Prevalence of onchocerciasis-associated epilepsy in Mvolo County, South Sudan: a door to door survey

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Abstract

In June 2020, a door-to-door household survey was conducted in Mvolo County, an onchocerciasis endemic area in South Sudan. A total of 2,357 households containing 15,699 individuals agreed to participate in the study. Of these, 5,046 (32.1%, 95%CI: 31.4-32.9%) had skin itching and 445 (2.8%, 95% CI: 2.6-3.1%) were blind. An epilepsy screening questionnaire identified 813 (5.1%) persons suspected to have epilepsy. Of them, 804 (98.9%) were seen by a medical doctor and in 798 (98.1%) the diagnosis of epilepsy was confirmed. The overall epilepsy prevalence was 50.8/1000 (95% CI: 47.6-54.4/1000) and prevalence of nodding syndrome was 22.4/1000 (95% CI: 20.1-24.9/1000). Younger age, being male, skin itching, blindness and living in a village close to the Naam river were risk factors for epilepsy. The annual incidence of epilepsy was 82.8/100,000 (95% CI: 44.1-141.6/100,000). In conclusion, a high prevalence and incidence of epilepsy was observed in Mvolo, South Sudan. Strengthening the onchocerciasis elimination programme is urgently needed to prevent epilepsy in this region.

1. Introduction

A high prevalence of epilepsy including nodding syndrome (NS) has been observed in onchocerciasis-endemic areas in South Sudan [1-4]. NS was first investigated by a team from the World Health Organization in 2011 in

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Mundri (Lui and Amadi) in Western Equatoria State [1]. In 2013, the epilepsy prevalence in Mvolo County in Western Equatoria was estimated by the South Sudan Relief and Rehabilitation Commission to be 8.4% (4,025/48,100) (Anthony Amba, personal communication). This high prevalence was confirmed during a rapid assessment of the epilepsy prevalence in Mvolo in Western Equatoria. In a survey of 22 households, 28 (16.7%) of 168 children were found to have epilepsy and in 13 (59%) of households there was at least one child with epilepsy [3].

In 1948, DJ Lewis, a medical entomologist, described Mvolo as a place with extremely intense *Simulium spp.* biting and high *Onchocerca volvulus* infection prevalence in the flies (in up to 10% of flies L3 larvae were identified in the heads) [5]. He described Mvolo as having only a police post with very few people residing in the area. Today Mvolo is a town surrounded by an agricultural area, where it is hypothesized that despite the risk for onchocerciasis, many people have settled because of the fertile land and the ample supply of fish from the Naam River.

Based on data obtained from cross-sectional epilepsy surveys performed before, during and after the implementation of onchocerciasis elimination programmes, it was suggested that it is possible to stop an NS epidemic and decrease the incidence of epilepsy in onchocerciasis endemic regions [6-8]. However, because the pre- and post-intervention surveys used different methodologies, different epilepsy definitions, and were carried out in different study areas by different research teams, the interpretation of these results is difficult. Therefore we initiated a prospective study in three onchocerciasis-endemic areas in South Sudan where a high prevalence of epilepsy was reported: Maridi, Mundri and Mvolo Counties [4]. The aim of this study is to compare the effect of bi-annual community directed treatment with ivermectin (CDTI) with and without community based vector control with annual CDTI on the incidence of epilepsy including NS [9]. As part of this initiative, baseline epilepsy surveys were conducted at the three study sites. Results of the survey in Maridi County were published in 2019 [4]. In this paper we present the results of the survey in Mvolo County, located in Western Equatorial State, South, South Sudan.

2. Methodology

2.1. Study setting

The study was conducted in villages in the Mvolo (N6.060121, E29.952274) area, located close to the fast flowing Naam River, which is infested with blackflies (Figure 1a & 1b).

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Figure 1a. Map showing South Sudan, Western Equatorial State and Mvolo county highlighted.

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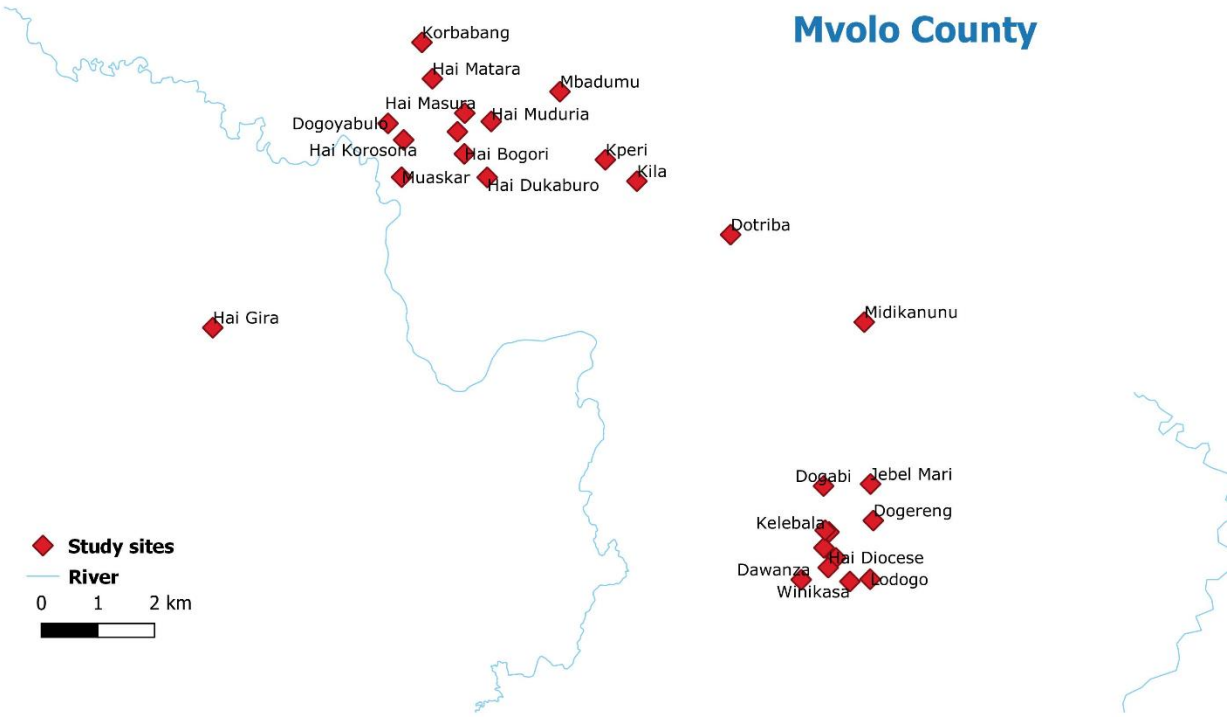

Figure 1b. Map showing the location of Mvolo County, and the villages visited during the house to house survey.

This river becomes very crowded during the fishing season since it is a focal point for communities where men fish, children swim, women wash clothes, and cows graze along the riverbanks (Figure 2).

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Figure 2. River Naam in Mvolo, a crowded area during fishing season.

The projected population of Mvolo is estimated at 67,864. *Jur* is the dominant ethnic group in Mvolo; other ethnic groups include Nyamusa, and Muro-Kodo. *Jur* is the dominant language in Mvolo and the common language of communication is local Arabic.

Farming and fishing are the main economic and livelihood activities; the main crops grown in Mvolo are sorghum, simsim (sesame), groundnuts, vegetables, maize, and millet. Goats, chicken and cattle are the main livestock in Mvolo; no pigs are kept in the area for cultural reasons.

The distribution of annual doses of ivermectin to residents of Mvolo started in 1996, but treatment was interrupted several times during periods of conflict (S Komyangi, personal communication).

2.2. Study design

A door-to-door survey was conducted in different villages in the Mvolo area. Two steps were used to identify people with epilepsy (PWE). In the first phase, households were visited by a trained research team consisting of 20 locally recruited research assistants; each household was visited by one research assistant. After obtaining informed consent, family members were interviewed using a validated questionnaire translated into the local language [10]. In the second phase, persons suspected to have epilepsy by the research assistants were referred to be interviewed and examined by a medical doctor who confirmed the diagnosis of epilepsy or suggested an alternative diagnosis. The 20 research assistants were selected by the Mvolo County Health Department, and the seven medical doctors by the academic affairs office of the College of Medicine at the University of Juba. Research assistants were chosen among the county community drug distributors who have at least secondary school level education and were trained on the use of the screening questionnaire for suspected epilepsy during a one-day

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training workshop. The seven medical doctors were trained on how to confirm the diagnosis of epilepsy. Both the research assistants and the medical doctors pilot tested the data collection tools prior to the actual data collection. All the training was organized by a medical doctor (SR). Moreover, during the home visits SR supervised the research assistants and the medical doctors, and also interviewed and examined selected persons with suspected epilepsy.

2.2.1. Definitions

A case of epilepsy was defined based on the International League against Epilepsy as an individual with at least two unprovoked seizures with a minimum of 24 hours separating the two episodes [11]. Nodding seizures were defined as the head dropping forward repeatedly in a person during a brief period of reduced consciousness. Onchocerciasis-associated epilepsy (OAE) was defined as a person meeting all the following six criteria: i) a history of at least two unprovoked epileptic seizures at least 24 hours apart; ii) living at least 3 years in an onchocerciasis endemic region; iii) living in a village with high epilepsy prevalence and with families with more than one child with epilepsy; iv) no other obvious cause of epilepsy; v) onset of epilepsy between the ages of 3 and 18 years; vi) normal psychomotor development before the onset of epilepsy.

As potential "obvious causes of epilepsy" we considered a history of severe malaria, encephalitis or meningitis, and head injury with loss of consciousness in the five years preceding the onset of epileptic seizures. Nakalanga features were defined as an association of growth retardation without obvious cause, delay or absence of external signs of secondary sexual development, intellectual disability, epilepsy and often facial, thoracic, and spinal abnormalities [9]. A person was considered blind if he/she was unable to recognize the five fingers of a hand. A "permanent household" was defined as a family who had lived in the village for at least 20 years. An "immigrant household" referred to a family who had lived in the village for less than 20 years.

2.2.2. Data collection, management

Screening of households by research assistants to identify persons suspected to have epilepsy was performed using a paper-based questionnaire (supplementary material 1). This questionnaire included five epilepsy screening questions to be addressed to each family member, adapted from a questionnaire that was previously validated in Mauritania [10]. If the answer to one of the five epilepsy screening questions was yes, then this person was considered to be suspected to have epilepsy and was seen by a clinician. Each household member was also asked whether they had taken ivermectin during the previous distribution. The questionnaire also contained questions about duration of residence, ethnicity, main income generating activity of the family, exposure to cattle or pigs, whether family members had recently developed epilepsy. For confirmation of epilepsy, medical doctors used a paper-based questionnaire with unique codes assigned to each suspected case (supplementary material 2). Clinicians assessed the type of epilepsy, potential triggers of seizures, potential obvious causes of epilepsy, epilepsy related co-morbidities (cognitive impairment, behavioural problems, burn scars) and onchocerciasis related clinical signs (skin lesions, vision problems), anti-seizure medication received, and ivermectin intake in the past. The distance of the study villages to the Naam-river in Mvolo was estimated using the village GPS coordinates and the point coordinates of the river.

2.3. Data analysis

Continuous variables were summarized using the median and interquartile range, and frequencies and percentages were used for categorical variables. The prevalence of epilepsy was calculated by dividing the number of clinically confirmed epilepsy cases by the total number of individuals screened. The overall epilepsy incidence in the general population was calculated by dividing the number of new cases of epilepsy in the previous 12 months, by the total number of the study population. Ivermectin coverage was defined as the percentage of the population that reported taking ivermectin in 2019. A multivariable logistic regression using the generalized estimating equations (GEE) adjusting for the similarity between the participants from the same family and families from the same village, with logit-link function was used to assess the potential risk factors of epilepsy. All two-way interactions between the predictors were considered in the model and a likelihood ratio test was used to identify potential interactions.

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3. Ethics approval and consent to participate

Ethics approval was obtained from the ethics committee of the Ministry of Health 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 thumb-printed informed consent was obtained from participants, parents or care-givers, and assent obtained from adolescents (aged 12–18 years). All personal information was encoded and treated confidentially.

4. Results

In total, 2,356 households including 15,699 individuals agreed to participate in the survey. The median number of household members was 4 (IQR:2-6); 2,035 (88%) families belonged to the Jur ethnic group. Farming was the main income generating activity for 2,292 (97.3%) families; 374 (15.9%) families reported fishing and 382 (16.2%) reported cattle keeping, 248 (10.5%) considered themselves employees and 177 (7.5%) traders; 1985 (92.0%) families lived for more than 10 years in the village, 371 (15.8%) were immigrant families (median (IQR) period of residence 9.0 (4.0-13.0) years).

4.1. Prevalence of epilepsy and potential onchocerciasis associated co-morbidities

A total of 15,699 individuals from 2,357 households agreed to participate in the survey. Of these, 5,065 (32.1%, 95%CI: 31.4-32.9%) had skin itching and 445 (2.8%, 95% CI: 2.6-3.1%) were blind (Table 2). An epilepsy screening questionnaire identified 813 (52‰) persons suspected to have epilepsy. Nine individuals suspected to have epilepsy were not seen by a clinician (Figure 2).

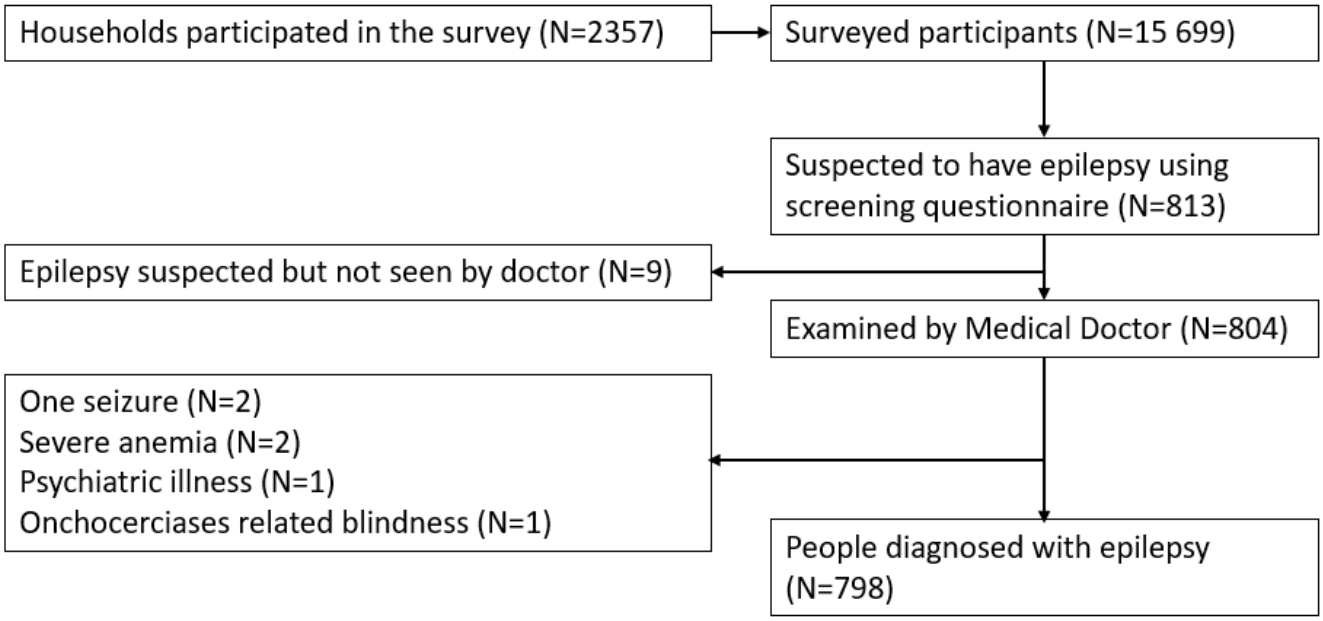

Figure 3. Study participants, from household epilepsy screening to epilepsy diagnosis by the medical doctor

4.2. Prevalence of Epilepsy

In 798 (98.1%) persons suspected to have epilepsy, the diagnosis of epilepsy was confirmed by the clinician. Of the six persons in which the diagnosis of epilepsy was not confirmed, two had a history of only one seizure, one had psychiatric problem, two presented with severe anaemia and one had onchocerciasis related blindness without epilepsy. The overall epilepsy prevalence was 50.8/1000 (95% CI: 47.6-54.4) and of nodding syndrome 22.4/1000 (95% CI: 20.1-24.7) (Table 1). Epilepsy prevalence was highest in the 16−20 and 21−25 year old age groups respectively 112.3/1000 (95%CI: 100.8-125.8) and 140.7/1000 (95%CI: 122.5-161.1) (Table 1).

Table 1. Prevalence of nodding syndrome and other forms of epilepsy by sex and age group

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	Total number of participants	Persons with epilepsy, n ‰ (95%CI)	Nodding syndrome, n ‰ (95%CI)
Sex			
Female	7847	378 (48.2, 43.7-53.1)	168 (21.9, 18.8-25.5)
Male	7845	419 (53.4, 49.7-58.6)	184 (23.5, 20.3-27.0)
Age groups in years			
0–4	1919	6 (3.1, 1.4-6.8)	3 (1.6, 0.5-4.6)
5–10	2928	31 (10.6, 7.5-15.0)	20 (6.8, 4.4-10.5)
11–15	2105	122 (58.0, 48.8-68.8)	67 (31.8, 25.1-40.2)
16–20	2459	277 (112.3, 100.8-125.8)	138 (56.1, 47.7-65.9)
21–25	1244	175 (140.7, 122.5-161.1)	73 (58.7, 46.9-73.2)
26–30	1447	109 (75.3, 62.8-90.1)	34 (23.5, 16.9-32.7)
31–35	754	35 (46.4, 33.6-63.9)	10 (13.3, 7.2-24.2)
36–40	1079	24 (22.1, 15.0-32.9)	4 (3.7, 1.4-9.5)
41–45	492	6 (12.2, 5.6-16.3)	1 (2.0, 0.4-11.4)
>45	1272	13 (10.2, 6.0-17.7)	2 (1.6, 0.4-5.7)
Overall	15,699	798 (50.8, 47.6-54.4)	352 (22.4, 20.1-24.7)

The highest number of PWE were observed in Hai Bogori village (10.4%), Hai Korosona village (8.8%) and Gira (7.9%), (Table 2).

Table 2. Number of persons confirmed to have epilepsy by study village.

Village	Distance to the Naam river (in km)	Participants in survey	Persons with epilepsy, n (%)	Itching, n (%)	Blind, n (%)
Dawanza	35.4	89	3 (3.4)	36 (40.4)	3 (3.4)
Hai Diocese	35.6	551	30 (5.4)	175 (31.8)	19 (3.4)
Dogabi	31.2	217	8 (3.7)	54 (24.9)	5 (2.3)
Dogereng	34.7	689	34 (4.9)	279 (40.5)	18 (2.6)
Dogoyabulo	0.7	377	20 (5.3)	111 (29.4)	6 (1.6)
Dokaburo	2.3	93	3 (3.2)	17 (18.3)	9 (9.7)
Dokati Ngobo	6.1	379	11 (2.9)	118 (31.1)	8 (2.1)
Dolo	24.3	216	3 (1.4)	20 (9.3)	2 (0.9)
Domeri	13.4	565	48 (8.5)	264 (46.7)	13 (2.3)
Dotriba	6.7	866	21 (2.4)	435 (50.2)	28 (3.2)
Gira	4.3	1181	93 (7.9)	467 (39.5)	38 (3.2)
Hai Bogori	1.9	694	72 (10.4)	214 (30.8)	32 (4.6)
Hai Dileb	1.8	194	6 (3.1)	26 (13.4)	19 (9.8)
Hai Kelibala	33.5	347	11 (3.2)	84 (24.2)	3 (0.9)

Hai Korosona	0.9	674	59 (8.8)	172 (25.5)	21 (3.1)
Hai Malakia	33.7	363	20 (5.5)	107 (29.5)	5 (1.4)
Hai Marara	1.9	1205	62 (5.1)	341 (28.3)	23 (1.9)
Hai Masura	2.0	230	16 (7.0)	61 (26.5)	6 (2.6)
Hai Zira	34.4	572	26 (4.5)	145 (25.3)	21 (3.7)
Jebel Mira	32.0	107	8 (7.5)	39 (36.4)	0 (0.0)
Korbabang	30.0	712	15 (2.1)	244 (34.3)	7 (1.0)
Kperi	4.4	938	44 (4.7)	159 (17.0)	39 (4.2)
Kulu	5.0	621	25 (4.0)	138 (22.2)	33 (5.3)
Lamu	26.0	364	5 (1.4)	124 (34.1)	7 (1.9)
Lodogo	37.6	80	3 (3.8)	24 (30.0)	4 (5.0)
Mbadumu	3.7	551	33 (6.0)	123 (22.3)	26 (4.7)
Medikanunu	9.4	321	15 (4.7)	135 (42.1)	5 (1.6)
Minikolome	7.7	1026	39 (3.8)	332 (32.4)	17 (1.7)
Muduria	0.9	484	24 (5.0)	105 (21.7)	9 (1.9)
Tiboro	22.1	281	22 (7.8)	118 (42.0)	7 (2.5)
Winikasa	37.0	261	5 (1.9)	90 (34.5)	11 (4.2)
Winikelo	5.3	107	6 (5.6)	67 (62.6)	0 (0.0)
Yeri Centre	35.4	344	8 (2.3)	222 (64.5)	1 (0.3)
Overall		15699	798 (5.1)	5046 (32.1)	445 (2.8)

4.3. Incidence of epilepsy

Thirteen PWE developed their first seizures in the 12 months preceding the household survey (annual incidence 82.8/100 000 (95%CI: 44.1-141.6/100 000).

4.4. Characteristics of epilepsy

Of the 798 PWE, 378 (47.4%) were female (Table 3). The median age (IQR) of PWE was 20 (17.0−25.0) years. Of the 709 PWE for which the age of onset of first seizure was known, the median (IQR) age of onset was 9.0 (6.0−13.0) years. The median (IQR) age of onset of the first nodding seizure was 7.0 (5.0−10.0) years. Thirteen (1.6%) PWE developed their first seizures during the previous year. 729 (91.8%) had at least one seizure in the previous 12 months. The most frequent seizure type was generalized convulsive seizures reported in 641 (80.3%); 352 (44.1%) were classified as persons with nodding seizures, 82 (10.3%) with only nodding seizures; in 270 (33.8%) a history of nodding seizures and other types of seizures. In 666 (83.7%) there was no specific trigger that caused the seizures but in 134 (16.3%) seizures were triggered by the sight of food.

One hundred and sixty-six (28.4%) PWE presented with cognitive impairment and in 51 (8.7%) there were behavioural problems. Papular nodular pruritic lesions were observed in 63 (7.9%) PWE and burn lesions in 115 (14.4%); 302 (37.8%) reported skin itching. Six hundred forty-four (80.7%) PWE were taking anti-seizure medication, mainly carbamazepine 545 (68.3%). Six hundred sixty-one (82.8%) had ever taken ivermectin and 645 (80.8%) had taken ivermectin in the year preceding the survey (Table 3).

Table 3. Characteristics of the 798 persons with epilepsy.

Characteristics	
Female, n (%)	378 (47.4)
Age (years), median (IQR)	20 (17.0-25.0)
Born in the village, n (%)	731 (91.6)

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Period (years) of residing in the survey area, median (IQR)	20 (15.0-25.0)
Epilepsy symptoms	
Age onset of the first seizure in all PWE, median (IQR)[d]	10.0 (6.0-15.0)
Age onset of the first nodding seizure, median (IQR)	7.0 (5.0-10.0)
Onset of the first seizure last year, n (%)	13 (1.6)
Seizures the last year, n (%)	729 (91.8)
Sudden loss of consciousness, n (%)	738 (92.5)
Loss of bladder control[#], n (%)	458 (62.1)
Foaming at the mouth[#], n (%)	654 (88.6)
Biting of the tongue[#], n (%)	499 (67.6)
Most frequent seizure types	
Generalized convulsive seizures, n (%)	614 (80.3)
Atonic seizures (drop attacks), n (%)	79 (9.9)
Absences, n (%)	79 (9.9)
Nodding seizures, n (%)	317 (39.7)
Focal motor seizures with decreased consciousness	4 (0.5)
Focal motor seizures without loss of consciousness, n (%)	1 (0.1)
Frequency of seizures	
Daily seizures, n (%)	210 (26.8)
Weekly seizures, n (%)	191 (24.4)
Monthly seizures, n (%)	342 (43.7)
Yearly seizures	39 (5.0)
Experienced seizure in the last 12 months, n (%)	729 (91.8)
Family members with epilepsy	
Family history of seizures, n (%)	483 (60.8)
Siblings (brother/sister)[*], n (%)	366 (75.6)
Father[*], n (%)	8 (1.6)
Mother[*], n (%)	1 (0.2)
Grandparent [*], n (%)	49 (10.1)
Seizures/head nodding triggers	
Spontaneous (no obvious trigger), n (%)	666 (83.7)
Sight of food, n (%)	134 (16.8)
Cold weather, n (%)	114 (14.3)
New moon appearance, n (%)	29 (3.6)
Sunlight/sunset, n (%)	10 (1.2)
Psychomotor development during childhood	
Normal growth prior to the seizure onset, n (%)	722 (90.8)
Normal psycho-motoric development prior to the seizure onset, n (%)	715 (89.9)
Intellectual disability prior to seizure onset, n (%)	63 (7.9)
Severe disease preceding the onset of epileptic seizures	
Measles, n (%)	39 (4.9)
Malaria, n (%)	110 (14.2)

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Encephalitis/meningitis, n (%)	19 (2.4)
Head injury with loss of consciousness, (%)	16 (2.0)
Prolonged post-traumatic coma, n (%)	6 (0.7)
Tuberculosis, n (%)	2 (0.2)
Persistent headache, n (%)	3 (0.2)
Diarrhoea, n (%)	4 (0.5)
Physical examination	
Blind, n (%)	32 (4.0)
Facial abnormalities, n (%)	18 (2.2)
Cervical lymph nodes, n (%)	12 (1.5)
Nakalanga manifestations, n (%)	51 (6.4)
Itching, n (%)	302 (37.8)
Burn lesions, n (%)	115 (14.4)
Papular/nodular pruritic skin, n (%)	63 (7.9)
Leopard skin, n (%)	15 (1.9)
Dry, thickened, wrinkled skin, n (%)	30 (3.8)
Neurological examination**	
Disoriented in place/time/person, n (%)	86 (10.8)
Paresis, n (%)	27 (4.6)
Behavioural problem, n (%)	51 (8.7)
Epilepsy classification	
Epilepsy without head nodding, n (%)	446 (55.9)
Head nodding, n (%)	82 (10.3)
Head nodding plus other seizure types, n (%)	270 (33.8)
Current seizure medication	
Never used anti-seizure medication, n (%)	112 (14.0)
Traditional treatment, n (%)	1 (0.1)
Ever used anti-seizure medication, n (%)	15 (1.9)
Currently use anti-seizure medication, n (%)	644 (80.7)
Anti-seizure medication	
Phenobarbital, n (%)	89 (11.1)
Phenytoin, n (%)	32 (4.0)
Carbamazepine, n (%)	545 (68.3)
Sodium valproate, n (%)	5 (0.6)
Ivermectin use	
Ever taken ivermectin, n (%)	661 (82.8)
Never received ivermectin, n (%)	95 (11.9)
Ivermectin intake the year before the survey	
No ivermectin, n (%)	119 (14.9)
Ivermectin intake, n (%)	645 (80.8)
Ivermectin intake not known, n (%)	34 (4.3)
Meeting the OAE criteria, n (%)***	556 (78.4)

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*n: count; IQR: Interquartile-range; #:60 missing; *denominator families with seizure history (n=470); **missing information neurological exam (n=214); *** missing information on OAE criteria (n=89).*

The first seizures appeared most frequently between 5−10 years of age (Fig 3).

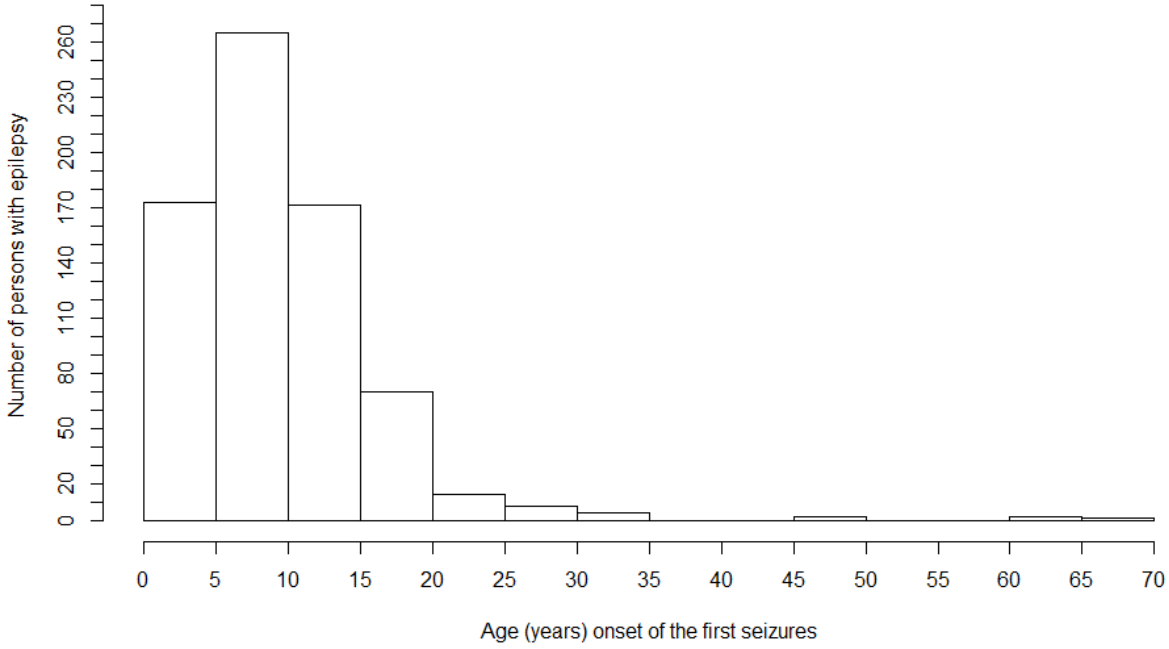

Figure 4. Age of onset of the first seizure among persons with epilepsy.

A large number 556 (78.4%) of the 709 PWE for which information about the criteria of OAE was available met these criteria. In 483 (60.8%) of PWE there was a history of epilepsy in the family and in 366 (75.6%) of them this was a sibling. Nakalanga features were observed in 51 PWE (were more than 20 years old and "looked like a child"). Of these 30 (58.8%) were male. Two (3.9%) had facial abnormalities and 10 (19.6%) thoracic or spinal abnormalities. In seven (13.7%) of the 21 women, 20 years old and above, breasts were not developed.

4.5. Risk factors for epilepsy

Younger age, male sex, skin itching, blindness and residing in village close to the Naam-river were risk factors for high prevalence of epilepsy (Table 4). The probability of living with epilepsy increased with increasing age (up to 25 years) but decreased above this age (Figure 5).

Table 4. Multivariate logistic regression model assessing risk factors for epilepsy

Parameter	Estimate	95% CI		P-value
Intercept	0.006	0.002	0.018	<0.001
Age (years)	1.291	1.194	1.397	<0.001
Age*age (years)	0.995	0.993	0.997	<0.001

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Male vs female	1.239	1.065	1.441	0.006
Farming vs no farming	0.996	0.832	1.192	0.963
Fishing vs no fishing	0.409	0.079	2.112	0.286
Employee vs non-employee	1.212	0.377	3.893	0.747
Cattle keeping vs no cattle in the households	0.744	0.297	1.863	0.528
Skin itching vs no itching	1.308	1.102	1.552	0.002
Blindness	2.031	1.280	3.222	0.003
Recent ivermectin vs no ivermectin intake	1.112	0.916	1.349	0.283
Distance to the river (kilometer)	0.986	0.978	0.993	0.001

CI: confidence limits; *age*age: quadratic effect of age to account for non-linear relationship with age and logit of living with epilepsy.*

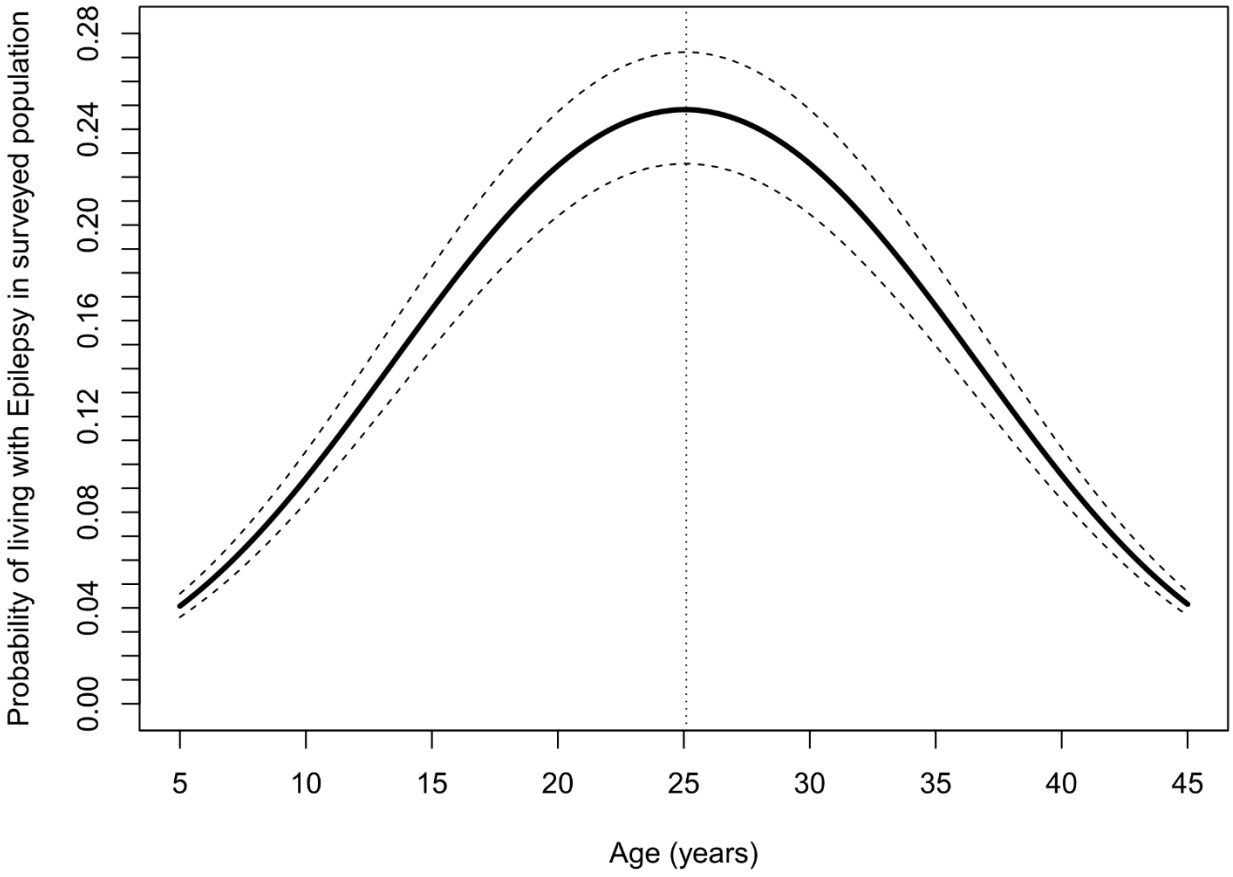

Figure 5. Adjusted probability of living with epilepsy as a function of age. The solid line represents point estimates and dashed lines represent 95% confidence bands.

Of the 798 PWE, 645 (80.8%) had taken ivermectin in 2019 compared to 9859 (71.5%) of the 13780 ivermectin eligible study population (> 4 years old) (p-value <0.001).

5. Discussion

Our study confirms the high prevalence and incidence of epilepsy in the Mvolo area in South Sudan. This prevalence (50.8/1000) is higher than the 44/1000 epilepsy prevalence reported in Maridi [12]. A large proportion of PWE (78.4%) met the OAE criteria. Only 44.1% had a history of nodding seizures. This is similar to the 45.5 % reported in Maridi [12]. A large percentage of the study population reported itching (32.1%) and 2.8% were blind. These findings suggest a very high level of past and ongoing *O. volvulus* transmission. This high level of transmission could be explained by the low past coverage of community directed treatment with ivermectin in the general population. A higher number of PWE had taken ivermectin in 2019 (80.8%) compared to the general population (71.5%) ($p<0.001$). A potential explanation for this could be the recent epilepsy onchocerciasis awareness campaigns which were launched to increase ivermectin coverage of eligible individuals. Despite the WHO recommendation that ivermectin treatment should not be given to severely ill individuals, nowadays it is universally accepted that epilepsy should not be considered a contra-indication for ivermectin use. On the contrary, there is evidence that ivermectin, in particular when given twice a year, may decrease the frequency of seizures in *O. volvulus* infected PWE [13].

Younger age, male sex, family income from an activity other than farming, skin itching and blindness and residing in a village close to the Naam river were risk factors for a high prevalence of epilepsy. Cattle keeping was not associated with a lower prevalence of epilepsy. It has been suggested that the presence of cattle may protect cattle herders from developing onchocerciasis-associated disease because blackflies may bite the cattle and therefore less often humans, and because of cross protecting *Onchocerca ochengi* antibodies [6,14]. It is however unknown whether *O. ochengi* infections are present in cattle in the Mvolo area.

Residing in a village close to the river Naam was associated with higher prevalence of epilepsy. The Naam is a rapid flowing river and a blackfly breeding site. Therefore persons living close to this river are exposed to bites of *O. volvulus* infected blackflies. Many studies have reported the higher prevalence of epilepsy in villages closer to the river [4,15].

The strength of our study is that all households were visited by a research team that included a clinician who was able to confirm or reject the diagnosis of epilepsy at the home of the PWE. However, several limitations of the study need to be mentioned. No laboratory studies nor imaging investigations were performed to identify the causes of epilepsy.

In conclusion, this study confirms the high prevalence of epilepsy including nodding syndrome in an onchocerciasis-endemic area where the onchocerciasis elimination programme was working sub-optimally. Strengthening the local onchocerciasis elimination programme is urgently needed to prevent children in Mvolo from developing OAE

Author Contributions:

Conceptualization, R.C, S.R., J.Y.C and M.Y.L.; methodology, R.C., A.D and S.R.; software, A.D. and S.O.; validation, R.C., S.R., C.N and A.D.; formal analysis, A. D.; Investigation, S.R., S.O. and G.A-E.; resources, R.C.; data curation, S.R., S.O. and A.D.; writing—original draft preparation, R.C and S.R; writing—review and editing, R.C., S.R., G.A-E., J.Y.C., C.N and A.D.; visualisation, C.N, A.D; supervision, R.C. S.R, M.Y.L. and J.Y.C.; project administration, S.R.; funding acquisition, R.C. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest:

The authors declare no conflict of interest.

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