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Clinical characteristics of onchocerciasis-associated epilepsy in villages in Maridi County, Republic of South Sudan



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ABSTRACT

Purpose: To describe the clinical manifestations of persons with epilepsy (PWE) in onchocerciasis endemic villages in South Sudan.

Methods: During a survey in Maridi County in May 2018, PWE were interviewed and examined in their households by a clinical officer or medical doctor. Onchocerciasis-associated epilepsy (OAE) was defined as ≥ 2 seizures without any obvious cause, starting between the ages of 3–18 years in previously healthy persons who had resided for at least 3 years in the onchocerciasis endemic area.

Results: Seven hundred and thirty-six PWE were included in the study; 315 (42.8%) were females; median age was 18 years. A variety of seizure types were reported: generalized tonic-clonic seizures in 511 PWE (69.4%), absences in 15 (2.0%), focal motor seizures with full awareness in 7 (1.0%), focal motor seizures with impaired awareness in 25 (3.4%), brief episodes of hallucinations in 316 (43.9%) and nodding seizures in 335 (45.5%). The median age of onset of all seizures was 10 years, and 8 years for nodding seizures. PWE with nodding seizures presented with more cognitive disabilities. The diagnostic criteria for OAE were met by 414 (85.2%) of the 486 PWE with complete information. Eighty (11.0%) PWE presented with Nakalanga features. Only 378 (51.4%) PWE were taking anti-epileptic treatment.

Conclusion: PWE presented with a wide spectrum of seizures. The high percentage of PWE who met the diagnostic criteria for OAE suggests that better onchocerciasis control could prevent new cases. Urgent action is needed to close the anti-epileptic treatment gap.

1. Introduction

Previous surveys have demonstrated that areas with high onchocerciasis transmission are prone to an increased prevalence of epilepsy [1]. To describe this epidemiological phenomenon, the term onchocerciasis-associated epilepsy (OAE) was proposed that includes

different seizure presentations including nodding syndrome (NS) [2,3]. NS was first investigated in 2001–2 in Lui and Amadi in Western Equatoria region, South Sudan, by a team led by the World Health Organization (WHO) [4]. Three small case control studies (82 pairs in total) performed during these investigations showed that infections with *Onchocerca volvulus* diagnosed by skin snips were more often

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present in NS cases compared to controls (OR 9.3–29.0) [4]. In 2011, the Centers for Disease Control and Prevention (CDC) confirmed this finding in a case-controlled study involving 38 pairs from two different communities in Maridi and Witto towns (OR = 3.2) [5]. In 2013, a rapid assessment of the prevalence of epilepsy in Mvolo, Western Equatoria region, showed that one in two households had at least one child with epilepsy [6]. Recently, an epilepsy survey in villages west of Juba County and in Tore Payam in Yei County, Central Equatoria region, also identified persons with NS (Dr. Louis Edward Danga, unpublished report). However until now no population-based study has investigated the epilepsy prevalence and the clinical spectrum of epilepsy in any onchocerciasis endemic region in South Sudan.

In addition to the classic features of onchocerciasis (skin changes and eye disorders), different types of epilepsy, growth retardation, delayed or absent external signs of sexual development, and facial, thoracic and spinal deformities have been observed in people living in onchocerciasis endemic areas [2]. The frequency of these different clinical manifestations and the underlying pathogenesis is unknown.

In May 2018, a door-to-door household survey was conducted in an onchocerciasis endemic area in Maridi, in the Western Equatoria region of South Sudan (Fig. 1).

We visited 44 villages in 8 study sites in the Maridi central area (Fig. 2).

A total of 2511 households were visited, corresponding to 17,652 individuals; 736 (4.2%) individuals had epilepsy confirmed by a clinical officer or medical doctor. Detailed prevalence and incidence data are published elsewhere. In this paper we describe the clinical features of the PWE identified in these villages.

2. Methods

2.1. Study setting

The population of Maridi County is estimated at 101,065 [7]. Water is mainly accessed from the Maridi River, which is fast flowing with several shallow rapids and a weir near the town that provides breeding sites for the *Simulium* vector (blackfly) that transmits *O. volvulus*.

Farming is the main economic and livelihood activity in these villages. The livestock are mainly goats and sheep; no pigs are kept in the Maridi villages.

2.2. Study design

The study protocol has been previously published [8]. In brief, all individuals in selected villages in the area around Maridi town were included in a door-to-door survey in May 2018. A two-step approach was used to identify persons with epilepsy. A pre-tested validated questionnaire consisting of five specific questions was used to screen for epilepsy [9]. Research assistants living in the affected villages were trained to conduct the screening process. Questionnaires were translated into the local language and back translated into English to ensure no loss of meaning, and pilot tested. Persons suspected to have epilepsy identified by the research assistants were visited in their homes by a clinical officer or medical doctor who took a detailed medical history and performed a targeted clinical examination to confirm or reject the diagnosis of epilepsy, using a structured pre-tested questionnaire. During clinical examination, the following elements were assessed: facial, thoracic or spinal abnormalities, presence of external signs of



Fig. 1. Map of South Sudan with the major cities including Maridi.

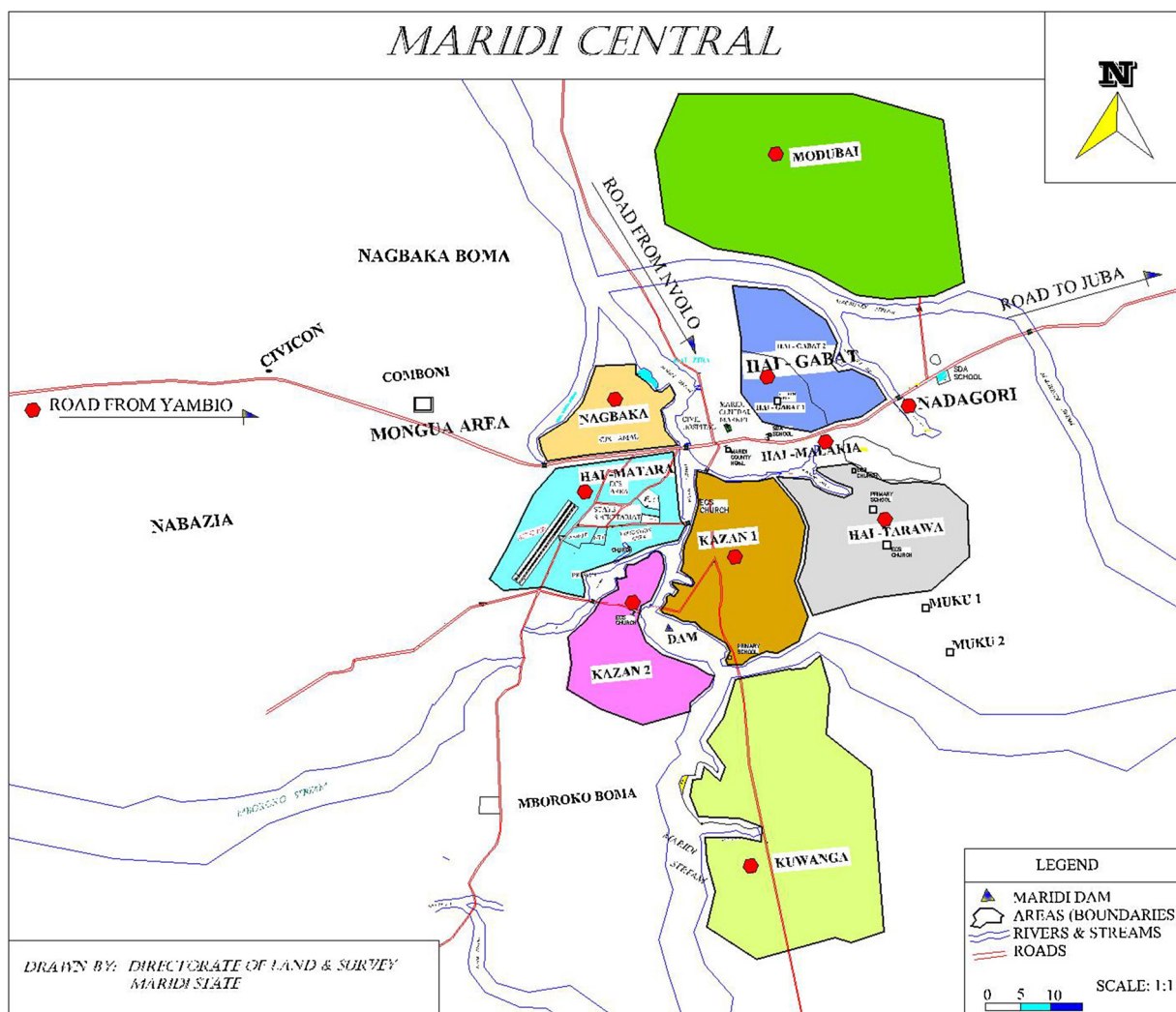


Fig. 2. Map of the Maridi central area showing the eight study sites.

sexual development in individuals > 16 years old with growth retardation, signs suggestive of onchocerciasis skin lesions (papular or nodular pruritic skin, leopard and lizard skin), neurological conditions (mental disability, psychiatric problems, gait disorders, muscular weakness) and degree of disability.

2.2.1. Definitions

Epilepsy was defined as recommended by the International League Against Epilepsy (ILAE) as an individual with at least two unprovoked seizures with a minimum of 24 h separating the two episodes [10].

A person with *active epilepsy* was defined as a person who is taking anti-epileptic treatment or who is not on anti-epileptic treatment but had at least one episode of seizures during the last 5 years.

Nodding seizures were defined as the head dropping forward repeatedly during a brief period of reduced consciousness.

A person with *OAE* was defined as a person meeting all the following six criteria [2]: 1) a history of at least two unprovoked epileptic seizures at least 24 h apart; 2) living for at least 3 years in an onchocerciasis-endemic region; 3) living in a village with a high prevalence of epilepsy including families with more than one child with epilepsy; 4) no other obvious cause of epilepsy; 5) onset of epilepsy between the ages of 3 and 18 years; 6) normal psychomotor development before the onset of epilepsy.

As potential “obvious” causes of epilepsy, a history of peri-natal trauma, severe measles, malaria, encephalitis or meningitis, or head

injury with loss of consciousness in the 5 years preceding the onset of seizures was considered.

Nakalanga features were defined as an association of growth retardation without an obvious cause, with facial, thoracic or spinal deformation and delay or absence of external signs of sexual development [9].

The level of autonomy of PWE was assessed using the modified Rankin Scale [11] and ranged from no disability to severe disability.

2.3. Study inclusion criteria

All persons suspected to have epilepsy during the house to house screening process who were confirmed by a clinical officer or medical doctor were included in the study.

2.4. Data collection, management

Data were collected by trained clinical officers and medical doctors using a questionnaire deployed on Open Data Kit (ODK, <https://opendatakit.org/>) software installed on tablet computers.

2.5. Data analysis

Means and standard deviations are presented for continuous outcome measures, while frequencies and percentages are presented for

categorical variables. Chi-squared tests were used to compare any group differences for categorical variables. For non-parametric continuous variables, either a Mann Whitney test or a Kruskal Wallis ranking test was performed when the medians for more than two variables were compared. More specifically, we analyzed the gender and age distribution of different types of epilepsy (epilepsy without nodding seizures, nodding seizures only, and nodding seizures with other forms of seizures), the frequency of the different forms of seizures, and the age of onset, clinical features, and family history of PWE with different types of epilepsy. Certain questions were not asked because of an error in formatting the ODK questionnaire, and for certain questions the answer was not known. To calculate the percentage of persons providing answers to each question, we excluded from the denominator any questions that were not asked, and any questions for which an answer was not obtained.

2.6. Ethics approval and consent to participate

Ethical approval was obtained from the ethics committee of the Ministry of Health of the Republic of South Sudan and from the ethics committee of the University of Antwerp, Belgium. The study aims and procedures were explained to all participants in the language of their choice and signed or finger-printed informed consent was obtained from participants, parents or carers, and assent obtained from adolescents (age 12–18 years). All personal information was encoded and treated confidentially.

3. Results

Seven hundred and thirty six PWE were included in the study, of which 421 (57.2%) were males and 315 (42.8%) were females. The median age of all PWE was 18 years (interquartile range (IQR):15–20); 6.5% were younger than 10 years; 62.2% were between the ages of 10–19 years (Table 1).

In 401 (54.5%) PWE there was a history of epileptic seizures without nodding; in 74 (10.1%) a history of only nodding seizures; and in 261 (35.5%) a history of nodding seizures followed by the development of other seizures types. The most frequent seizure type was generalized tonic-clonic seizures (Table 2).

In 621 (84.4%) PWE there was a history of losing consciousness; in 594 (80.7%) there was foaming at the mouth; in 384 (52.2%) seizures were associated with loss of bladder control and in 477 (64.8%) with biting of the tongue. In 335 (45.5%) PWE there was a history of nodding seizures and in 316 (43.9%) brief episodes of hallucinations were reported. The latter were less frequently reported in persons with a

Table 1 Gender and age distribution of different types of epilepsy.

	Epilepsy without nodding (%) N = 401 (54%)	Nodding seizures only (%) N = 74 (10.1%)	Nodding and other seizure types (%) N = 261 (35.5%)	Total number of PWE* (%) N = 736 (100%)	P value
Gender (males)	226 (56.4%)	38 (51.4%)	157 (60.2 %)	421 (57.2%)	0.4 (differences between the 3 categories)**
Median age (years), range	18 (IQR:15–22)	16 (IQR:12–18)	17 (IQR:14–19)	18 (IQR:15–20)	< 0.001***
Age distribution					< 0.001 (differences between all age categories)**
0–9 years	26 (6.5%)	8 (10.8%)	13 (5%)	47 (6.4%)	
10–19 years	221(55.1%)	53 (71.6%)	184 (70.5%)	458 (62.2%)	
20–29 years	125 (31.2%)	12 (16.2%)	60 (23%)	197 (26.8%)	
30–39 years	17 (4.2%)	1 (1.4%)	3 (1.2%)	21 (2.9%)	
40–49 years	7 (1.8%)	0	1 (0.4%)	8 (1.1%)	
≥ 50 years	5 (1.3%)	0	0	5 (0.7%)	

* PWE = persons with epilepsy, IQR = interquartile range.

** Chi-square p value.

*** P value derived from the Kruskal Wallis test.

Table 2 Frequency of seizure types (n = 736).

Seizure types	Frequency	(%)
Generalized tonic-clonic seizures	511	69.4%
Generalized myoclonic seizures	82	11.1%
Generalized atonic seizures	35	4.8%
Absences	15	2.0%
Nodding seizures	335	45.5%
Brief episodes of hallucinations	316	43.9%
Focal motor aware seizures	7	1.0%
Focal motor seizures with impaired awareness	25	3.4%
Focal to bilateral tonic-clonic seizures	0	0%
Unclassified	21	2.9%

* Answers only available for 719 PWE.

Table 3 Age of onset of the different epilepsy types.

Age of onset	Epilepsy without nodding (%) N = 380*	Nodding seizures only (%) N = 72*	Nodding and other seizure types (%) N = 256*	Total number of PWE (%) N = 708*	P value
Median age at onset (range)	11 (IQR:7-15)	7 (IQR:5-9)	9 (IQR: 6-11)	10 (IQR:6-13)	< 0.001**
Age of onset					< 0.001***
0–9 years	136 (35.8 %)	55 (76.4%)	145 (56.6%)	336 (47.5%)	
10–19 years	216 (56.8 %)	17 (23.6%)	110 (43 %)	343 (48.4%)	
20–29 years	19 (5 %)	0	1 (0.4%)	20 (2.8%)	
30–39 years	5 (1.3 %)	0	0	5 (0.7%)	
40–49 years	1 (0.3%)	0	0	1 (0.1%)	
≥ 50 years	3 (0.8 %)	0	0	3 (0.4%)	

* information not available for all persons with epilepsy (PWE), IQR = interquartile range.

** P value derived from the Kruskal Wallis test.

*** Chi-square p-value.

history of only nodding seizures (12/74–16.2%) compared with persons with nodding and other types of seizures (127/252–50.4%) and with persons with seizures without nodding (177/393–45%) (p < 0.001). In 708 (96.2%) PWE information about the year of onset of seizures was obtained. The median age of onset of seizures was 10 years (IQR: 6–13); 647 (87.9%) developed their first seizures between the ages of 3–18 years. In 30 PWE (4.2%) seizures started before 3 years of age. The median age at onset of seizures was 8 years for nodding seizures and 11

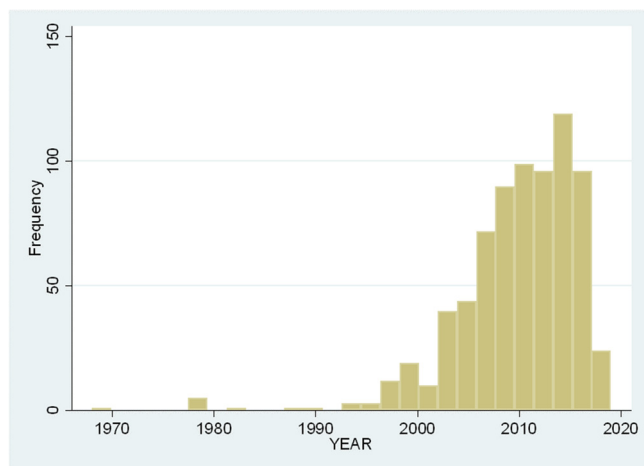


Fig. 3. Reported number of new onset epilepsy cases over time.

years for other seizure types. In PWE with only nodding seizures, 76.4% started seizures in the 0–9 year group compared to only 35.8% in persons without nodding seizures ($p < 0.001$) (Table 3).

Two hundred and eighty four (40.0%) PWE developed their first seizures in the 5 years preceding the survey, 85 (12.0%) in the two years before and 66 (9.3%) in the year before; 57 (86.4%) of the latter were 3–18 years old. Numbers of new onset epilepsy increased as from the year 2000 (Fig. 3).

Two hundred and eight (29.6%) of the 703 PWE for which information was obtained reported at least one seizure daily, 370 (52.6%) at least weekly, and 637 (90.6%) at least monthly.

In 414 of the 486 (85.2%) PWE for which data were available on all OAE criteria, OAE criteria were met. Seventy two PWE were not considered to have OAE for one or more of the following reasons: in 34 (47.2%) the seizures did not start between the ages of 3–18 years; and in 38 (52.7%) the medical history revealed a possible cause of epilepsy, including a perinatal event [1], measles [7], malaria [29] and head injury [3]. An additional 14 infants less than 3 years old also met the OAE criteria when the age of onset of epilepsy and duration of living in

the village were not taken into account. PWE with nodding seizures who developed other forms of epilepsy presented more often with cognitive and other disabilities, psychiatric co-morbidities, thoracic or spinal deformities, and muscle wasting (Table 4).

Eighty PWE (11.0%) presented with Nakalanga features; 10 (2.7%) of the 377 PWE examined that were > 16 years did not have secondary sexual characteristics. Nodding seizures were more frequently triggered by the sight of food than other seizure types.

Using the NS criteria proposed during the 2012 meeting organized by the World Health Organization (WHO) in collaboration with the Ugandan Ministry of Health and the US Centers for Disease Control and Prevention (CDC) in Kampala [12], 311 of 335 persons with a history of nodding seizures (92.8%) met the criteria of probable NS. Among those not meeting the criteria, in 16 nodding seizures started before 3 years of age, and in two after 18 years of age. Blindness was more frequent in persons with nodding and other seizure types. The mean age of those with blindness of both eyes was 19 years (IQR 15–29 years).

Case report

A 21 year old man whose illness started at the age of 7 years. He initially complained of persistent headache and blurred vision and then developed nodding seizures followed by generalized tonic-clonic seizures. Before the onset of seizures his growth and psychomotor development had been normal and he had never experienced any serious illness. Seizures could start when he was given food but also could appear at any time without an obvious trigger. He lost his sight at the age of 10 years. On physical examination he “looked like a child” (body weight 27 kg, height 130 cm), was very weak, had dry skin, a pigeon chest, kyphosis, and generalized muscle atrophy with difficulty in walking (Fig. 4a). He was blind in both eyes with anterior chamber iritis, sclerosing keratitis and left sided proptosis (Fig. 4b).

He was mentally severely impaired, not able to take care of himself. He lived with his mother in a temporary house, less than 2 km away from the Maridi Dam. His mother had 9 children, one of whom died of epilepsy; 3 other siblings also had epilepsy. The frequency of his seizures decreased when he took carbamazepine 200 mg per day, however his mother (his father had left her) struggled to buy anti-epileptic drugs. At the time of the survey he was experiencing daily seizures. He had never taken ivermectin.

In 405 (58.0%) of the 698 PWE in which the question was asked

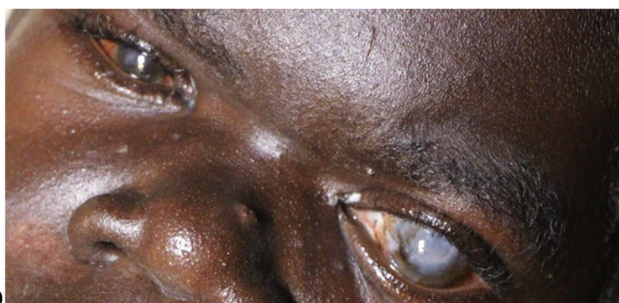
Table 4
Clinical features of PWE with different epilepsy types.

	Epilepsy without nodding seizures N = 401 (54.5%)	Nodding seizures only N = 74 (10.1%)	Nodding and other seizure types N = 261 (35.5 %)	Total number of PWE N = 736	P-value*
Physical examination done	340 (84.8%)	64 (86.5%)	229 (87.7%)	633 (86.0%)	
Mental status and Disabilities					
Cognitive disability	326/340 (96%)	63/64 (98.4%)	212/229 (92.6%)	601/633 (94.9%)	0.09
Psychiatric abnormalities	8/340 (2.4%)	2/64 (3.1%)	14/229 (6.1%)	24/633 (3.8%)	0.07
Paresis	12/340 (3.5%)	3/64 (4.7%)	17/229 (7.4%)	32/633 (5.1%)	0.1
Walking abnormality	18/340 (5.3%)	5/64 (7.8%)	26/229 (11.4%)	49/633 (7.7%)	0.03
Deformity and dysmorphic features					
Thoracic, or spinal abnormality	9/340 (2.7%)	5/64 (7.8%)	37/229 (16.2%)	51/633 (8.1%)	< 0.001
Facial abnormality	13/340 (3.8%)	3/64 (4.7%)	19/229 (8.3%)	35/633 (5.5%)	0.07
Muscle wasting	33/340 (9.7%)	19/64 (29.7%)	66/229 (28.8%)	118/633 (18.6%)	< 0.001
Blindness	0	1/64 (1.6%)	4/229 (1.7%)	5/633 (0.8%)	
One eye					
Both eyes	0	0	6/229 (2.6%)	6/633 (0.9%)	
Dermatological findings					
Normal skin	277/340 (81.5%)	48/64 (75.0%)	163/229 (71.2%)	488/633 (77.1%)	0.06
Papular/nodular pruritic skin	11/340 (3.2%)	7/64 (10.9%)	13/229 (5.7%)	31/633(4.9%)	0.06
“Leopard skin”	1/340 (0.3%)	1/64 (1.6%)	4/229 (1.8%)	6/633 (1%)	0.06
“Lizard skin”	5/340 (1.5%)	1/64 (1.6%)	6/229 (2.6%)	12/633 (1.9%)	0.06
Mean Rankin disability score (1-5)	1.4 (SD: 0.7)	1.6 (SD: 1.0)	1.8 (SD: 1.0)	1.6 (SD: 0.9)	0.0001
Severe disability (score > 3)	10/401 (2.5%)	3/74 (4.1%)	13/261 (5.7%)	26/736 (3.5%)	0.2
Seizures triggered by sight of food	7/401 (1.7%)	32/41 (80%)	144/261 (55.4%)	183/701 (26.1%)	< 0.001

* Chi-square p-value.



a



b

Fig. 4. 21 year old man with OAE, with nodding seizures, Nakalanga features (a) and bilateral blindness (b).

there was a family history of epilepsy and in 354 (50.7%) there was a sibling with epilepsy (Table 5).

Only 378 (51.4%) PWE were taking anti-epileptic treatment at the time of the survey; 209 (28.4%) had taken anti-epileptic treatment in the past. Reasons for no longer taking anti-epileptic treatment included financial difficulties to buy the medication in 171/206 (83%) and non-availability of medication in 13/206 (6.3%).

Three hundred and thirty five (46.3%) of 723 ivermectin eligible PWE (individuals at least 5 years old in 2017) had ever taken ivermectin; 192 (57.3%) of the 335 had taken ivermectin in 2017.

4. Discussion

This is the largest study describing the clinical features of PWE in an onchocerciasis endemic area. PWE presented a wide spectrum of seizure types and Nakalanga features. Nodding seizures usually began at an earlier age than other seizure types. As PWE grew older, nodding seizures were replaced with other types of seizures (most often generalized tonic-clonic seizures) or nodding seizures persisted together with other types of seizures, as previously reported [13]. The most frequent seizure types were generalized tonic-clonic seizures. PWE with a history of nodding seizures were more severely impaired mentally and physically than PWE without nodding seizures. The fact that blindness was only observed in persons with a history of nodding seizures suggests that these individuals were more heavily infected with *O. volvulus*. The fact that hallucinations and thoracic abnormalities were less frequently reported in persons with a history of only nodding seizures could be explained by the fact that such persons are in an earlier stage of disease and only later develop other forms of seizures, as previously reported [13]. Nodding seizures were more often triggered by the sight of food compared with other seizure types. This confirms what has been reported previously [4,14,15] but the reason remains unclear. At the time of the survey only 51.4% PWE reported taking anti-epileptic treatment and consequently many PWE reported high frequencies of seizures.

A high percentage (91.8%) of PWE met the diagnostic criteria for OAE suggesting that *O. volvulus* infection was the main trigger causing epilepsy in this study area. If this is the case, implementation of bi-annual CDTi should markedly reduce the incidence of epilepsy in the years to come.

A recently published postmortem study suggests that NS is a tauopathy and a neurodegenerative disease [16]. However, tau accumulation, as in Alzheimer disease, may be the consequence rather than a primary event [17]. Our study suggest that *O. volvulus* infection is the trigger causing a spectrum of epilepsy types including NS and that these different conditions are associated with different degrees of co-morbidities.

A strength of our study is that all PWE were seen by clinical officers or a medical doctor in their households. This allowed us to describe the clinical spectrum of epilepsy in these onchocerciasis endemic villages. Indeed if persons suspected to have epilepsy are referred to a health centre to be seen by a medical doctor, there is a risk that certain individuals, especially those who are too sick or unable to walk, may never reach the clinic.

However, our study has several limitations. The clinical diagnosis of epilepsy was made by clinical officers or medical doctors without

Table 5
Family history of seizures.

	Epilepsy without nodding seizures N = 399*	Nodding seizures only N = 40*	Nodding seizures and other seizure types N = 259*	Total number of PWE N = 698*	P-value**
Family history of seizures	219 (54.9%)	22 (55%)	164 (63.3%)	405 (58%)	0.1
Sibling with epilepsy	190 (47.6%)	22 (55%)	142 (54.8%)	354 (50.7%)	0.8

* Information not available for all persons with epilepsy (PWE).

** Chi-square p-value.

confirmation by a neurologist. Also, only 86% of the PWE were available for physical examination and family members may not have had perfect recollection or knowledge to answer the questions accurately. Body weight and height were not measured even in the persons reported to have Nakalanga features. The results concerning the frequency of the different types of seizures need to be interpreted with caution. Percentages reported for nodding seizures and generalized tonic-clonic seizures are probably reliable because they were well known and easily recognizable by the community. On the other hand focal seizures, being more subtle, may have been underestimated. Only a low number of focal motor seizures was reported and the frequency of focal non-motor seizures remains to be determined. Brief episodes of hallucination were frequently reported but the types of hallucinations and when they occurred were not specified. Cognitive disability and the presence of psychiatric co-morbidity were only assessed by interviewing family members and without using a validated test. No laboratory investigations were performed. A high percentage of PWE met the OAE criteria but this does not prove the epilepsy was caused by onchocerciasis. Skin snip and *O. volvulus* antibody testing were not performed, and other causes of epilepsy were excluded only by medical history. According to a meta-analysis of 119 papers in 2014 on the prevalence of epilepsy in sub-Saharan Africa, the median prevalence of epilepsy was 1.4% [18]. From all studies included in this analysis, less than 10% of epilepsy was considered due to head trauma, and the fraction of epilepsy attributable to antenatal or perinatal causes in sub-Saharan Africa was reported as 0.33 [19]. This means that in most African countries the prevalence of epilepsy caused by a perinatal event is about 0.46% and less than 0.14% due to head injury. Thus the maximum epilepsy prevalence considering these two causes is 0.6%. Given that no particular reason predisposes Maridi to more perinatal events or head trauma as causes of epilepsy than other rural regions in Africa, these events cannot explain the high prevalence observed in this study. Given the absence of pigs in the Maridi villages, cysticercosis is unlikely to be a cause of the epilepsy in this study. Certain PWE were not at home during the survey and consequently answers were not obtained for all the questions asked. Also due to a formatting error in the ODK platform, the question about family history of seizures was omitted by some interviewers.

From our data, the number of persons who developed epilepsy appeared to increase from the year 2000 onward. However, these numbers need to be interpreted with caution as life expectancy of PWE in Maridi is short, as the majority of PWE, 706 (96.1%), were less than 30 years old. Therefore, with a median age of onset of epilepsy around the age of 10 years it is expected that most PWE do not live for more than 20 years. Therefore it is expected that in 2018 very few PWE would have had an onset of seizures reported before 2000.

The 51.4% reported anti-epileptic treatment use is probably an overestimation of the percentage of persons taking anti-epileptic drugs. This is illustrated by the case report in this paper. Indeed during the survey it was noted that he was on anti-epileptic treatment but when we revisited his household it was clear he only received carbamazepine intermittently at a sub-optimal dose when there was money to pay for it.

5. Conclusions

PWE in onchocerciasis endemic villages in the Maridi area presented with a wide spectrum of seizures including nodding seizures and Nakalanga features. A great majority of PWE met the diagnostic criteria for OAE, suggesting that better onchocerciasis control could prevent new cases. Epilepsy management algorithms in these areas must be adjusted to reflect the varied seizure types. Urgent action is needed to prevent children from developing OAE and to treat all PWE in onchocerciasis endemic regions with appropriate anti-epileptic treatment to reduce OAE associated morbidity and mortality, and as a corollary, improve the quality of life of PWE and their families.

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Authors' contributions

RC wrote the first draft of the paper. All authors were involved in the development of the study design and essential study tools. Based on different expertise and experience, all authors critically reviewed specific sections of the paper.

Competing interests

No conflict of interest declared.

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References

- [1] Colebunders R, Nelson Siewe FJ, Hotterbeekx A. onchocerciasis-associated epilepsy, an additional reason for strengthening onchocerciasis elimination programs. *Trends Parasitol* 2018;34(3):208–16.
- [2] Colebunders R, Nelson Siewe FJ, Hotterbeekx A. onchocerciasis-associated epilepsy, an additional reason for strengthening onchocerciasis elimination programs. *Trends Parasitol* 2018;34(3):208–16.
- [3] Colebunders R, Njamnshi AK, van Oijen M, Mukendi D, Kashama JM, Mandro M, et al. Onchocerciasis-associated epilepsy: from recent epidemiological and clinical findings to policy implications. *Epilepsia Open* 2017;2(2):145–52.
- [4] Tumwine JK, Vandemaele K, Chungong S, Richer M, Anker M, Ayana Y, et al. Clinical and epidemiologic characteristics of nodding syndrome in Mundri County, southern Sudan. *Afr Health Sci* 2012;12(3):242–8.
- [5] Centers for Disease C, Prevention. Nodding syndrome—South Sudan, 2011. *MMWR Morb Mortal Wkly Rep* 2012;61(3):52–4.
- [6] Colebunders R, Hendy A, Mokili JL, Wamala JF, Kaducu J, Kur L, et al. Nodding syndrome and epilepsy in onchocerciasis endemic regions: comparing preliminary observations from South Sudan and the Democratic Republic of the Congo with data from Uganda. *BMC Res Notes* 2016;9:182.
- [7] National Bureau of Statistics. National Bureau of Statistics: population distribution by age group by sex by payam. release Meditor. Population distribution by age group by sex by payam, vol. 2. National Bureau of Statistics; 2013 2013 <http://www.ssnbss.org/home/document/census/populationdistribution-by-age-group-sex-and-payam-greater-bahr-el-gazal> (Accessed 4 August 18).
- [8] G. Abd-Elfarag, M.Y. Logora, J.Y. Carter, M. Ojok, J. Songok, S. Menon, F. Wit, R. Lako, R. Colebunders, The effect of bi-annual community-directed treatment with ivermectin on the incidence of epilepsy in onchocerciasis endemic villages in South Sudan: a study protocol. *Infect Dis of Poverty*, In press.
- [9] Diagona M, Preux PM, Tuillas M, Ould Hamady A, Druet-Cabanac M. [Depistage de l'épilepsie en zones tropicales: validation d'un questionnaire en Mauritanie]. *Bull Soc Pathol Exot* 2006;99(2):103–7.
- [10] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Helen Cross J, Elger CE, et al. A practical clinical definition of epilepsy. *Epilepsia* 2014;55(4):475–82.
- [11] Zhao H, Collier JM, Quah DM, Purvis T, Bernhardt J. The modified rankin scale in acute stroke has good inter-rater-reliability but questionable validity. *Cerebrovasc Dis* 2010;29(2):188–93.
- [12] World Health Organisation. International scientific meeting on nodding syndrome, Kampala, Uganda 30 July – 1 August 2012 meeting report 2012 (Accessed 21 September 18). http://www.who.int/neglected_diseases/diseases/Nodding_syndrom_Kampala_Report_2012.pdf.
- [13] Winkler AS, Wallner B, Friedrich K, Pfausler B, Unterberger I, Matuja W, et al. A longitudinal study on nodding syndrome—a new African epilepsy disorder. *Epilepsia* 2014;55(1):86–93.
- [14] Dowell SF, Sejvar JJ, Riek L, Vandemaele KA, Lamunu M, Kuesel AC, et al. Nodding syndrome. *Emerg Infect Dis* 2013;19(9):1374–84.
- [15] Sejvar JJ, Kakooza AM, Foltz JL, Makumbi I, Atai-Omoruto AD, Malimbo M, et al. Clinical, neurological, and electrophysiological features of nodding syndrome in kitgum, Uganda: an observational case series. *Lancet Neurol* 2013;12(2):166–74.
- [16] Pollanen MS, Onzivua S, Robertson J, McKeever PM, Olawa F, Kitara DL, et al.

- Nodding syndrome in Uganda is a tauopathy. *Acta Neuropathol* 2018.
- [17] Gotz J, Chen F, van Dorpe J, Nitsch RM. Formation of neurofibrillary tangles in P3011 tau transgenic mice induced by abeta 42 fibrils. *Science* 2001;293(5534):1491–5.
- [18] Ba-Diop A, Marin B, Druet-Cabanac M, Ngoungou EB, Newton CR, Preux PM. Epidemiology, causes, and treatment of epilepsy in sub-Saharan Africa. *Lancet Neurol* 2014;13(10):1029–44.
- [19] Ngugi AK, Bottomley C, Kleinschmidt I, Wagner RG, Kakooza-Mwesige A, Aengibise K, et al. Prevalence of active convulsive epilepsy in sub-Saharan Africa and associated risk factors: cross-sectional and case-control studies. *Lancet Neurol*. 2013;12(3):253–63.