Original article

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Clinical presentation of epilepsy in six villages in an onchocerciasis endemic area in Mahenge, Tanzania

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ABSTRACT – *Aims*. To describe the clinical manifestations of epilepsy and access to antiseizure treatment in Mahenge in Central Tanzania, an onchocerciasis endemic area with a high prevalence of epilepsy.
Methods. A door-to-door epilepsy prevalence survey was conducted in four rural and two sub-urban villages. Trained community workers used five screening questions to identify persons suspected to have epilepsy. Such individuals were interviewed and examined by a neurologist or a medical doctor with additional training in epilepsy, and were tested for *Onchocerca volvulus* antibodies.
Results. A total of 221 out of 8,062 (2.74%) surveyed individuals were confirmed to have epilepsy. The median age at seizure onset was 12 years (interquartile range: 7-16). Seventy-nine persons with epilepsy (PWE) (36.1%) had a family member with epilepsy, which was a sibling in 52.1%. Tonic-clonic seizures (142 individuals; 64.2%) were the most common seizure type. Nodding seizures were reported in 12.7% of PWE; the majority of them living in rural villages. Persons with nodding seizures reported more frequent seizures, presented with more psychiatric symptoms, and more often had onchocerciasis antibodies than those with other seizure types. The high rate of individuals with a seizure onset at between seven and 16 years is characteristic of onchocerciasis-associated epilepsy (OAE). Of the PWE, 77.9% met the criteria for the clinical case definition of OAE. Eighty-three PWE (37.6%) were not taking any antiepileptic medication. Phenobarbital was the antiepileptic drug most commonly prescribed in 76.1% of treated PWE.

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Conclusion. The high prevalence of epilepsy in rural villages in Mahenge most likely is related to the high prevalence of OAE. To prevent children developing OAE, strengthening the onchocerciasis elimination programme in Mahenge is urgently needed. Moreover, a decentralised epilepsy treatment programme is also needed to provide uninterrupted access to affordable antiepileptic drugs for the many PWE living in rural villages in the Mahenge area.

Key words: epilepsy, nodding syndrome, Nakalanga syndrome, onchocerciasis, Tanzania, treatment

Epilepsy affects approximately 50 million people worldwide, with up to 80% living in low- and middle-income countries (Ngugi *et al*., 2013), and is particularly prevalent in sub-Saharan Africa (SSA) (Chin, 2012). Epilepsy is two or three times more common in SSA than in industrialised countries in non-tropical climate zones (Paul *et al*., 2012). In 2005, the Global Campaign Against Epilepsy coalition estimated the prevalence of epilepsy in Africa to be 11.29 per 1,000 population, resulting in an estimated 3.4 million affected individuals (Chin, 2012). This is 26% higher than the worldwide mean prevalence of 8.93 per 1,000 population (Chin, 2012). In Africa, epilepsy prevalence peaks in the 20-29-year age group (Paul *et al*., 2012). A study in Kenya showed that mortality in people with active convulsive epilepsy was six times higher than that of the general population (Ngugi *et al*., 2014).

There are many causes of epilepsy, however, in SSA, confirming the diagnosis of epilepsy and identifying its cause is difficult because of inadequately trained healthcare personnel and a lack of laboratory diagnostic instruments, electroencephalography (EEG), and neuroimaging (CT). Risk factors for epilepsy in SSA include birth trauma, central nervous system infections, and traumatic brain injury (Preux and Druet-Cabanac, 2005). Parasitic infestations, such as cysticercosis, toxoplasmosis, and onchocerciasis are among the possible triggers of the epilepsy in some areas of SSA (Kariuki *et al*., 2015).

In onchocerciasis-endemic areas in SSA, a high prevalence of epilepsy has been reported (Boussinesq *et al*., 2002; Dowell *et al*., 2013; Colebunders *et al*., 2016a). Those areas include the Democratic Republic of Congo (Pion *et al*., 2009), Cameroon (Boussinesq *et al*., 2002; Prischich *et al*., 2008), South Sudan (Tumwine *et al*., 2012), northern Uganda (Iyengar *et al*., 2014) and south-western Tanzania, where a special form of epilepsy, the "nodding syndrome" (NS), was already described in 1965 (Aall-Jilek, 1965). The presenting clinical feature of NS is a paroxysmal spell in which the head nods forward repeatedly (Sejvar *et al*., 2013). The syndrome is considered to appear between the age of three and 18 years (Dowell *et al*., 2013). The natural history is not well known, but has been described to start with nodding seizures, often gradually progressing to other seizure types, cognitive deterioration, psychiatric dysfunction, and physical decline (Dowell *et al*., 2013; Winkler *et al*., 2014; Idro *et al*., 2018). Some children develop stunted growth and present with delayed or absent secondary sexual characteristics. Children with NS are reported to be healthy until the nodding episodes begin. They often die as a result of uncontrolled seizures that lead to aspiration, drowning or burn injury (Dowell *et al*., 2013).

The Mahenge Mountains in the Ulanga district of Tanzania is an area endemic for onchocerciasis. The national Onchocerciasis Control Programme has conducted community-directed annual treatment with ivermectin (CDTI) since 1997. In 1989, a population-based door-to-door survey in this area revealed an incidence of 73.3 new cases of epilepsy per 100,000 persons/years and a prevalence of epilepsy that varied between villages, from 0.51 to 3.7%.

In January 2017, we conducted an epilepsy prevalence survey in two rural (Matumbala, Vigoi) and two semi-urban villages near Mahenge (Mdindo, Msogezi), and documented a high prevalence of epilepsy in the rural villages (3.5%) where there was also evidence of higher *O. volvulus* transmission (Mmbando *et al*., 2018). In February 2018, another epilepsy prevalence survey was conducted in the rural villages of Sali and Mzelezi. In this paper, we describe the prevalence of epilepsy in the latter two villages and the clinical presentation of persons with epilepsy (PWE) identified during both surveys.

Methods

The methodology of the two door-to-door epilepsy surveys in the Mahenge area has been described before (Greter *et al*., 2018). In summary, five validated screening questions were used by trained community workers to identify persons suspected of epilepsy (Diagana *et al*., 2006). It was asked whether a family member:

– had ever lost consciousness and experienced either loss of bladder control or foaming in the mouth;

– had ever experienced absence(s) or sudden loss of contact with the surroundings for a short duration of time;
– had ever experienced sudden, uncontrollable twitching or shaking of arms, legs or head, for a period of a few minutes;
– had sometimes experienced sudden and brief bodily sensations, seen or heard things that were not there, or smelt strange odours;
– and ever been told to have epilepsy. The questions had been translated in Kiswahili.
If the response to one of these questions was positive, the person was suspected to have epilepsy and was sent for examination by a neurologist or a medical doctor with training in epilepsy.

Definition of epilepsy and classification

A person was considered to have confirmed epilepsy if he or she had at least two events of unprovoked seizures occurring more than 24 hours apart (Fisher *et al*., 2014) and if the diagnosis was confirmed by a neurologist or a medical doctor with additional training in epilepsy.
Nodding seizure was defined as an episode of reduced consciousness during which the head dropped forward repeatedly. Nakalanga syndrome was defined as a combination of growth retardation (stunting) without obvious cause, delay or absence of external signs of sexual development, intellectual impairment, epileptic seizures, and often acquired facial dysmorphia with small mandible, large lips, protruding front teeth, and kypho-scoliosis (Föger *et al*., 2017). Onchocerciasis-associated epilepsy (OAE) was defined as a previously healthy person who has lived for at least three years in an onchocerciasis-endemic village with a high prevalence of epilepsy, who developed epilepsy without an obvious cause between the age of three and 18 years (Preux and Druet-Cabanac, 2005).

Neurological assessment

After informed consent was obtained, the person suspected to have epilepsy or a parent or guardian was interviewed in Kiswahili language by a neurologist or medical doctor with training in epilepsy, using a standardised questionnaire. This questionnaire included questions about the medical history of the patient, year of onset of the seizures, description of type of epilepsy (tonic-clonic seizures, focal seizures, absences, nodding seizures), frequency of seizures and factors triggering the seizures. Care was taken not to prime the participant answering the questions towards the term "nodding" or the provoking factors, which comprised avoidance of any physical demonstration or providing closed questions. Subjects were also asked whether they were treated with antiepileptic drugs (AEDs), and records from health facilities providing AEDs in the area were reviewed to assess whether they had attended these clinics during the last two years.
On physical -including neurological- examination, persons suspected to have epilepsy were assessed for subcutaneous onchocerciasis nodules, skin lesions, and visual impairment. A limited number (35 patients from Sali village) of consecutive PWE were examined by fundoscopy. Measurement of height and weight were obtained using a stadiometer and digital scale, respectively. Persons suspected to have epilepsy were tested for antibodies against *O. volvulus* IgG4 antigen using the Ov16 test (OV16 rapid test, SD Bioline, Inc, Gyeonggi-do, South Korea).

Medical record review

The medical records of PWE identified during the surveys were reviewed at the Mahenge Hospital and Msogezi dispensary to verify the type of AED and the dose they received.

Data management and statistical analysis

Data were collected electronically with tablet computers using open data kit (ODK) software. The clinical characteristics of PWE were compared between persons with and without a positive OV16 serological test. We also compared the frequency of seizures in persons who received ivermectin medication during the last mass drug administration against those who did not receive the ivermectin medication. Basic anthropometric measurements (weight and height) were used to calculate body mass index (BMI) and z-scores (BMI for age and height for individuals aged 1-19 years) using the WHO 2007 Growth reference data (20). Kruskal-Wallis test was used to test whether frequency of epilepsy was similar within familial aggregation groups. In all analyses, a p-value <0.05 was considered significant.

Ethics

The study was approved by the ethics committee of the National Institute for Medical Research of Tanzania (NIMR/HQ/R.8a/Vol.IX/2278) and the ethics committee of the University of Antwerp, Belgium. Written informed consent (with thumb printing for those who could not write) was obtained from all patients or their parents/guardians who participated in the study, in the presence of a witness. Assent was obtained from children between the ages of 12 and 18.

Table 1. Characteristics of 221 people with confirmed epilepsy in six villages in the Mahenge area.

Strata	Village	Number screened	No. PWE (%)	Sex of PWE male (%)	Median age of PWE (IQR)	Median age at onset of epilepsy (IQR)
Rural	Matumbala	972	16 (1.6)	7 (43.7)	31.5 (18.9-43.2)	13 (5-18)
	Vigoi	1646	23 (1.4)	12 (52.2)	23.7 (17.5-31.5)	10 (7-14)
	Sali	1176	43 (3.7)	14 (38.9)	21.4 (15.6-29.6)	10 (6-12)
	Mzelezi	1769	51 (2.9)	24 (51.1)	22.6 (17.6-25.6)	12 (6-19)
Sub-urban	Mdindo	941	33 (3.5)	17 (51.5)	27.5 (22.5-36.5)	12 (11-15)
	Msogezi	1558	55 (3.5)	26 (47.3)	25.5 (17.5-33.5)	10 (6-16)

PWE: persons with epilepsy; IQR: interquartile range.

Results

A total of 8,062 individuals were screened. Of those, 380 (4.7%) were suspected to have epilepsy and six of these were not seen by a doctor. The reasons for this were mainly travel or being away for farming. Of the suspected individuals, 221 (59.2%) were confirmed to have epilepsy. Of the 153 individuals suspected but not confirmed to have epilepsy, the diagnoses included: 27 (17.6%) with febrile seizures or psychogenic attacks, seven (4.6%) with syncope, six (3.9%) with cerebral palsy, five (3.9%) with peripheral neuropathy, six (3.9%) with psychiatric symptoms without epilepsy, four (2.6%) with encephalopathy, four (2.6%) with tremors, three (1.9%) with hyperventilation or anxiety, two (1.3%) with alcohol-induced seizures, two (1.3%) with vertigo, two (1.3%) with spasm, two (1.3%) with stroke, two (1.3%) with a single seizure, two (1.3%) with intellectual impairment without seizures, one (0.6%) with eclampsia, one (0.6%) with Parkinson disease, 18 (11.7%) with another diagnosis, 47 (30.7%) with no distinctive medical condition, and 12 (7.8%) with diagnosis missing.

The prevalence of epilepsy was highest in the four rural villages (2.9-3.7%). The median age of PWE was 23.6 years (IQR: 17.9-33.5), while median age at seizure onset was 12 years (interquartile range: 8 -16) (*table 1*).

Classification of epileptic seizures

The age at examination of the majority of PWE was 20-29 years, while the median age at seizure onset was 10-12 years in the sub-urban villages. The main type of seizure reported by the 221 PWE was tonic-clonic seizure in 142 (64.2%), myoclonic or atonic seizure in 34 (15.4%) absence seizure in 18 (8.1%), focal seizure in seven (3.2), secondary generalised seizures in nine (4.1%), and other forms of seizures in 11 (5.0%). Thirty-one (14.0%, 31/221) individuals had a history of head nodding seizures. Most people with nodding seizures were observed in Mzelezi while very few were observed in the sub-urban villages with lower epilepsy prevalence (Matumbala and Vigoi) (*figure 1*). The mean age at onset of nodding seizures was 11 years compared to 13.3 years for those with other forms of epilepsy. The minimum age at onset of nodding seizures was three years.

Clinical conditions possibly related to epilepsy aetiology

Medical history data concerning possible conditions that could have caused epilepsy were available in 163 (73.7%) PWE. Conditions identified included severe malaria in 22/172 (12.8%), possible perinatal asphyxia suggested by delayed cry at birth in 12/163 (7.4%),

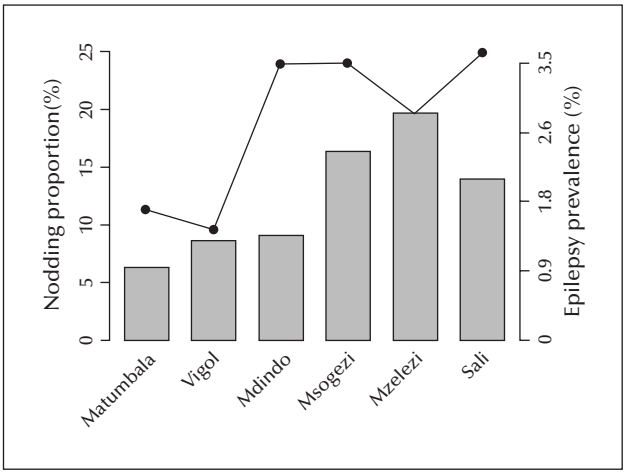

Figure 1. Distribution of prevalence of epilepsy (line) and proportion of PWE with nodding seizures (bars) by village.

meningitis in 6/170 (3.5%), and an unspecified severe febrile illness in 28/199 (9%). Of the 22 PWE who mentioned having had severe malaria, 15/148 (10.1%) were living in a rural village and 7/24 (29.2%) in a sub-urban village; *p*=0.01.

Family history of seizures

Of 219 PWE, 78 (35.6%) indicated that they have a family member with epilepsy (*table 2*). The majority (55.1%) were siblings. Individuals with a family member with epilepsy were more likely to have more frequent seizures than those with no family member with epilepsy. The risk of seizures increased significantly from OR= 3.3 (*p*=0.035) for one seizure to OR=4.4 (*p*=0.013) for three seizures, and thereafter declined to no significant risk (OR= 2.7, *p*=0.16) for four or more seizures when compared to those with no family members with epilepsy (*table 3*). The proportion of PWE using AEDs was not different between families with and without another member with epilepsy, (60.6%) and (63.6%), respectively; *p*=0.68, however, the proportion of non-adherence to AEDs (defined as not taking AEDs regularly) was significantly higher in families with a history of seizures (39.2%) compared to 16% in families with no history of seizures; *p*=0.002.

Clinical presentation of PWE

Persons with nodding seizures had a higher frequency of seizures and were more likely to present psychiatric problems, be intellectually impaired and disoriented, present Nakalanga features, and have a slightly lower height for age z-scores (*table 4*).

A higher proportion of persons with nodding seizures were taking AEDs, however, compliancy was as poor as that for persons with other forms of epilepsy. Fundoscopy was normal in all the PWE examined.

Table 2. Family members with epilepsy of the 219 PWE.

Family relation	No. PWE (%)	Median age (years)	IQR (years)
Siblings (brother/sister)	43 (52.1)	22.5	17.6-37.5
Father	4 (4.1)	20.7	7.2-23.5
Mother	6 (7.7)	12.6	10.5-17.5
Grandparent	4 (4.1)	9.0	2.0-26.8
Child	6 (7.7)	54.2	48.6-54.6
Cousins	1 (1.3)	14.6	-
Nephew	3 (3.8)	21.1	19.6-22.6
Uncle/aunt (maternal)	6 (7.7)	12.0	9.5-20.6
Uncle/aunt (paternal)	5 (6.4)	17.6	15.6-23.6

PWE: persons with epilepsy.

Detailed description of two persons with Nakalanga features

The first was a 23-year-old male, weighing 34 kg with a height of 142 cm (BMI: 16.9) who was living with his grandparents (*figure 2*). His perinatal history was uneventful except for an episode of febrile seizures at the age of two months; he was treated for malaria with full recovery. He developed normally until the age of eight years, when he had a sickness that was characterised by sluggishness, inability to walk, and fever. He was admitted at Mahenge hospital and was treated with antibiotics. From this period, he started presenting with brief episodes of head nodding, 5-10 per day, worsening during food intake. He was initially treated with carbamazepine at 200 mg, twice daily, and phenobarbital at 100 mg, twice daily, at the Mahenge Epilepsy Clinic, but the phenobarbital had to be stopped because he became too sleepy. Carbamazepine at 200 mg, twice daily, was effective in decreasing the frequency of seizures but the seizures continued intermittently. He never took ivermectin before the onset of head nodding. He never lost consciousness, nor developed convulsive seizures. He was the second born in a family of six siblings; the other five doing well. He stopped attending school during his second class in primary school at the age of eight years due to severe intellectual disability and uncontrolled head nodding. He could neither read nor write. He had hair on his upper lip and a few hairs on his chin, wide-spaced teeth, a moderately sized mandible and maxilla, and a short trunk but no spinal deformity. He is now treated with carbamazepine at 300 mg, twice daily, with some decrease in seizure frequency.

The second was a 35-year-old male, weighing 45 kg with a height of 149 cm (BMI: 20.3) (*figure 3*). From the age of seven years, he started presenting with brief head-nodding episodes. The perinatal history was uneventful and he never took ivermectin. Seizures were triggered by food intake and cold weather. Two years later, he developed generalized tonic-clonic seizures, two to three times a month, while nodding episodes continued. Physical examination showed kyphosis, mild pectus excavatum, and chronic papulo-macular onchodermatitis, more marked on the extremities.

Table 3. Distribution of seizures by family history of epilepsy and associated odds ratios.

Seizure frequency	Seizure family history		OR (95% CI)	*p* value
	No	Yes		
0 seizure	23 (15.86)	4 (4.94)	1	
1 seizure	54 (37.24)	31 (38.27)	3.30 (1.01 - 10.73)	0.035
2 seizures	36 (24.83)	26 (32.1)	4.15 (1.22 - 14.14)	0.013
3 seizures	17 (11.72)	13 (16.05)	4.40 (1.12 - 17.19)	0.020
4+ seizures	15 (10.34)	7 (8.64)	2.68 (0.64 - 11.26)	0.160
Total	145 (100)	81 (100)		

Table 4. Characteristics of patients with nodding seizures and others forms of epilepsy.

	Nodding seizures (*n*=31)	Other forms of epilepsy (*n*=190)	*p* value
Age (median, IQR)	22.50 (17-26)	23.69 (19-34)	χ^2=0.85 (0.355)
Sex (males)	16 (53.3)	85 (47.0)	χ^2=0.419 (0.518)
Positive Ov16 test	21 (70%)	81 (52.6%)	χ^2=3.44 (0.064)
Seizures in week preceding the survey	16 (51.6)	46 (24.3)	χ^2=9.79 (0.002)
Psychiatric symptoms*	12 (38.7)	40 (21.05)	χ^2=4.618 (0.032)
Nakalanga features	9 (29.0)	15 (8.0)	χ^2=13.3 (<0.001)
Height for age z-scores (mean, 95%CI)	-2.42 (-3.38 - -2.42)	-1.46 (-1.93 - -0.99)	*t*=1.82, (0.074)
Intellectually disabled	16 (51.6)	45 (23.9)	χ^2=10.40 (0.001)
Normal gait	26 (83.9)	178 (93.9)	χ^2=3.61 (0.057)
Taking AEDs	26 (83.9)	112 (59.0)	χ^2=7.06 (0.008)
Regular use of AEDs (good adherence)**	14 (45.2)	78 (44.8)	χ^2=0.001 (0.97)

*Mainly behavioural problems such as aggressiveness; **non-adherence was defined as not taking AEDs regularly.

Neurological examination showed: preserved vision and hearing as far as testable; profound intellectual disability with anarthria; and generalised rigidity with hypokinesia, catatonic-like posturing with stooped gait, dropped hands, and intermittent coarse tremors, but preserved ability to walk unassisted. He had never been to school because of the seizures. Seizure frequency decreased upon initiation of phenobarbital at 120 mg. However, due to a shortage of the drug at the nearby health facility and financial constraints of the family, treatment was intermittent, and he stopped taking the drug from 2000. He is now treated with carbamazepine at 300 mg, twice daily, which seems to control seizures. More persons with Nalalanga features are presented in *table 5*.

Association between epilepsy and *O. volvulus* antibodies

Of 374 individuals suspected to have epilepsy, 295 (78.9%) including 187 (63.4%) individuals with confirmed epilepsy were tested for *O. volvulus* antibodies using the OV16 rapid test (*table 6*). PWE from the rural area were more often positive for this test; 88.2% compared to PWE from the urban area 75.3%; *p*=0.021. Similarly, patients with nodding seizures were more likely to be positive for the OV16 test (20. 6%) compared to those with negative tests (10.2%), however, the difference was not significant (*p*=0.064). The prevalence of OV16 positivity among PWE was not significantly different compared to those without confirmed epilepsy,

Figure 2. A 23-year-old male with Nakalanga features and his relative of the same age without abnormal features.

Figure 3. Nakalanga features in a 35-year-old patient with thoracic deformity, profound intellectual disability and hypokinesia.

but PWE positive for the OV16 test were significantly older than OV16 test-negative PWE. For 172 PWE, information was available concerning all the criteria for clinical case definition of OAE, and 134 (77.9%) met the criteria for OAE.

Treatment of epilepsy

Eighty-three (37.6%) of 221 PWE (65/185 [35.7%] in rural and 18/39 [46.1%] in semi-urban settings) were not taking any AEDs (χ^2=1.49, p=0.222). Of 138 PWE who indicated using AEDs, phenobarbital was the most frequently prescribed single drug (105; 76.1%). A small number of PWE used phenytoin (10; 7.2%), carbamazepine (4; 2.9%) or a combination of phenobarbital plus phenytoin (11; 8%) and phenobarbital plus carbamazepine (7; 5.1%). One PWE combined a traditional remedy with carbamazepine. The AED doses could not be assessed reliably.

Although the risk of experiencing one or more seizures during the month preceding the survey was not significantly different in individuals who were on AEDs compared to those who were not on AEDs, the risk was significantly lower in patients who were taking AEDs regularly (good adherers) (*table 7*). The risk of experiencing seizures decreased with increasing age, was lower in PWE from a sub-urban village, and was higher among persons with psychiatric symptoms.

Table 5. Clinical characteristics of PWE with Nakalanga features.

	Socio-demography					Seizure-related information				Clinical manifestations			Onchocerciasis
	Age (yrs)	**Sex**	**HAZ score****	**Height (cm)**	**Growth status**	**Age at onset**	**Frequency**	**Nodding seizures**	**Epileptic siblings**	**Cognitive impairment**	**Normal sexual development**	**Deformity**	**Ov16 test**
1	37.5	M	NA	141	Below mean adult height*	11	2 per month	No	Yes	Yes	Yes	No	+
2	19.6	M	-3.4	152	Severely stunted	4	2 per month	No	No	Yes	Yes	No	-
3	12.6	M	-3.2	130	Severely stunted	6	3 per week	Yes, current	No	Yes	Yes	No	+
4	21.2	M	NA	151	Normal height*	7	4 per day	No	Yes	Yes	Yes	Facially abnormal	-
5	13.6	M	-4.0	130	Severely stunted	6	4 per day	Yes, in the past	Yes	Yes	Yes	No	+
6	31.3	M	NA	145	Below mean adult height*	8	3 per week	Yes, in the past	No	Yes	Yes	No	+
7	14.6	F	-4.4	131	Severely stunted	11	3 per week	Yes, current	No	Yes	Yes	No	+
8	16.7	F	-3.6	138.5	Severely stunted	5	4 per day	Yes, in the past	No	Yes	Yes	No	+
9	21.6	M	NA	152	Normal height*	11	2 per month	No	No	Yes	Yes	Facially abnormal	+
10	21.6	M	NA	154.5	Normal height*	NK	2 per month	No	No	Yes	Yes	Facially abnormal	-

*Height below mean estimated as height below 2 SD of normal height derived from non-epileptic study participants who were aged 20 years or more. Mean height for men was 162 cm (SD: 7.2) while that of females was 152.8 cm (SD: 7.8). **For participants aged 5-19 years, based on World Health Organization growth curves. NA: not applicable; NK: not known.

Table 6. Clinical characteristics of PWE according to OV16 status.

	OV16 positive *n*=102 (54.5%)	**OV16 negative n=85 (45.5%)**	***p* value**
Male gender (*n* [%])	46 (46.9)	39 (47.6)	0.934
Age (median [IQR])	25.4 (18.6–37.5)	22.6 (16.13–31.7)	0.048
BMI (≥20y) (mean ± SD)	19.90 ± 0.37	21.01 ± 0.46	0.059
BMI for age z-scores (1-19y) (mean ± SD)	-0.69 ± 0.29	-0.96 ± 0.22	0.449
Height for age z-scores (1-19y) (mean ± SD)	-2.13 ± 0.237	-1.57 ± 0.25	0.111
Age at onset of epilepsy (mean ± SD)	14.1 ± 9.6	12.3 ± 7.7	0.172
Nodding seizures (*n* [%])	21 (20.6)	9 (10.16)	0.064
Psychiatric symptoms (*n* [%])	27 (26.5)	17 (20.0)	0.30
Setting (rural vs. rural) (*n* [%])	90 (88.2)	64 (75.3)	0.021

Gender, median age, presence of nodding seizures, and psychiatric symptoms were compared using χ^2-test, while other variables were compared using t-test.

Clinic record review

Of the 127 PWE identified during the survey in 2017 in Matumbala, Vigoi, Mdindo and Msogezi, only 60 (47.2%) had records in either Mahenge or Msogezi clinics which are the facilities serving the four villages. Mdindo had the highest number of PWE registered (60.6%) while Vigoi had the lowest (39.1%). Four (6.3%) individuals without confirmed epilepsy were being treated as PWE. The study doctor with training in neurology (MM*) had diagnosed them with non-epileptic seizures, psychiatric symptoms, and no seizures.

At the Msogezi dispensary, PWE were only prescribed phenobarbital, while at Mahenge Hospital clinic, multiple AEDs were prescribed. Of the 39 PWE medical records reviewed, 27 (69.2%) received phenobarbital, three (7.7%) phenytoin, eight (20.5%) carbamazepine alone, and one (2.6%) carbamazepine combined with phenobarbital. The median daily dosage for the different AEDs at the Mahenge Hospital clinic were: phenobarbital at 90 mg, phenytoin at 300 mg, and carbamazepine at 400 mg, while at the Msogezi dispensary, the median dosage of phenobarbital was 200 mg.

Table 7. Multivariable model showing factors associated with frequency of seizures (one or more episode per month) among the 185 PWE with complete information.

Explanatory Variable	**OR**	**95%CI**	***p* value**
Use of AEDs	0.703	0.100 - 4.940	0.724
Treatment non-adherence	3.177	1.178 - 8.567	0.022
Age (years)	0.979	0.956 - 1.002	0.079
Living in sub-urban village	0.165	0.058 - 0.47	0.001
Psychiatric symptoms	3.003	1.317 - 6.851	0.009

Discussion

This paper describes the characteristics of PWE identified during community surveys in six villages endemic for onchocerciasis in Mahenge, Tanzania. Generalised tonic-clonic seizures (64.2%) and generalised myoclonic or atonic seizures (14.9%) were the most common types of seizures; nodding seizures were observed in only 12.7% of PWE.

In most PWE, no obvious other cause could be identified and their psycho-motoric development before the onset of seizures had been normal. The peak onset of epilepsy between the ages of seven and 16 years is a characteristic of OAE as observed elsewhere in Africa (Colebunders *et al*., 2016b, 2017). This study shows that OAE may present with a wide variety of types of seizures including nodding seizures.

The higher frequency of seizures, psychiatric symptoms, and intellectual disability in persons with nodding seizures shows that this type of seizure is a more disabling form of OAE. The explanation why certain children with *O. volvulus* infection develop nodding seizures, Nakalanga features, or another form of epilepsy still needs to be elucidated. One explanation could be that children develop nodding seizures

when they became heavily infected with *O. volvulus* at a young age. An argument for this hypothesis is a recent study in South Sudan which showed that the age at onset of nodding seizures was around eight years, while the age of other forms of seizures was around 10 years (Colebunders *et al*., 2018). In our study, the age at onset of epilepsy was 11 years for nodding seizures and 13.3 years for other forms of epilepsy.

The high percentage of PWE (38.6%) who were not taking any AEDs illustrates the epilepsy treatment gap in SSA (Mbuba *et al*., 2008; Ba-Diop *et al*., 2014). The low intake of AEDs could be due to a shortage of drugs in health facilities, epilepsy-related stigma attributed to a low level of knowledge about epilepsy in the community, long distance to the health facility (Mbuba *et al*., 2008; Harimanana *et al*., 2013; Ibinda *et al*., 2017), the cost of the AED or inadequately skilled health facility personnel (Mbuba *et al*., 2008). The disparity in dosages of phenobarbital provided at the facilities (median dose of 90 mg in adults at the Mahenge Hospital clinic compared to a median dose of 200 mg at the Msogezi dispensary for a similar patient population) suggests that certain PWE in Msogezi receive a dose of AED that is too high. This is an indication of the low level of knowledge about epilepsy management among the health personnel and lack of supportive supervision.

The fact that more frequent seizures were reported in PWE who had a family member with epilepsy than in those with no family member with epilepsy correlates with the low adherence to AEDs, as supported by the findings. This could be attributed to a higher socioeconomic burden of the epilepsy in such a household, which provides little resources, including family support to take care of several people with the disease, and family perception that epilepsy is a common disease in the family; stigma could also contribute to poor care and accessibility to AEDs (Ba-Diop *et al*., 2014).

Epilepsy is an important public health problem in Mahenge. Hence, there is a need to identify factors associated with the treatment gap observed in the study area. Increasing epilepsy awareness among the community, and especially political leaders, and policy makers through local councils will hopefully improve awareness and eventually lead to a reconsideration of the importance of epilepsy.

Our study has several limitations. Not all persons suspected to have epilepsy were seen by a medical doctor. Moreover, the aetiological diagnosis of epilepsy was only made by medical history taking and neurological examination. Recall bias may have influenced the diagnosis. OV16 testing was the only test performed for PWE. We were unable to perform imaging studies. Therefore, we do not know the potential contribution of neurocysticercosis in causing the higher epilepsy prevalence in the rural villages. However, this contribution is probably limited because less than 10% of households in these villages rear pigs, which are all kept in small elevated huts preventing their contact with human stools. Also, an in-depth assessment of psychiatric symptoms of PWE was not performed. Therefore, it was not possible to differentiate psychiatric co-morbidities from symptoms caused by the encephalopathy of certain PWE.

In conclusion, the high prevalence of epilepsy in rural villages in Mahenge, without an obvious cause and with a seizure onset between the ages of seven and16 years, in previously healthy children, suggests that a large part of the epilepsy (77.9%, using the OAE criteria) is directly or indirectly caused by *O. volvulus* infection. This form of epilepsy can be prevented by strengthening the onchocerciasis elimination programme. Moreover, the burden on PWE and their family can be relieved by improving access to quality AEDs and care. A decentralised epilepsy treatment programme is needed in the Mahenge area to provide uninterrupted access to affordable AEDs to the many rural-based PWE. To optimise epilepsy care in this challenging setting, involvement of community health workers is paramount. Not only would this reduce management expenses, it would also directly narrow the epilepsy treatment gap (Brown, 2007). □

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