Original article

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Persons with onchocerciasis-associated epilepsy and nodding seizures have a more severe form of epilepsy with more cognitive impairment and higher levels of *Onchocerca volvulus* infection

Gasim Abd-Elfarag [1], Jane Y. Carter [2], Stephen Raimon [3], Wilson Sebit [4], Abozer Suliman [5], Joseph Nelson Siewe Fodjo [6], Peter Claver Olore [7], Kai Puok Biel [5], Morrish Ojok [7], Makoy Yibi Logora [8], Robert Colebunders [6]

[1] Global Child Health Group, Department of Paediatrics and Department of Global Health, Academic Medical Center, University of Amsterdam, The Netherlands
[2] Amref International University, Nairobi, Kenya
[3] Maridi State Hospital, Maridi, Republic of South Sudan
[4] National Public Health Laboratory, Republic of South Sudan
[5] Maridi Health Sciences Institute, Maridi, Republic of South Sudan
[6] Global Health Institute, University of Antwerp, Belgium
[7] Amref Health Africa, Juba, Republic of South Sudan
[8] Neglected Tropical Diseases Unit, Ministry of Health, Juba, Republic of South Sudan

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ABSTRACT – *Aims*. Following previous reports of very high epilepsy prevalence in the onchocerciasis-endemic villages in Maridi County, South Sudan, a study was conducted to investigate the association between the level of *Onchocerca volvulus* infection, epilepsy, and related outcomes.
Methods. In December 2018, persons with epilepsy (PWE) were recruited from villages where an epilepsy prevalence of 4.4% (range: 3.5-11.9%) was documented. We enrolled 318 participants from whom two skin snips were taken for microscopic detection of *O. volvulus* microfilariae (mf). Seizure history was obtained for all PWE and their degree of disability assessed using the modified Rankin scale.
Results. Almost all (84.9%) PWE had detectable mf in their skin snips. Onchocerciasis-infected PWE experienced nodding seizures more often than uninfected PWE (p=0.034). Moreover, persons with nodding seizures

Correspondence:
Robert Colebunders
Global Health Institute,
University of Antwerp,
Doornstraat 331,
2610 Antwerp, Belgium
<robert.colebunders@uantwerpen.be>

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had more frequent seizures ($p<0.001$) and higher disability scores ($p<0.001$), and were more often cognitively impaired and younger at the time of their first epileptic seizure (nine years vs 12 years, $p<0.001$) compared to PWE without nodding seizures. Based on multivariate models, nodding seizures were associated with higher mf densities (aOR: 1.022; 95% CI: 1.005-1.041). Epilepsy onset at a younger age was associated with a worse outcome. Higher frequency of seizures, longer duration of epilepsy and younger age were associated with increased disability. Regular antiepileptic drug use was associated with better cognitive and disability outcomes.
Conclusion. PWE with nodding seizures have a more severe form of onchocerciasis-associated epilepsy, with earlier seizure onset and higher levels of *O. volvulus* infection. Younger PWE were prone to worse epilepsy outcomes, which would be prevented with regular antiepileptic treatment.

Key words: onchocerciasis, epilepsy, nodding syndrome, microfilariae, disabilities, seizures, South Sudan

The association between onchocerciasis (river blindness) and epilepsy was already reported in 1938 by Casis Sacre (Casis Sacre, 1938), but there is no consensus yet in the scientific community and among stakeholders involved in onchocerciasis control that onchocerciasis can cause epilepsy. Persons with nodding syndrome (NS) (Dowell *et al*., 2013) and other forms of epilepsy are often found to cluster in certain villages and within families in meso- and hyper-endemic onchocerciasis areas (Boussinesq *et al*., 2002; Colebunders *et al*., 2018a). Therefore, it was suggested that NS, a type of epilepsy characterised by repetitive forward dropping of the head, intellectual disability with or without stunted growth and/or underdeveloped secondary sexual characteristics (Nakalanga features) are a phenotypic presentation of onchocerciasis-associated epilepsy (OAE) (Colebunders *et al*., 2018a).

High numbers of persons with NS and other forms of epilepsy have been reported in the Western Equatoria region of South Sudan since 1990 (Lacey, 2003; Tumwine *et al*., 2012; Colebunders *et al*., 2016). In May 2018, during a door-to-door household survey, we documented an epilepsy prevalence of 4.4% (range: 3.5-11.9%) in onchocerciasis-endemic villages in Maridi County (Colebunders *et al*., 2018b). The 11.9% prevalence was observed in Kazana-2, a village close to the Maridi dam, a blackfly breeding site (the vector transmitting onchocerciasis) (Colebunders *et al*., 2018b). Epidemiological criteria for onchocerciasis-associated epilepsy (OAE) (Colebunders *et al*., 2018a) were met by 85.2% of the persons with epilepsy (PWE) in these villages (Colebunders *et al*., 2018c). Seizure types included generalized tonic-clonic seizures (69.4%) and nodding seizures (45.5%). Eighty (11.0%) of the PWE presented with Nakalanga features (Colebunders *et al*., 2018c). The overall median age at onset for all seizures was 10 years, while that for nodding seizures only was eight years (Colebunders *et al*., 2018c). PWE with nodding seizures presented with more cognitive disabilities (Colebunders *et al*., 2018c).

Little is known about the impact of *Onchocerca volvulus* infection and the severity of epilepsy and its complications. A recent cohort study in the Mbam valley, an onchocerciasis endemic area in Cameroon, showed that the risk of developing epilepsy increased with increasing microfilariae (mf) density (Chesnais *et al*., 2018). We hypothesised that the intensity of *O. volvulus* infection is associated with the severity of epilepsy-related symptoms and complications in persons with OAE.

Material and methods

Study setting and participants

The study was conducted in December 2018 in Maridi County in South Sudan. Study villages included Kazana-1, Kazana-2, Hai-Tawara, Hai-Gabat, and Hai-Matara. These villages are hyper-endemic for onchocerciasis and have a long history of sub-optimal onchocerciasis control, mainly due to lack of funding, inadequate implementation of mass drug administration of ivermectin, and insecurity. Most of the villagers are involved in subsistence farming.

PWE identified during the epilepsy survey in May 2018 in the Maridi area (Colebunders *et al*., 2018b) were asked to participate in the study. Consenting PWE were interviewed and examined clinically by a medical doctor. Monthly seizure frequency was obtained via verbal reports from PWE and/or their caretakers. The participants' degree of autonomy was assessed using the modified Rankin scale (Zhao *et al*., 2010); the Rankin score ranged from one (no significant disability) to five (severe disability). Cognitive impairment was investigated by questioning caretakers about the PWE's

coherence in speech and obedience to instructions (Colebunders *et al*., 2018c). Screening for onchocercal skin disease (papular onchodermatitis, "leopard skin" lesions, and "lizard" skin lesions) and for the presence of subcutaneous nodules was performed. All participants provided skin snips for *O. volvulus* detection.

Sample collection and processing

Skin snipping was performed at village health centres. Two skin snips were obtained from every participant, one from each posterior iliac crest using sterilized skin punches. Skin snips were immediately placed in different wells of a 96-well microtiter plate containing three drops of normal saline and incubated for 24 hours at room temperature to allow mf to emerge into the fluid. After the incubation period, the mf in the solutions were examined microscopically using x40 magnification and counted by a trained technician. Mf density of positive samples was obtained from the arithmetic mean from both skin snips and expressed as mf per skin snip. One punch was used per subject, and punches were sterilised between subjects using steam under pressure (autoclave).

In all five study villages, we used two types of skin punches: the 2-mm corneoscleral punch (World Precision Instruments Hitchin Hetfordshire, UK) and the 2-mm AA6052 Holth Corneoscleral Punch (Appasamy Associates & Group of Co, Tamilnadu, India). These two types of punches yielded two different sizes of skin snips, large and small. Therefore, we calculated the mean number of mf obtained using each type of punch, and adjusted the mf densities of participants to a common scale before analysis.

Data analysis

In descriptive statistics, continuous variables were expressed as median and interquartile range (IQR) and compared across different groups using the Mann Whitney U test. Chi-square tests were used to assess differences in proportions, and the Fisher exact test was used for counts below five. Stunting was defined as a height-for-age z-score less than -2z according to the World Health Organization (WHO) growth charts for children aged 0-19 years (World Health Organization, 2019a, 2019b).

Four epilepsy-related parameters (seizure frequency, nodding seizures, cognitive impairment, and Rankin disability score) were the outcomes of interest. Logistic regression models were used for binary outcomes, an ordinal logistic regression for the Rankin scores, and a negative binomial regression model for seizure frequency given the over-dispersion observed in the number of seizures per month. Univariate and multivariate analyses were performed to investigate the association between mf density and each epilepsy-related outcome. Adjustments were made for purposefully selected independent variables including age, gender, and previous treatments. Additional multivariate analyses were performed using the presence of nodules as an indicator of *O. volvulus* infection in place of mf density. Data were analysed using R version 3.5.1.

Results

A total of 318 PWE were enrolled, of whom 270 (84.9%) had skin snips positive for *O. volvulus* microfilariae (*table 1*). Nodding seizures (p=0.034) and dermatological lesions (p=0.012) were more frequent among skin snip-positive participants.

The mean mf density obtained using the large punches (33.3 mf/skin snip) was roughly twice that obtained by the smaller punches (16.5 mf/skin snip); therefore, we halved the mf density for all skin snips obtained with the large punches.

The overall median mf density was 11.5 (IQR: 5.6-24.5) mf/skin snip, and this varied significantly across villages: 3.5 (IQR: 0-8) mf/skin snip for PWE in Hai-Gabat, 9.5 (IQR: 6.0-12.5) mf/skin snip in Hai-Tarawa, 11.5 (IQR: 5.7-22.6) mf/skin snip in Hai-Matara, 17.5 (IQR: 8.3-28.9) mf/skin snip, in Kazana-2, and 24.9 (IQR: 8.1-41.9) mf/skin snips in Kazana-1; $p<0.001$. On the other hand, ivermectin use in 2017 (p=0.540) and previous use of an antiepileptic medication (p=0.862) did not differ between study villages. Participants with nodding seizures had a higher parasitic load, more seizures and started seizures at an earlier age compared to PWE without nodding seizures (*table 2*).

Univariate analyses of the epilepsy-related outcomes showed that increasing mf density was associated with higher seizure frequency and higher odds of having nodding seizures (*table 3*).

Based on multivariate analysis, higher mf densities and younger age increased the odds of developing nodding seizures (*table 4*). Regular antiepileptic drug use was associated with better cognitive and disability outcomes. In addition, the severity of epilepsy significantly worsened with decreasing participant age. Higher frequency of seizures, longer duration of epilepsy and younger age were associated with increased disability.

The presence of nodules was also associated with higher odds of having nodding seizures (aOR: 8.870; 95% CI: 1.554-167.658; p=0.043) (*see supplementary material*).

Table 1. Characteristics of 318 persons with epilepsy stratified by skin snip status.

	Overall	Negative skin snip *n*=48	Positive skin snip *n*=270	*P-value*
Sociodemographic characteristics				
Gender: male (%)	162 (50.9)	22 (45.8)	140 (51.9)	0.437[a]
Age in years: median (IQR)	17.0 (14.0–19.0)	18.0 (15.5–20.0)	17.0 (14.0–19.0)	0.134[b]
Village: *n* (%)				
Kazana-1	60 (18.9)	1 (2.1)	59 (21.9)	<0.001[a]
Kazana-2	42 (13.2)	2 (4.2)	40 (14.8)	
Hai-Gabat	31 (9.7)	14 (29.2)	17 (6.3)	
Hai-Matara	144 (45.3)	21 (43.8)	123 (45.6)	
Hai-Tarawa	41 (12.9)	10 (20.8)	31 (11.5)	
Seizure characteristics				
Age at seizure onset in years: median (IQR)[i]	10.0 (7.0–13.0)	10.5 (7.0–14.0)	10.0 (7.0–12.0)	0.554[b]
Seizure frequency/month: median (IQR)[ii]	8.0 (2.0–75.0)	6.0 (2.0–30.0)	12.0 (2.0–90.0)	0.178[b]
Nodding seizures: *n* (%)[iii]	158 (52.3)	17 (37.8)	141 (54.9)	0.034[a]
Cognitive status and disability scores of participants				
Cognitive impairment: *n* (%)	120 (37.7)	23 (47.9)	97 (35.9)	0.115[a]
Rankin disability score: median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.176[b]
Other clinical features				
Dermatological lesions: *n* (%)[vi]	73 (24.7)	4 (9.5)	69 (27.2)	0.012[c]
Itching: *n* (%)[vii]	181 (57.5)	28 (59.6)	153 (57.1)	0.750[a]
Stunting: *n* (%)[iv]	23 (9.7)	3 (9.4)	20 (9.8)	1.000[c]
Muscle wasting: *n* (%)[v]	91 (29.0)	14 (29.2)	77 (28.9)	0.966[a]
Burns: *n* (%)[ii]	51 (16.1)	11 (22.9)	40 (14.9)	0.166[a]
Presence of nodules: *n* (%)[ii]	10 (3.2)	1 (2.1)	9 (3.4)	0.638[a]
Previous treatment				
Previous AED use: *n* (%)[ii]	273 (86.4)	39 (81.2)	234 (87.3)	0.257[a]
Regular AED use: *n* (%)[ii]	156 (49.1)	17 (35.4)	139 (51.9)	0.036[a]
Ivermectin use in 2017: *n* (%)[viii]	79 (25.6)	16 (34.0)	63 (24.1)	0.153[a]

IQR: interquartile range; AED: antiepileptic drug. [a]Chi-square test. [b]Mann Whitney u test. [c]Fisher exact test.
Data missing for: [i]6 patients; [ii]2 patients; [iii]16 patients; [iv]82 patients; [v]4 patients; [vi]22 patients; [vii]3 patients; [viii]10 patients.

Discussion

Our study shows that *O. volvulus* infection was detected in 84.9% of PWE in Maridi, confirming previous reports of high onchocerciasis prevalence among PWE during a small case-control study performed in Maridi in 2010 (Centers for Disease Control and Prevention, 2012). In the latter study, *O. volvulus* mf were detected in 88.0% of NS cases and 44.0% of controls (Centers for Disease Control and Prevention, 2012). In December 2018, in Maridi, we also performed skin snips in 34 consenting adults without epilepsy (mean age: 34 years); 50% of them were skin snip-positive with a much lower median mf density of 1.8 mf/snip compared to 11.5 mf/snip among PWE (R Colebunders, unpublished).

Our previous survey in Maridi reported that PWE with nodding seizures presented with more cognitive disabilities when compared with PWE without nodding (Colebunders *et al.*, 2018c). In the present study, we demonstrate that nodding seizures are also associated with a higher parasitic load of *O. volvulus*. It appears that higher mf densities predispose to the development of a more severe phenotypic presentation of OAE, that is NS. However, the possible pathophysiological mechanisms underlying this

Table 2. Comparison of PWE with and without nodding seizures.

	PWE without nodding seizures *n*=144	**PWE with nodding seizures *n*=158**	***P-value***
Age in years (IQR)	17.5 (15.8-20.0)	16.0 (12.0-18.0)	<0.001[a]
Age at epilepsy onset (IQR)	12.0 (9.0-14.2)	9.0 (7.0-11.0)	<0.001[a]
Microfilarial density (IQR)	9.4 (3.5-21.8)	14.9 (7.5-26.0)	0.001[a]
Seizure frequency (IQR)	2.0 (1.3-12.0)	60.0 (4.0-90.0)	<0.001[a]
Rankin disability score (IQR)	1.0 (1.0-1.0)	1.0 (1.0-2.0)	<0.001[a]
Cognitive impairment: *n* (%)[i]	44 (30.8)	72 (45.6)	0.008[b]
Presence of nodules: *n* (%)[ii]	1 (0.7)	9 (5.8)	0.020[c]
Dermatological lesions: *n* (%)[iii]	21 (15.6)	48 (33.1)	<0.001[b]
Muscle wasting: *n* (%)[iv]	25 (17.7)	63 (40.1)	<0.001[b]
Stunting: *n* (%)[v]	7 (7.5)	14 (10.4)	0.451[b]

IQR: interquartile range; AED: antiepileptic drug. [a]Mann Whitney u test. [b]Chi-square test. [c]Fisher exact test.
Data missing for: [i]1 patient; [ii]2 patients; [iii]22 patients; [iv]4 patients; [v]73 patients

Table 3. Univariate analysis of epilepsy outcome variables and mf density.

Dependent variable	**Independent variable**	**Model used**	**Estimate (95% CI)**	***p value***
Seizure frequency	Mf density	Negative binomial regression	1.013 (1.002–1.025)	0.020
Rankin disability score	Mf density	Ordinal logistic regression	1.008 (0.993–1.022)	0.302
Cognitive impairment	Mf density	Logistic regression	1.002 (0.987–1.017)	0.781
Nodding seizures	Mf density	Logistic regression	1.023 (1.007–1.040)	0.005

process still remain unknown. We must note that over 85% of PWE in the study villages were previously documented as having OAE characteristics, thus suggesting that *O. volvulus* infection might be the predominant aetiology for epilepsy (and particularly NS) in this population (Colebunders *et al*., 2018c). Notwithstanding, other factors that could account for epilepsy in these villages include perinatal events, head injury, and childhood infections such as malaria and measles (Colebunders *et al*., 2018c).

The presence of subcutaneous nodules also increased the odds of having nodding seizures. This finding corroborates with the works of Kaiser *et al*. (Kaiser *et al*., 2011) and Pion *et al*. (Pion and Boussinesq, 2012), which suggested an association between the presence of onchocercal nodules and epilepsy in onchocerciasis-endemic villages. In contrast to mf density, which can be altered by the migration of mf in the skin and annual ivermectin treatment, nodule detection is a better proxy for long-standing *O. volvulus* infection which may date back to the period before the onset of epilepsy. As such, the significant association between nodule detection and nodding seizures may actually indicate that these participants had been heavily infected several years ago, thereby increasing their risk of developing a more severe form of epilepsy (Chesnais *et al*., 2018).

The high onchocerciasis prevalence among our study participants testifies to the sub-optimal onchocerciasis control in the area. Indeed, we previously reported a very low ivermectin coverage among the village residents in Maridi, particularly for children aged 5-10 years (Colebunders *et al*., 2018b), similar to observations from several other onchocerciasis hyper-endemic regions (Siewe Fodjo *et al*., 2019a). To optimize onchocerciasis control and reduce the transmission of the parasite, better coverage rates should be attained and the inclusion of under-fives during

Table 4. Multivariate analysis of factors associated with epilepsy-related outcomes.

Outcome: Seizure frequency			
	aIR	**95% CI**	***p value***
Microfilarial density	1.010	0.999–1.022	0.080
Age	0.928	0.896–0.963	<0.001
Female gender	0.650	0.461–0.915	0.011
Ivermectin use in 2017	1.206	0.819–1.811	0.344
Regular antiepileptic drug use	0.825	0.578–1.177	0.262
Outcome: Nodding seizures			
	aOR	**95% CI**	***p value***
Microfilarial density	1.022	1.005–1.041	0.014
Age	0.871	0.818–0.924	<0.001
Female gender	0.706	0.429–1.153	0.166
Ivermectin use in 2017	1.141	0.639–2.044	0.656
Outcome: Cognitive impairment			
	aOR	**95% CI**	***p value***
Microfilarial density	0.993	0.976–1.010	0.449
Age	0.970	0.909–1.031	0.329
Female gender	0.832	0.499–1.384	0.477
Seizure frequency	1.009	1.004–1.014	<0.001
Epilepsy duration	1.122	1.044–1.211	0.002
Ivermectin use in 2017	0.925	0.509–1.656	0.793
Regular antiepileptic drug use	0.464	0.275–0.775	0.004
Outcome: Rankin disability score			
	aOR	**95% CI**	***p value***
Microfilarial density	0.996	0.979–1.013	0.683
Age	0.915	0.849–0.979	0.014
Female gender	0.797	0.471–1.345	0.396
Seizure frequency	1.011	1.006–1.015	<0.001
Epilepsy duration	1.193	1.104–1.296	<0.001
Ivermectin use in 2017	0.789	0.433–1.409	0.429
Regular antiepileptic drug use	0.341	0.195–0.584	<0.001

aIR: adjusted incidence risk. aOR: adjusted odds ratio. CI: confidence interval

ivermectin mass drug administration should also be considered, but this requires clinical trials to assess the safety of ivermectin in this population.

Important to note is the very low ivermectin intake in 2017 (25.6%) by PWE. This is much lower than the overall ivermectin coverage in persons above the age of 11 years (50-60%) (Colebunders *et al*., 2018b). Lower coverage among PWE compared to the general population has also been reported in Cameroon (Siewe Fodjo *et al*., 2019b), and could be due to the fact that having epilepsy is considered as a contraindication to ivermectin in some communities.

Finally, our findings highlight that OAE is more detrimental to younger children because younger PWE were prone to worse epilepsy outcomes. Cognitive impairment and disability increased with increasing seizure frequency and duration of epilepsy, in line with the findings of Idro and collaborators (Idro *et al*., 2018). This has devastating consequences on the community, because many children eventually become disabled or even die, thus altering the demography and development prospects of the affected villages (Kamgno *et al*., 2003). Fortunately, timely and regular AED treatment would ameliorate epilepsy outcomes, particularly cognitive performance and disability.

The strength of our study resides in the fact that a large number of PWE with different types of seizures were examined in an area where there has been little ivermectin distribution in the past, and where there are no pigs, thus neurocysticercosis cannot explain the high prevalence of epilepsy. The door-to-door study performed in May 2018 revealed that 46.3% of

the population in the villages in Maridi never took ivermectin (Colebunders *et al*., 2018b). The explanation for this is that, despite the initiation of the CDTI programme more than 15 years ago, this programme was interrupted for many years and only re-started in 2017. As major limitations in our study, we need to mention the use of two different types of skin punches without weighing the skin snips. This may have affected the precision of the reported mf density. Also, past seizure history was obtained by questioning participants/caretakers, and thus subject to recall bias. Cognitive assessment was not performed using a validated battery of tests. Furthermore, there was probably an underestimation of the nodule prevalence because participants were not examined thoroughly due to privacy concerns, and partly as a result of the lack of experience of some local investigators; hence the low nodule prevalence of 3.2% in spite of the high onchocerciasis endemicity and the low ivermectin exposure. Finally, no other laboratory examinations, apart from skin snips, were performed to exclude other causes of epilepsy and we did not include healthy controls matched for village, age, and gender.

Conclusion

This study shows that persons in Maridi with a history of nodding seizures have higher *O. volvulus* parasitic loads compared to other PWE. This confirms the clinical findings that the development of nodding seizures leads to a more severe form of OAE, associated with more frequent seizures and serious disabilities (Colebunders *et al*., 2018c). □

Supplementary data.
Summary didactic slides and supplementary table are available on the www.epilepticdisorders.com website.

Ethics approval and consent to participate.
Ethical approvals were obtained from the ethics committees of the Ministry of Health of the Republic of South Sudan and the University of Antwerp, Belgium. The purpose and procedures of the study were explained to all participants in their local languages. Participants were free to abstain from participation in the study or to withdraw consent to participate at any time. No direct benefits for participation in the study were provided. All participants were asked to sign an informed consent form and only consenting individuals were enrolled. Minors >12 years and <18 years signed an assent form, while parents or legal guardians consented for younger participants. All individual data were encoded and treated confidentially. All the study sites received ivermectin for onchocerciasis control immediately after data collection.

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None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) Which characteristics differ between persons with nodding syndrome and other forms of onchocerciasis-associated epilepsy?

(2) What is the median age at onset of nodding seizures?

(3) Which factors are associated with increased disability in persons with epilepsy in Maridi?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".