract (9.3%) and glaucoma (4.8%).

Table 3 Eye Diagnosis of 1,559 Persons with an Eye Problem (n = 3,118 Eyes Examined) in Raga County, 2023

Diagnosis	Frequency (n)	Percentage (%)
Cataract	289	9.3
Glaucoma	151	4.8
Onchocerciasis chorioretinitis	292	9.4
Allergic conjunctivitis	1,453	46.6
Vernal keratoconjunctivitis	18	0.6
Corneal scar/ dystrophies sclerosing keratitis	167	5.6
Onchocerciasis optic neuropathy	237	7.6
Refractive errors (presbyopia)	119	3.8
Others	392	12.6
Total	3,118 eyes	100

Table 4 History of Clinical Onchocerciasis and Epilepsy in the Study Participants by Age Group in Raga County, 2023

	Total	Onchocerciasis*		Epilepsy**	
Age group	N (100%)	Yes: n (%)	No: n (%)	Yes: n (%)	No: n (%)
0-9 years	53	2 (3.8%)	51 (96.2%)	I (I.9%)	52 (98.1%)
10-19 years	61	4 (6.6%)	57 (93.4%)	7 (11.5%)	54 (88.5%)
20-29 years	138	24 (17.4%)	114 (82.6%)	8 (5.8%)	130 (94.2%)
30-39 years	239	63 (26.4%)	176 (73.6%)	22 (9.2%)	217 (90.8%)
40-49 years	331	111 (33.5%)	220 (66.5%)	6 (1.8%)	325 (98.2%)
50-59 years	262	99 (37.8%)	163 (62.2%)	8 (3.1%)	254 (96.9%)
60-69 years	244	108 (44.3%)	136 (55.7%)	5 (2.1%)	239 (98.0%)
≥70 years	231	109 (47.2%)	122 (52.8%)	5 (2.2%)	226 (97.8%)
Overall	1,559	520 (33.4%)	1,039 (66.6%)	62 (4.0%)	1,497 (96.0%)

Note: *Presenting either onchocerciasis skin lesions (hypopigmented areas, nodules), itching, and/or eye lesions (keratitis or chorioretinitis, optic neuropathy). **Diagnosis based on self- or family-reported occurrence of seizures

Table 5 Association of Clinical Manifestations of Onchocerciasis* and Epilepsy

		Epilepsy**				
Onchocerciasis*		Yes: n (%)	No: n (%)	Total: n (%)		
	Yes: n (%)	33 (53.2)	487 (32.5)	520 (33.4)		
	No: n (%)	29 (46.8)	1,010 (67.5)	1,039 (66.6)		
Total: n (%)		62 (4.0)	1,497 (96.0)	1,559		

Note: *Presenting either onchocerciasis skin lesions (hypopigmented areas, nodules), itching, and/or eye lesions (keratitis or chorioretinitis, optic neuropathy).** Diagnosis based on self-or family-reported occurrence of seizures.

Clinical manifestations of onchocerciasis were observed in one-third of participants: 520/1,559 (33.4%). Furthermore, 62 (4.0%) of participants were reported to have epilepsy, while a family history of epilepsy was reported in 181 (11.6%) participants. Age-specific clinical findings are summarized in Table 3 and reveal a peak epilepsy prevalence of 11.5% in the 10−19 years age group. Meanwhile, the age-specific prevalence of onchocerciasis clinical manifestations steadily increased with age to reach a maximum of 47.2% in the ≥70-year-old age group (Table 4).

A significantly higher proportion of persons with epilepsy presented onchocerciasis clinical manifestations (53.2%) compared to persons without epilepsy (32.5%); Chi-square without Yates correction p = 0.0007 (Table 5).

Discussion

Our review of unpublished ophthalmological data collected pre-CDTI in Western Bahr El Ghazal and the 2023 eye survey data show the importance of onchocerciasis ocular disease burden in Raga County. The pre-CDTI data showed that the most severe vision problems in villages with a high prevalence of *O. volvulus* infection were caused by onchocerciasis eye disease.

During the 2023 survey, the most frequently observed eye disease was conjunctivitis. This conjunctivitis was most likely the consequence of the presence of *O. volvulus* microfilariae in the conjunctiva. This may lead to itching and

conjunctivitis, characterized by increased pigmentation around the limbus, some redness of the conjunctiva and conjunctival discharge. Other onchocerciasis-related manifestations among the participants included: onchocerciasis chorioretinitis and optic neuropathy observed in, respectively, 9.2% and 7.6% of the participants, and corneal scars and dystrophies and vernal kerato-conjunctivitis observed in, respectively, 5.6% and 0.6% of the participants. Cataracts were observed in 9.3% and glaucoma in 4.8% of the participants; these two conditions have been reported to be associated with onchocerciasis (17).

However, it remains unclear what exact proportion of cataract and glaucoma in our study population can be attributed to onchocerciasis. Existing literature describes the following major ophthalmological findings that can be caused by onchocerciasis: corneal changes, such as sclerosing keratitis and snowflake opacities; torpid iritis characterized by typical pear-shaped deformity of the iris; secondary cataracts; chorioretinopathy; and optic neuritis. ^{19–21} Major causes of blindness caused by onchocerciasis are sclerosing keratitis and chronic torpid iritis, chorioretinopathy, and optic neuropathy. ^{19–21} When mf dies, the host immunological response causes ocular inflammation leading to progressive loss of vision and eventually blindness. ^{1,19,22,23} Death of individual microfilariae within the cornea is associated with snowflake opacities, and massive death will lead to sclerosing keratitis. ¹⁹

The pathogenesis of chorioretinal changes in onchocerciasis is still controversial. It has been suggested that autoimmune reactions involving cross-reacting antigens between *O. volvulus* and interphotoreceptor retinoid-binding proteins and immune complex deposition may play a role, ^{24–26} but this has not been confirmed. Ivermectin intake is expected to reduce the number of microfilariae in the anterior chamber of the eye and indirectly reduce the inflammation. However, ivermectin may not reverse severe or long-standing damage to the eyes, in particular, the choroid and retina.

A high proportion of the participants reported to have epilepsy (4.0%) or reported a family history of epilepsy (11.6%). This self-reported epilepsy prevalence was similar to the observed epilepsy prevalence in the general population in other onchocerciasis-endemic areas such as Maridi, Mundri, and Mvolo. Importantly, a significantly higher proportion of persons with epilepsy presented onchocerciasis clinical manifestations (53.2%) compared to persons without epilepsy (32.5%) suggesting that also in Raga, similar to other onchocerciasis-endemic areas with high *O. volvulus* transmission, onchocerciasis is associated with epilepsy. 27

The strength of our 2023 study is that a large number of persons with eye problems in an onchocerciasis-endemic area with limited past exposure to ivermectin were investigated by two senior ophthalmic clinical officers supervised by an experienced ophthalmologist (KLLS).

However, our study also has several limitations. Most importantly, the diagnosis of onchocerciasis was only made based on clinical manifestations and no *O. volvulus* antibody test nor skin snip testing was performed. Also, slit-lamp examination to identify microfilariae in the anterior chamber was not performed. However, the ocular manifestations observed in 2023 were comparable with the observations pre-CDTI. CDTI was implemented in South Sudan in 2004, but therapeutic coverage has been low, and there have been interruptions because of insecurity and the COVID-19 pandemic. Therefore, most likely also in 2023, a large proportion of the visual problems in Raga were caused by onchocerciasis.

Only persons with eye problems were examined. Therefore, we do not have data about the prevalence of blindness and eye problems in the investigated communities. Moreover, only self-reported data about epilepsy was collected with no clinical confirmation of the diagnosis, and thus must be interpreted with caution. Finally, no history about previous ivermectin intake was obtained.

Conclusion

In 2023, despite more than 15 years of CDTI, the main cause of blindness in Raga County is still onchocerciasis-related ocular disease, observed in 22.6% of the persons with eye disease. Onchocerciasis clinical signs (eye disease) were more frequent among persons with epilepsy, supporting an epidemiological association between the two conditions. Furthermore, epilepsy was most common among the 10–19-year-old which is consistent with onchocerciasis-associated epilepsy.⁷ The overall high onchocerciasis-related morbidity (blindness and epilepsy) suggests that there is high ongoing *O. volvulus* transmission in Raga County. The latter is most likely because of low CDTI coverage.

A population-based study needs to be conducted to determine the exact prevalence of onchocerciasis, blindness, and epilepsy in Raga County. Nevertheless, to reduce the onchocerciasis-associated morbidity in Raga County, the onchocerciasis elimination program needs to be strengthened. It will be very important to obtain high ivermectin intake among children 5–18 years to protect them to develop onchocerciasis-associated epilepsy. Two recently published studies conducted in onchocerciasis-endemic areas, one in Maridi in South Sudan, and the other in Mahenge in Tanzania have shown that switching from annual to bi-annual CDTI was able to obtain an important decrease in the incidence of epilepsy. There is now robust epidemiological evidence that onchocerciasis is associated with epilepsy in areas with high *O. volvulus* transmission. 7,27,31,32

In 2023, bi-annual CDTI was initiated, but the challenge will be to continue this program with high ivermectin therapeutic coverage. Moreover, an eye unit needs to be established at the Raga County hospital where screening and managing of simple eye diseases can be done as well as referring or booking surgical cases. Community workers need to be trained in eye care services and a cataract surgical eye camp will need to be organized at regular intervals. In addition, epilepsy treatment centers need to be established in the area where anti-seizure medication could be provided free of charge by trained primary health care workers.

Author Summary

Data obtained in South Sudan in Western Bahr El Ghazal, including Raga County, before the introduction of Community Directed Treatment with Ivermectin (CDTI) showed that the most severe vision problems in villages with a high prevalence of *O. volvulus* infection were caused by onchocerciasis eye disease. In 2023, despite more than 15 years of CDTI in a survey in Raga County among 1, 559 persons with eye diseases, onchocerciasis-related blindness, specifically onchocerciasis chorioretinitis, sclerosing keratitis and dystrophy, maculopathy, and optic neuropathy, remained a leading cause of visual impairment. Onchocerciasis-related clinical symptoms (including ocular problems) were more frequent among persons with epilepsy compared to their non-epileptic counterparts. This highlights the urgency to strengthen the onchocerciasis elimination program by increasing ivermectin treatment coverage, and the establishment of eye care and epilepsy treatment centers in the affected region.

Data Sharing Statement

Data will be made available by the corresponding author upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have declared that no competing interests exist.

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