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Clinical presentations of onchocerciasis-associated epilepsy (OAE) in Cameroon

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ABSTRACT

Background: A high prevalence of epilepsy has been observed in several onchocerciasis-endemic countries, including Cameroon. However, little is known on the clinical presentations of the affected persons with epilepsy (PWE). A community-based study was conducted with the aim of describing the spectrum of seizures in selected onchocerciasis-endemic villages in Cameroon and documenting relevant medical history in patients with onchocerciasis-associated epilepsy (OAE).

Methods: We carried out door-to-door surveys in 5 onchocerciasis-endemic villages in Cameroon and recruited all consenting PWE. Epilepsy was diagnosed using a 2-step approach consisting of the administration of a standardized 5-item questionnaire followed by confirmation of the suspected cases by a neurologist. Onchocerciasis-associated epilepsy was defined as ≥2 seizures without an obvious cause, starting between the ages of 3–18 years in previously healthy persons having resided for at least 3 years in an onchocerciasis-endemic area. Ivermectin use by PWE was verified. Seizure history, relevant past medical, and family history, as well as neurological findings, were noted.

Results: In all, 156 PWE were recruited in the 5 villages. The modal age group for epilepsy onset was 10–14 years. The diagnostic criteria for OAE were met by 93.2% of the PWE. Participants had one or more of the following seizure types: generalized tonic–clonic seizures (89.1%), absences (38.5%), nodding (21.8%), focal nonmotor (7.7%), and focal motor seizures (1.9%). One case (0.6%) with the "Nakalanga syndrome" was identified. More than half (56.4%) of PWE had at least one seizure per month. In one village, 56.2% of PWE had onchocercal skin lesions.

Conclusion: People with epilepsy in onchocerciasis-endemic villages in Cameroon present with a wide clinical spectrum including nodding seizures and Nakalanga features. A great majority of participants 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.

1. Introduction

The quest to know more about epilepsy dates back to the days of Hippocrates, and since then, scientists have been seeking to better understand this condition [1]. In recent decades, epidemiological findings have suggested an association between epilepsy and onchocerciasis

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[2–6]. Villages with high onchocerciasis transmission have been shown to have a high prevalence of epilepsy, with reports of clinical manifestations such as nodding seizures and the Nakalanga syndrome [7,8]. The term onchocerciasis-associated epilepsy (OAE) was first suggested by Kaiser and colleagues to describe these onchocerciasis-related seizure disorders [9], and a clinical definition for OAE was recently proposed [10].

The exact pathophysiological mechanisms underlying OAE are yet to be elucidated. There is conflicting evidence about the presence of *Onchocerca volvulus* (Ov) in the cerebrospinal fluid (CSF) of persons with epilepsy in onchocerciasis-endemic areas [11,12]. The Ov microfilariae were first noted in CSF by Hissette in 1932 [13], and later by Mazzotti during diethylcarbamazine treatment of the disease [14]. Duke et al. detected microfilaria in the CSF, blood, and skin of heavily infested individuals, all of them with more than 100 microfilaria/mg of skin [11]. It is possible that König and colleagues did not detect Ov in CSF of their Tanzanian study participants because the microfilarial density was too low (median density of 1.5 microfilariae/mg of skin). Moreover, in the study by Duke, study participants were asked to lie on their back for 30 min prior to the lumbar puncture and the procedure was also done in that position to avoid gravitational settlement of microfilaria in the lower part of the spinal subarachnoidal space. In the study by König et al., it is not clear whether this lumbar puncture procedure was followed [12]. Furthermore, it is possible that the polymerase chain reaction (PCR) protocol used for detecting Ov DNA in skin samples was not sensitive enough to detect much smaller amounts of DNA in CSF. A prospective cohort study of children in the Mbam valley in Cameroon (in the same region as the current study), showed a microfilaria load-dependent increased risk to develop epilepsy later in life following childhood Ov infection and the estimated contribution of infection with *O. volvulus* to epilepsy was very high (population-attributable fraction of 91.7%, 95% confidence interval [CI] 56.7–98.4; $p = 0.0021$) [15]. This evidence of a temporal association between Ov infection and development of epilepsy constitutes a convincing argument for incriminating the parasite in the pathogenesis of OAE.

To date, there are no population-based studies that have investigated the different seizure types presented by persons living with epilepsy in onchocerciasis-endemic areas. For some time, researchers have mainly focused their investigations on the clinical aspects and etiology of the nodding and the Nakalanga syndromes [16–18]. Both conditions however, represent only a fraction of the full spectrum of OAE [19]. In this paper, we describe the clinical manifestations of persons with epilepsy (PWE) in selected onchocerciasis-endemic villages in Cameroon where the crude prevalence of epilepsy can reach 13.6% [2,5].

2. Methods

2.1. Study sites and population

The study was conducted in five onchocerciasis-endemic villages in Cameroon between July 2017 and January 2018. Four of these villages namely Nyamongo, Bilomo, Ngongol, and Bayomen are located in the Mbam valley, Centre Region while the fifth village (Kelleng) is located in the Sanaga valley, Littoral Region (See Fig. 1). All five villages are located less than 10 km from river banks where blackflies (vectors that transmit the onchocerciasis parasite) breed and are known to be hyperendemic for onchocerciasis [2,5]. Onchocerciasis control measures (annual community-directed treatment with ivermectin [CDTI]) were instituted by the health authorities in the study area in 1998 [20,21].

The study populations were of the Sanaga ethnic group for the villages in the Mbam and of the Batti tribe in Kelleng. Subsistence farming and small commercial businesses were the main income-generating activities. The populations were stable, with limited migration into or out of the villages and no history of major conflicts or wars.

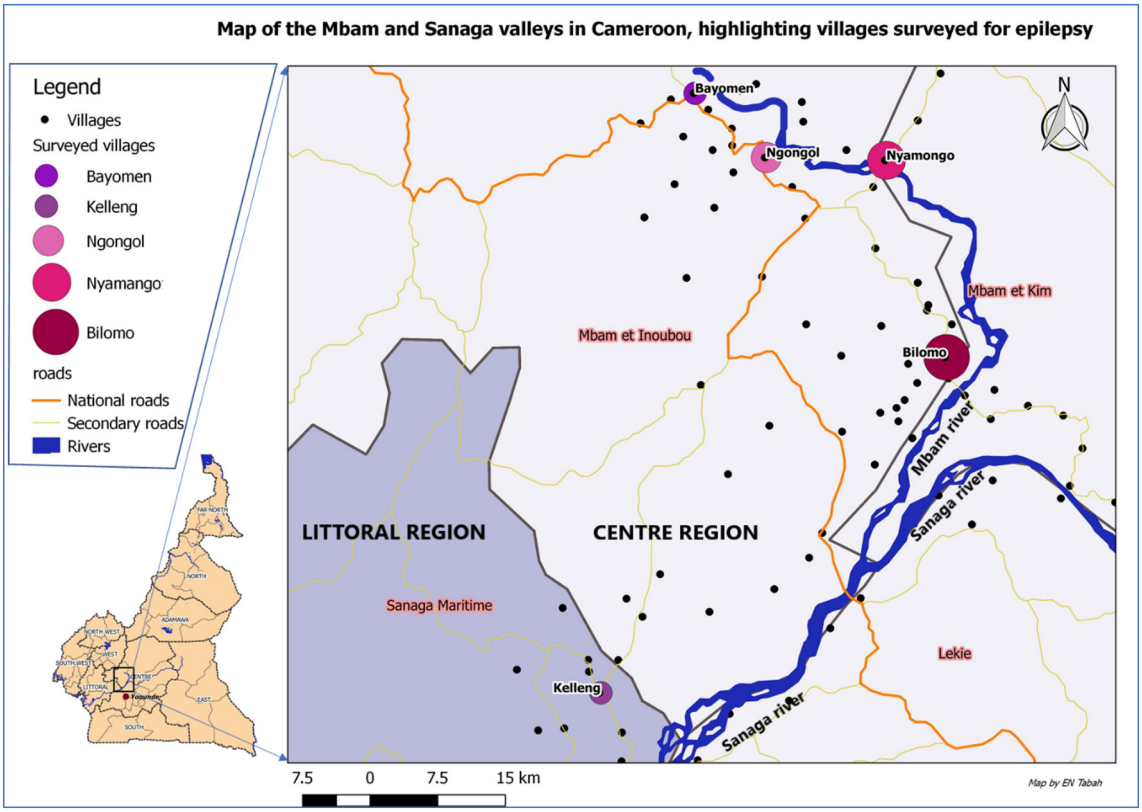

Fig. 1. Map showing the five villages surveyed during the study.

2.2. Study procedures

Prior to our arrival in a village, the local chief was contacted and the study objectives were explained to him and his collaboration sought. The consenting chief then organized a sensitization of the entire village community and provided community health workers and/or community distributors of ivermectin to assist the research team. Our research team included neurologists (AKN, LN, CSE), physicians with special training in epilepsy (SFJN, MMK, DF, RC), dermatologists (ACZKB, GN), and a physician specialized in neuroepidemiology (ENT). For the door-to-door survey, after obtaining a written informed consent from the household head or his representative, we used a 2-step approach for epilepsy diagnosis. A screening questionnaire made use of the 5 standard questions validated by Diagana and colleagues [22] for epilepsy surveys. The 5 screening questions were as follows: (i) Loss of consciousness and/or loss of bladder control and/or foam at the mouth? (ii) Absence (s) or sudden lapse(s) of consciousness during a short time? (iii) Involuntary clonic movements or muscular jerks of arm(s) and/or leg(s) (i.e., convulsions) that start suddenly and stop within minutes? (iv) Does the subject sometimes experience sudden and brief bodily sensations, see or hear things that are not there or smell strange odors? (v) Did someone tell the subject that he/she had epilepsy or that he/she already had epileptic fits? All members of the household were reviewed by the physicians (SFJN, MMK, DF, ENT, CB, RC) during the screening phase. The second step was the confirmation of epilepsy in suspected individuals by a neurologist (AKN, LN, CSE), or a physician trained in epilepsy diagnosis (SFJN, MMK, DF, RC).

All confirmed PWE who were residents in the village for at least 6 months and gave their informed consent were included in the study. All participants went through a clinical evaluation with emphasis on seizure descriptions, birth history, family history, past medical history, antiepileptic treatment, and ivermectin use. A physical examination with complete neurological assessment was done. In Bilomo and Kelleng, the participants had a skin examination by a dermatologist (ACZKB, GN) to diagnose onchodermatitis. The presence of anti-*Onchocerca* antibodies was tested in PWE from 2 villages (Bilomo, Kelleng) using the SD Bioline Onchocerciasis Ov16 IgG4 rapid diagnostic test (RDT) (Standard Diagnostics, Gyeonggi-do, South Korea).

2.3. Definitions

Epilepsy was defined as the occurrence of at least two unprovoked seizures separated by 24 h or more in the past five years, adapted from the operational definition of the International League Against Epilepsy (ILAE) guidelines of 2014 [23]. This definition excludes any seizure related to an acute cause such as fever, any acute affection of the central nervous system (CNS), acute metabolic imbalance, alcohol, and substance abuse/withdrawal.

Our definition for OAE was adapted from previously published criteria [10] and included the following: (i) being a PWE according to the ILAE 2014 definition above; (ii) age of onset of seizures between 3 and 18 years; (iii) no obvious cause for epilepsy from the history and physical examination; (iv) having lived in an onchocerciasis-endemic area for at least 3 years; (v) no history of abnormal psychomotor development prior to epilepsy onset.

Nodding seizures (NS) were defined as reported repetitive, involuntary drops of the head to the chest in a previously normal person, with onset between the ages of 3 and 18 years and frequency of 5–20 nods/min [24].

The "Nakalanga" syndrome was defined as a variable association of growth retardation without an obvious cause between the ages of 3 and 18 years, delay or absence of external signs of sexual development and mental retardation. Usually epilepsy, facial, thoracic, and spinal abnormalities are common manifestations [10,16].

Seizure classification was based on the recent ILAE guidelines [25], which highlight the modes of onset of the seizures (generalized, focal, or unknown) and further expand them into motor and nonmotor categories. Nodding seizures were specially categorized because they constitute a major clinical entity when investigating OAE [7,10,19].

The degree of autonomy of PWE was grossly assessed based on the extent to which the participant's daily life activities such as bathing, eating, and dressing up were affected by epilepsy, ranging from normal autonomy to total inability to execute routine tasks.

Family clustering of PWE was defined as the occurrence of two or more confirmed cases of epilepsy within the same household.

Onchodermatitis was defined based on the classification by Murdoch et al. [26]. Nine categories were considered: Acute papular onchodermatitis, chronic papular onchodermatitis, lichenified onchodermatitis, atrophy, depigmentation, palpable onchocercal nodules, lymphadenopathy, hanging groins, and lymphedema. All reported skin lesions were confirmed by a dermatologist.

2.4. Data processing and analysis

Field data were collected on paper forms and entered into Epi-info version 7.2.2.2 and Microsoft Excel 2016 for analysis. Height-for-age of PWE was estimated using the Centers for Disease Control and Prevention (Atlanta, USA) growth curves for individuals aged 2–20 years [27]; for participants older than 20 years, their height as recorded during the survey was assumed to be similar to their height when they were 20, and was used directly on the curve. Any height-for-age value below the 5th percentile was considered as short stature. Continuous data were expressed as means ± standard deviation (SD). Proportions were compared using the Chi-squared test with a statistical significance level of 95%.

3. Results

3.1. Study population

A total of 557 households were surveyed. Out of the 166 persons suspected to have epilepsy in the first step, 156 were confirmed as PWE in the second step thus giving a positive predictive value of 94% for the 5 questions in epilepsy diagnosis. The 10 persons who were excluded had the following differential diagnoses of epilepsy: 5 provoked seizures (2 febrile seizures, 1 head trauma in the acute phase, 1 acute CNS disease, 1 seizure due to alcohol abuse), 1 syncope, 2 psychiatric disorders, 1 monoparesis following a stroke, and 1 healthy individual with occasional dizziness.

All the PWE were encountered in their family residence during the door-to-door visits. The 156 confirmed PWE from the five villages consented to participate in the study. Bilomo contributed the greatest number of PWE (61 PWE; 39.1%), while Bayomen had the least number of PWE (15 PWE; 9.6%) (Table 1). The age range was 5–81 years, and the mean age of the study population was 26.3 ± 9.9 years. The population

Table 1
Age and sex distribution of study participants per village.

Age group (years)	Bilomo		Kelleng		Ngongol		Nyamongo		Bayomen		TOTAL	
	F	M	F	M	F	M	F	M	F	M	F	M
5–9	1	0	0	0	0	1	0	0	0	0	1	1
10–14	4	1	0	1	0	2	1	2	0	0	5	6
15–19	5	4	0	1	0	2	3	4	2	2	10	13
20–24	6	11	1	2	5	2	6	5	1	2	19	22
25–29	8	6	4	0	2	3	1	3	2	0	17	12
30–34	6	3	2	1	0	1	5	1	0	0	13	6
35–39	2	1	0	1	1	1	3	2	4	0	10	5
≥40	2	1	1	2	1	2	3	2	0	2	7	9
TOTALS	34	27	8	8	9	14	22	19	9	6	82	74
	61		**16**		**23**		**41**		**15**		**156**	

F = female; M = male.

Table 2
Seizure types and clinical features of study participants.

		Bilomo n = 61	Kelleng n = 16	Ngongol n = 23	Nyamongo n = 41	Bayomen n = 15	Overall n = 156
Mean age of onset (years)[a]		12.4 ± 4.2	14.1 ± 7.7	10.7 ± 3.6	12.8 ± 4.9	10.3 ± 3.6	12.2 ± 4.8
Mean duration of epilepsy (years)[a]		12.7 ± 8.7	14.3 ± 7.5	15.5 ± 10.1	13.5 ± 8.1	16.5 ± 9.1	14.3 ± 9.6
Seizure type	Generalized tonic–clonic	54 (88.5%)	12 (75.0%)	22 (95.6%)	37 (90.2%)	14 (93.3%)	139 (89.1%)
	Focal motor	1 (1.6%)	1 (6.3%)	1 (4.4%)	0 (0%)	0 (0%)	3 (1.9%)
	Absence	19 (31.1%)	9 (56.3%)	12 (52.2%)	17 (41.5%)	3 (20.0%)	60 (38.5%)
	Focal nonmotor	3 (4.9%)	0 (0%)	4 (17.4%)	4 (9.8%)	1 (6.7%)	12 (7.7%)
	Nodding	9 (14.8%)	3 (18.8%)	8 (36.4%)	11 (26.8%)	3 (20.0%)	34 (21.8%)
Seizure frequency	Daily: >30/month	4 (6.6%)	0 (0%)	1 (4.3%)	4 (9.8%)	0 (0%)	9 (5.8%)
	Monthly: >12/year	31 (50.8%)	5 (31.3%)	13 (56.5%)	21 (51.2%)	9 (60%)	79 (50.6%)
	Yearly: <12/year	24 (39.3%)	10 (62.5%)	9 (39.1%)	13 (31.7%)	5 (33.3%)	61 (39.1%)
	Unknown	2 (3.3%)	1 (6.2%)	0 (0%)	3 (7.3%)	1 (6.7%)	7 (4.5%)
Bruises, wounds, or scars		13 (21.3%)	1 (6.3%)	5 (21.7%)	1 (2.4%)	3 (20.0%)	23 (14.7%)
Burns or burn scars		5 (8.2%)	2 (12.5%)	7 (30.4%)	4 (9.8%)	4 (26.7%)	22 (14.1%)
Reduced autonomy		10 (16.4%)	1 (6.3%)	9 (39.1%)	13 (31.7%)	3 (20.0%)	36 (23.1%)
Nakalanga syndrome		0 (0%)	0 (0%)	0 (0%)	1 (2.4%)	0 (0%)	1 (0.6%)
Palpable onchocercal nodules		3 (4.9%)	1 (6.3%)	0 (0%)	0 (0%)	0 (0%)	4 (2.6%)
Pruritus		6 (9.8%)	6 (37.5%)	2 (8.7%)	10 (24.4%)	2 (13.3%)	26 (16.7%)

[a] 8 Missing data.

of PWE was female-dominant (sex ratio Male/Female = 1/1.1). The observed modal age group for our study population was 20–24 years, which accounted for 26.3% of PWE. The majority of our study population (85.9%) were farmers; some (8.3%) had other professions while a few (mostly children) had no occupation (5.8%).

3.2. Clinical features of participants

The mean age of epilepsy onset was 12.2 ± 4.8 years. Persons with a history of NS had an earlier onset of seizures compared with persons with other forms of epilepsy, with mean onset at 10.75 years vs. 12.72 years; p = 0.013. Several seizure types were identified (Table 2).

Two or more seizure types were reported in 62 (39.7%) PWE. Thirty-four PWE (21.8%) had experienced nodding seizures either exclusively (13 PWE; 8.3%) or associated with other forms of seizures (21 PWE; 13.5%). At the time of the survey, only 95 (60.9%) PWE took antiepileptic drugs (AEDs) regularly and 88 (56.4%) still had at least one seizure every month.

Wounds and bruises as well as scars resulting from trauma during seizures were observed in 23 PWE (14.7%) while burns or burns scars were seen in 22 PWE (14.1%). Two participants (1.3%) were blind.

The execution of routine daily activities was reduced at various degrees in 36 PWE (23.1%). The PWE who experienced nodding seizures had higher rates of reduced autonomy (19/34; 55.9%) compared to nonnodding PWE (17/122; 13.9%): p < 0.0001.

Eighty-six PWE (including 23 with nodding seizures) had complete data from which the height-for-age could be calculated, of which 28 (32.6%) were below the 5th percentile. We found that 11/23 (47.8%) PWE with nodding seizures and 17/63 (27.0%) nonnodding participants had short stature (p = 0.07).

One hundred and thirty-eight (93.2%) out of the 148 PWE who could recall the age of epilepsy onset had their first seizure between the age of 3 and 18 years, and also fulfilled the other diagnostic criteria for OAE. The age of onset of epilepsy peaked at the 10–14 years age group (Fig. 2). No PWE with NS had the onset of seizures before 5 or after 20 years (Fig. 3).

3.3. Onchodermatitis in PWE

Nine (56.2%) of the 16 PWE in Kelleng village had onchocerciasis-related skin lesions, with 5 participants having two or more different types of onchodermatitis. No PWE was seen with lymphadenopathy or lymphedema (Table 3).

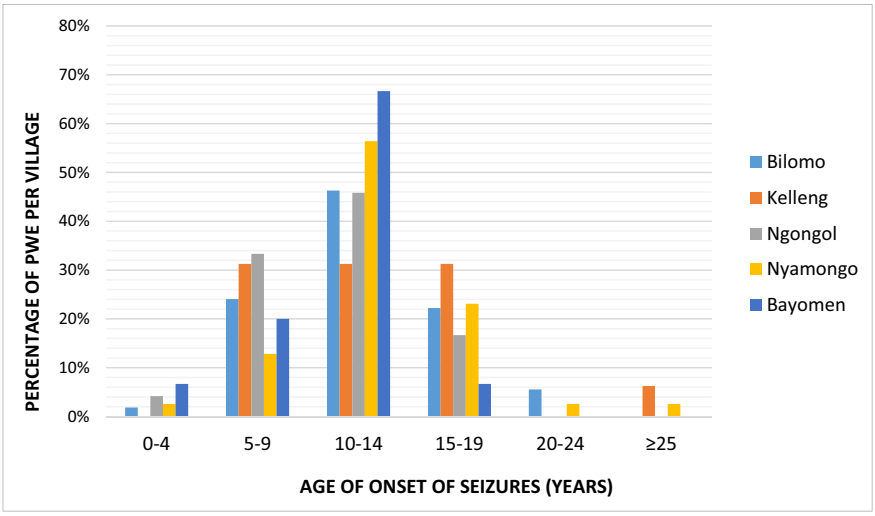

Fig. 2. Bar chart for ages of epilepsy onset.

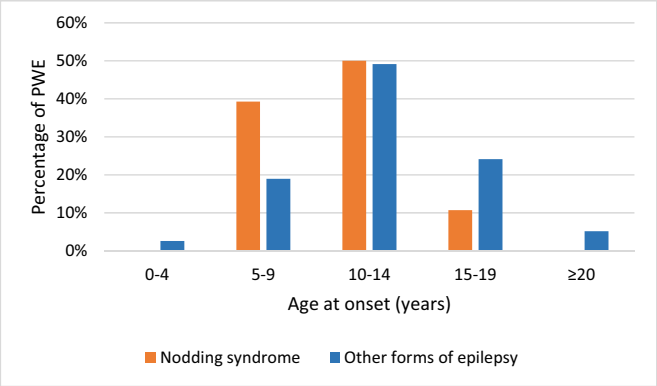

Fig. 3. Bar chart showing the age of onset of nodding seizures vs other forms of epilepsy.

Table 3
Onchodermatitis in PWE in Kelleng (n = 16).

	Number of PWE	Percentage
APOD	1	6.3%
CPOD	2	12.5%
LOD	4	25.0%
ATR	1	6.3%
DPM	7	43.8%
Palpable nodules	1	6.3%
Lymphadenopathy	0	0%
HG	1	6.3%
LYM	0	0%
No onchodermatitis	7	43.8%

APOD: Acute papular onchodermatitis; CPOD: chronic papular onchodermatitis; LOD: lichenified onchodermatitis; ATR: atrophy; DPM: depigmentation; HG: hanging groins; LYM: lymphedema.

3.4. Past medical history

The past medical history of PWE showed that family history of epilepsy was significantly more frequent than any other event (Table 4).

3.5. Family clustering of PWE

In the five surveyed villages, 27 (4.8%) households had two or more PWE as follows: Bilomo (13/193 households; 6.7%); Kelleng (1/40 household; 2.5%); Ngongol (1/86 household; 1.2%); Nyamongo (9/150 households; 6.0%); and Bayomen (3/88 households; 3.4%). Furthermore, in 21 (77.8%) of these households, we found siblings with different seizure types.

3.6. Treatment of PWE

Only 60.9% of PWE were on regular AED treatment. Thirty-seven PWE (23.7%) had resorted to traditional medicine for epilepsy (Table 5). Nineteen (55.9%) of PWE with a history of nodding seizures and 75 (61.5%) of PWE with other types of seizures received regular AED treatment (p = 0.56).

Fig. 4 shows the choice of antiepileptic drugs (AEDs) used by our study population as well as the frequency of use of AEDs. The most frequently used AEDs were carbamazepine and phenobarbital. It is worth noting that 10.9% of PWE had never taken any AED before.

3.7. Ov16 antibody testing

The results of the Ov16 antibody testing was positive in 46 (59.7%) of the 77 PWE who were tested. No difference was observed between PWE who were Ov16 positive and negative in terms of type of onchodermatitis, type of seizure, seizure frequency and stature.

Table 4
Past medical history of PWE.

	Bilomo n = 61	Kelleng n = 16	Ngongol n = 23	Nyamongo n = 41	Bayomen n = 15	Overall n = 156
Birth dystocia	1 (1.6%)	0 (0%)	0 (0%)	1 (2.4%)	0 (0%)	2 (1.3%)
Seizures with fever[a]	5/45 (11.1%)	2/10 (20.0%)	1/17 (5.9%)	3/25 (12.0%)	0/10 (0%)	11/107 (10.3%)
CNS infection	1 (1.6%)	1 (6.3%)	1 (4.3%)	3 (7.3%)	0 (0%)	6 (3.8%)
Measles	1 (1.6%)	0 (0%)	3 (13.0%)	1 (2.4%)	2 (13.3%)	7 (4.5%)
Head trauma	2 (3.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.3%)
Family history of epilepsy[b]	37 (60.7%)	4 (25.0%)	10 (43.5%)	28 (68.3%)	9 (60.0%)	88 (56.4%)[c]

[a] Missing data: Not all participants could provide this information, thus reduced denominators.
[b] Notion of a 1st degree relative to the PWE (parent or sibling), dead or alive, known to have epilepsy.
[c] Greater proportion of PWE affected by family history compared to other factors: p < 0.0001.

Table 5
Treatment received by PWE.

		Bilomo n = 61	Kelleng n = 16	Ngongol n = 23	Nyamongo n = 41	Bayomen n = 15	Overall n = 156
AED type	Phenobarbital	28 (45.9%)	4 (25.0%)	15 (65.2%)	11 (26.8%)	5 (33.3%)	63 (40.4%)
	Carbamazepine	24 (39.3%)	11 (68.8%)	3 (13.0%)	19 (46.3%)	8 (53.3%)	65 (41.6%)
	Valproate	1 (1.6%)	0 (0%)	1 (4.3%)	2 (4.9%)	0 (0%)	4 (2.6%)
	Phenytoin	0 (0%)	0 (0%)	3 (13.0%)	0 (0%)	1 (6.7%)	4 (2.6%)
	None	8 (13.1%)	1 (6.3%)	1 (4.3%)	9 (22.0%)	1 (6.7%)	20 (12.8%)
AED frequency	Never	8 (8.2%)	1 (6.3%)	1 (4.3%)	9 (22.0%)	1 (6.7%)	17 (10.9%)
	Irregular	18 (34.4%)	5 (31.3%)	4 (17.4%)	9 (22.0%)	5 (33.3%)	44 (28.2%)
	Regular	35 (57.4%)	10 (62.5%)	18 (78.3%)	23 (56.1%)	9 (60.0%)	95 (60.9%)
Traditional medicine use		14 (23.0%)	2 (12.5%)	7 (30.4%)	13 (31.7%)	1 (6.7%)	37 (23.7%)
Ivermectin use in 2016/2017		11 (18.0%)	6 (37.5%)	13 (56.5%)	3 (7.3%)	6 (20.0%)	39 (25.0%)[b]
Ivermectin use before the onset of seizures[a]		31/54 (57.4%)	5/15 (33.3%)	1/11 (9.1%)	6/18 (33.3%)	2/10 (20.0%)	45/108 (41.7%)[b]

[a] Missing data.
[b] Significant difference in proportions: p = 0.0043.

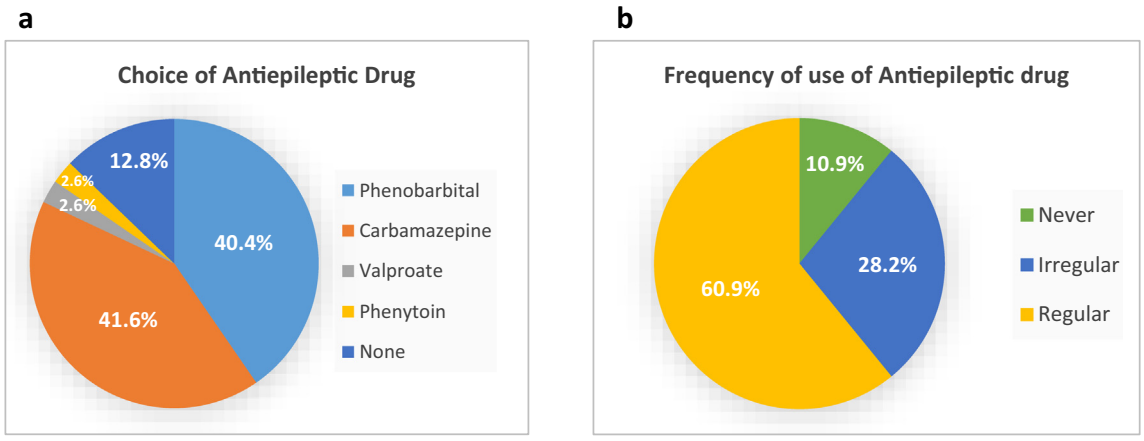

Fig. 4. a: Choice of antiepileptic drug. b: Frequency of use of antiepileptic drug.

3.8. Case reports

3.8.1. Nodding seizures

Case 1. A 12-year-old male residing in Bilomo village from birth, started having seizures at the age of 7 years with nodding seizures, at a frequency of 5 head drops/min and lasting for about 1 min, especially after waking up from sleep. During these seizures, he is unaware of his surroundings and is unresponsive to external stimuli. No AEDs were given for the seizures, and at time of study, he was having 3 episodes of nodding seizures per month without any other type of seizures. A mild cognitive disorder characterized by short-term amnesia was noticed since the age of 7 years. He had normal physical and mental development before the onset of epilepsy. He had not taken ivermectin until recently when he received his first dose at the age of 12 years. There was no history of epilepsy in the family. Besides amnesia, there were no other findings on physical examination and neurological assessment.

Case 2. A 14-year-old male, born and residing in Kelleng: His mother reported normal childbirth and proper psychomotor development before the onset of epilepsy. At the age of 1 year, he had an episode of a febrile convulsion. Epilepsy started at 8 years of age with nodding episodes alternating with absences. Each nodding episode lasted 5–10 min, with a frequency of 10 nods/minute while absences lasted for about 1 min and were accompanied by drooling. Seizures were triggered by exposure to cold. He had taken carbamazepine irregularly, and at the time of study, was presenting with 20 seizures every month, all seizure types included. He had received ivermectin only 4 times since birth including one dose prior to the first unprovoked seizure. There was no family history of epilepsy. He was underweight: body weight of 38 kg for a height of 1.65 m giving a Body Mass Index (BMI) of 14 which is below the 5th percentile [27]. Pubic hair was sparsely present but he had no facial dysmorphic features. The dermatological examination revealed pruritus with scratch marks, hanging groins (HG), and depigmentation (DPM) of both lower limbs (leopard skin). Neither cognitive nor behavioral signs were observed.

Case 3. A 26-year-old male participant, who was born and grew up in Ngongol: Birth and early childhood were uneventful. The age of onset of epilepsy was 6 years, when he started presenting nodding seizures with brief moments of total loss of contact with the surroundings. His family could not remember the duration and frequency of nodding episodes but recalled that they were triggered by food and were most frequent at night. Given that his parents did not know that the nodding movements were seizures, AEDs were not started until the age of 9 years, when the nodding seizures disappeared and were replaced by generalized tonic–clonic seizures. Phenobarbital 100 mg daily was initiated, but he continued to present 2 generalized tonic–clonic seizures every month. He also presented rare episodes of aggressive behavior. Physical examination was normal. He did not receive ivermectin until after the seizures had started, and has been receiving it yearly since then. No family history of epilepsy was noted.

3.8.2. Family clustering of epilepsy

A native family in which 3 siblings were suffering from epilepsy was encountered in Nyamongo.

Case 4. The eldest case was a 42-year-old female, born and bred in Nyamongo, with an uneventful birth and early childhood. She declared not taking ivermectin regularly and did not remember the year her last dose was taken. At the age of 15 years, she reports experiencing both generalized tonic–clonic seizures and brief episodes of absences; AED use was sporadic, and consequently, she had a total of 4 seizures per month including absences and tonic–clonic seizures at the time of the survey. The physical examination revealed burn scars on the arms and lower limbs. No cognitive symptoms were observed.

Case 5. A 36-year-old female with normal childbirth and childhood, whose seizures started at the age 14 years (generalized tonic–clonic and absences): She took ivermectin irregularly (last dose taken two years ago) and received both traditional and medical treatment (carbamazepine) on a regular basis. Her seizure frequency (both absence and tonic–clonic seizures) was 5 per year, and physical examination was normal.

Case 6. The youngest affected sibling was a 24-year-old male with unremarkable birth and childhood history. He admits refusing to take ivermectin systematically because of fear of adverse effects. Seizure onset was at the age of 15 years, when he started with episodes of head nodding seizures, occurring exclusively in the morning after waking up, accompanied by reduced awareness but without complete loss of consciousness. No specific factor (cold, food, noise) was reported to trigger the nodding seizures. Despite receiving regular treatment with phenobarbital and traditional plant extracts, he still had 20 nodding episodes every month at the time of the survey, each reportedly lasting for about 30 min. Mild cognitive symptoms were observed (difficulty understanding instructions, aggressiveness, and amnesia). The rest of the neurological examination was normal. The physical examination showed discrete dysmorphic features on the face, and mild scoliolordosis. Secondary sexual development was normal.

3.8.3. Nakalanga features

Case 7. A 35-year-old female who was born and had grown up in Nyamongo, whose birth details could not be recalled, but no febrile seizure nor severe disease had occurred during childhood. She had begun schooling but dropped out early at the primary level for unclear reasons. Her seizures started at the age of 13 years with nodding episodes without a specific triggering factor, sometimes followed immediately by generalized tonic–clonic seizures. After starting carbamazepine treatment, the nodding episodes continued, but the generalized seizures became less frequent. She also experienced visual hallucinations a few times every year. At the time of the study, she was presenting with 1–2 seizures per month (generalized tonic–clonic seizures and/or nodding). Physical examination revealed a stunted growth (weight of 37 kg and height of 135 cm; height-for-age below the 5th percentile) but without any visible signs of abnormal secondary sexual development. There was a hunchback deformity because of extreme kyphosis (Fig. 5). She had leopard skin depigmentation on the right leg. Cognitive deficits included speech difficulties and temporospatial disorientation. She had never received ivermectin before the beginning of epilepsy, but after the onset of seizures, she had already taken about 10 doses. There was no family history of epilepsy, but her father living in the same household was blind.

4. Discussion

4.1. General characteristics of the study population and relation to OAE criteria

We report the clinical characteristics of 156 PWE living in five onchocerciasis-endemic villages in Cameroon. One hundred and thirty-eight (93.2%) of the 148 PWE, who could recall, had their first epileptic seizure between the ages of 3 and 18 years. Such ages of epilepsy onset are common in persons with OAE [8,10] as was previously reported in onchocerciasis-endemic villages in Cameroon [5,28] and the Democratic Republic of Congo [3]. Furthermore, 56.4% of PWE in our study had a family history of epilepsy, and all the villages in the study had at least one household with two or more PWE, demonstrating epilepsy clustering, another criterion in favor of OAE [10]. Other potential causes of epilepsy such as perinatal brain injury, brain trauma, measles, CNS infection, and febrile illness were reported in less than 10% of PWE in this study.

The peculiarity of PWE in onchocerciasis-endemic areas is reflected in the OAE diagnostic criteria [10], which were met by 93.2% of our participants. As depicted by our study population, persons with OAE have a normal psychomotor development until the onset of seizures between the ages of 3 and 18 years. Family clustering was frequent, and could be explained by an increased collective exposure of families to infected blackflies based on the distance of the home or farm from the blackfly breeding site [2], time spent out in the fields, and low usage of ivermectin. A similar pattern of family clustering of epilepsy has been observed in many onchocerciasis endemic regions [29–32].

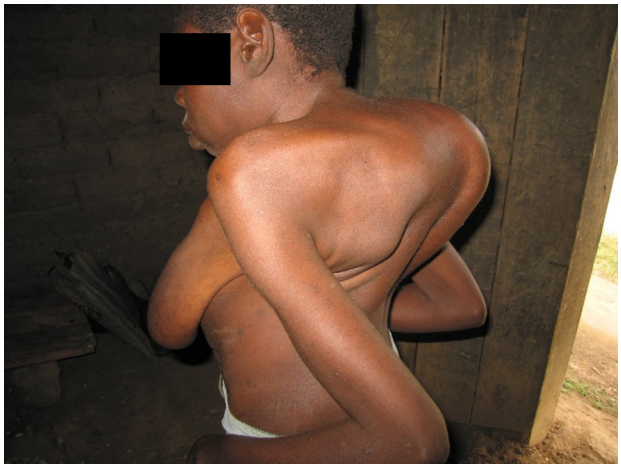

Fig. 5. Participant with Nakalanga features in Nyamongo.

The PWE in our study were young, with a mean age of 26.3 ± 9.9 years, and just one-tenth of the participants were above 40 years of age. This suggests that most PWE die before 58 years of age, which is the average life expectancy in Cameroon [33]. Higher mortality rates among PWE in onchocerciasis-endemic areas were previously reported in the Mbam, Cameroon [34], and in Uganda [35]. A major contributor to early deaths in persons with OAE is the poor medical management of the condition resulting in complications. Up to 56.2% of the study participants still had at least one seizure every month and more than 14% presented with signs of traumatic complications and/or burns. These findings suggest an insufficiency in the quality and frequency of antiepileptic treatment received by PWE in this area. Only 60.9% of participants took AEDs regularly; this could be related to the general poverty in such settings, because finances were shown to be the major barrier to acquiring AEDs in the Mbam valley [36]. Moreover, 23.7% of PWE still resort to traditional medicine, a practice which has been shown to be detrimental, as this usually delays medical treatment and increases the risk of refractory scenarios upon the initiation of AEDs [37]. This situation once more highlights the urgent need for better epilepsy management in onchocerciasis-endemic settings [38], including the training of local healthcare workers in epilepsy care, uninterrupted provision of appropriate AEDs, and sensitizing the communities, including traditional healers [37] about OAE.

4.2. Clinical characteristics of participants

4.2.1. Seizure types and Nakalanga syndrome

Several seizure types were identified, with the most frequent being the generalized tonic–clonic seizures (89.1%), followed by absences (38.5%), nodding seizures (21.8%), focal nonmotor seizures (7.7%), and focal motor seizures (1.9%). Multiple seizures types in a single PWE were frequent (39.7%). Nodding seizures generally started earlier than other seizure types (Fig. 3) and could either persist or be replaced later by other forms of epilepsy as previously reported [39]. Additionally, a 35-year-old woman presented with the Nakalanga syndrome as described in other onchocerciasis-endemic zones [10,16,40]. Given her age, it is obvious that during her childhood CDTI had not been initiated yet; therefore, she could have harbored high loads of microfilariae in the absence of ivermectin prophylaxis. Furthermore, given that her father went blind many years prior to the introduction of CDTI, one could therefore speculate a particularly high exposure to *O. volvulus* in this household. It is unclear whether the early school drop-out reported for this case was due to cognitive problems prior to seizure onset. Prospective studies are needed to investigate whether cognitive decline in OAE may also appear in certain individuals before the onset of seizures. The normal development of external sexual characteristics could be explained by the fact that seizures began at the age of 13 when she must have attained puberty already, which was not reversed after the onset of symptoms [40]. The Nakalanga syndrome is probably caused by endocrine dysfunctions [41], but more studies are needed to establish a clear mechanism. The presence of nodding seizures and the Nakalanga syndrome in our sample strongly suggests the incrimination of *O. volvulus* in triggering most of the seizures [7,10]. Clinicians working in onchocerciasis-endemic settings must be aware of these clinical presentations to ensure proper OAE care and prevention via optimal onchocerciasis control.

Our study documents for the first time a wide clinical spectrum of OAE and reports varied seizure types in the same individual with OAE

and even among siblings of the same household. Siblings had different seizure types in 77.8% of the households with multiple PWE. The variety in clinical manifestations is unlikely to be related to a single genetic trait that predisposes the family to epilepsy, as environmental factors including high exposure to *O. volvulus* must have played a role. In view of the multiple seizure types, we recommend that at least phenobarbital [42] and valproate [43] should be made available as baseline AEDs in onchocerciasis-endemic regions.

4.2.2. Autonomy of PWE

The autonomy of PWE with nodding seizures was reduced compared with that of other PWE in our study ($p < 0.0001$). In addition, we found a trend of smaller stature among PWE with nodding seizures compared to the rest of the study population, although this difference was not statistically significant ($p = 0.07$). These findings are consistent with previous reports that mention stunting and cognitive impairment as part of the clinical picture of OAE, particularly nodding and the Nakalanga syndromes [36].

4.2.3. OAE, onchodermatitis lesions, and Ov16 results

Only 59.7% of participants tested positive for Ov16 antibodies using RDT, although 93.2% met the diagnostic criteria for OAE. The fact that some OAE cases had negative Ov16 serological results could be explained by the low sensitivity of the test particularly if persons have been treated with ivermectin [44].

Most frequent onchodermatitis lesions in our participants were chronic lesions (depigmentation, chronic papular onchodermatitis, lichenified onchodermatitis, and hanging groins). This suggests a long standing infection with *O. volvulus* in the PWE. No clear pattern was observed between Ov16 results and onchodermatitis, probably because of the high ongoing Ov transmission, coupled with intermittent ivermectin use that affects the skin lesions and Ov16 test results. Furthermore, Ov16 RDT is an antibody test and informs only about exposure to, or transmission of Ov unlike microfilaria in skin snips that indicates an ongoing infection.

4.2.4. Treatment with ivermectin

We observed a significant decrease in ivermectin use among PWE in recent years with less than 30% coverage in 2016/2017 compared with 41.7% before the onset of seizures ($p = 0.0043$). This could be attributed to the general misconception in some villages that PWE are not eligible to receive ivermectin. Meanwhile, the microfilarial load has been shown to be a determining factor in developing OAE [2,10], and this load falls drastically following ivermectin administration, thereby reducing the risk to develop epilepsy. Additionally, ivermectin has been shown to reduce seizure frequency in PWE [45]. Communities must therefore be properly educated to emphasize the importance of ivermectin use including among PWE.

4.3. Study limitations

Our study had several limitations: Data collected on medical history could be subject to recall bias. Moreover, laboratory and radiological investigations were not performed and the vaccination history could not be obtained to identify other possible causes of epilepsy. Nevertheless, from the medical history, we were able to exclude perinatal brain damage as an important cause of epilepsy in our study population. We were unable to determine the exact fraction of epilepsy attributable to neurocysticercosis. The onset of epilepsy due to neurocysticercosis may also occur between the ages 11–20 years similar to OAE [46], but the mean age of onset is usually after 25 years [46,47]. Therefore, cysticercosis is generally connected to late-onset epilepsy [47,48] as opposed to adolescent-onset epilepsy observed in this study. Furthermore, a previous survey by Dongmo et al. in the Mbam valley of Cameroon did not find an association between epilepsy and cysticercosis [49] making it unlikely for *Taenia solium* to be a major confounder in our study.

5. Conclusion

There exists a spectrum of seizure disorders in onchocerciasis-endemic villages in Cameroon, with the most frequent seizure types being generalized tonic–clonic episodes, absences, and nodding seizures. Two or more seizure types occur in 39.7% of PWE. The majority (93.2%) of epilepsies started between 3 and 18 years of age, and only 10.3% of PWE live beyond 40 years. More research is needed to clarify the physiopathology of the OAE. In the meantime, proper epilepsy management strategies need to be implemented in at risk villages, with a continuous supply of affordable AEDs including at least valproate and phenobarbital. Our study confirms the existence of OAE in Cameroon and calls for more attention from the stakeholders toward this neglected condition.

5.1. Ethical considerations

All information in this study was treated confidentially. Ethical approvals for the study were obtained from the University of Antwerp (Registration number B300201731362) and the National Ethics Committee of Cameroon (Registration number 2017/02/875/CE/CNERSH/SP). Administrative authorization was granted by the Ministry of Public Health of Cameroon (D30-177/L/MINSANTE/SG/DROS/TMC), and all recruited PWE gave a signed informed consent to participate in the study.

Availability of data and material

All collected data are confidentially kept at both the Global Health Institute, University of Antwerp (Belgium) and the Brain Research Africa Initiative (BRAIN), Cameroon. The datasets are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

AKN and RC (Conception); AKN, RC, ACZK, TGY, (Design); AKN, ACZKB, CB, TGY, ENT, CK, SFJN, LN, NLN, SEC, MKM, DF, WYN, GAN (Data collection); ENT, SFJN and AKN (Data analysis and interpretation); SFJN wrote the first draft and all authors critically reviewed, corrected and approved the final version of the manuscript.

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