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Epilepsy in the Sanaga-Mbam valley, an onchocerciasis-endemic region in Cameroon: electroclinical and neuropsychological findings

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Abstract

Objective: Epilepsy is highly prevalent in onchocerciasis-endemic African regions. Various types of epilepsy have been described in such regions based essentially on clinical characteristics.

Methods: We conducted a clinical, neurophysiological and neuropsychological study of epilepsy in the onchocerciasis-endemic region of Ntui, Sanaga-Mbam area, Cameroon.

Results: One hundred and eighty-seven persons with presumed epilepsy were recruited in an epilepsy clinic in Ntui. Epilepsy was clinically confirmed in 144 (79%) subjects, 69 (46.0%) of them met the onchocerciasis-associated epilepsy (OAE) criteria, and 51 of 106 tested (48.1%) presented Ov16 antibodies. Electroencephalograms

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(EEG) were recorded in 91 participants, of which 36 (33%) were considered abnormal and 27 of 36 (75%) revealed bifrontotemporal spike and slow waves. Concerning the neuropsychological evaluation, 29% showed severe global cognitive impairment, 28% severe episodic memory impairment, and 66% severe frontal cognitive impairment. Half of the persons with epilepsy (PWE) suffered from a mental disorder.

Significance: In PWE in the Sanaga-Mbam area in Cameroon, we observed EEG patterns similar to those described among persons with OAE, including nodding syndrome in other onchocerciasis-endemic areas. Most PWE presented with severe cognitive impairment. We hypothesize that onchocerciasis may induce neurocognitive disorders and epilepsy via a mechanism that involves mainly the frontal and temporal regions of the brain.

KEYWORDS

onchocerciasis, epilepsy, neuropsychology, electrophysiology, nodding syndrome, Cameroon

1 | INTRODUCTION

The median prevalence of epilepsy in sub-Saharan Africa is estimated at 1.4% (compared to 0.5% in high-income countries).¹ There are various explanations for this higher prevalence in Africa, including higher frequency of brain damage from prenatal or perinatal causes, head trauma, and various infections affecting the central nervous system (CNS) such as neurocysticercosis, cerebral malaria, and meningitis.²

Within sub-Saharan Africa, important geographical disparities have been observed, with a very high prevalence in certain onchocerciasis-endemic areas: for example, 35 per 1000 people in the Mahenge region in Tanzania,³ and >80 per 1000 people in some villages in South Sudan⁴ and the central region of Cameroon.⁵ These epilepsy prevalences are much higher than those observed in areas with very low onchocerciasis prevalence such as Ifakara (Tanzania) and Kintampo (Ghana) both having an epilepsy prevalence of 14.8 per 1000 people, as well as in areas without onchocerciasis: Kilifi (Kenya) with epilepsy prevalence of 7.8 per 1000 people; Agincourt (South Africa) with prevalence 7.0 per 1000; and Iganga-Mayuge (Uganda) with prevalence 10.3 per 1000.⁶

There is growing epidemiological evidence for a strong association between onchocerciasis and epilepsy in regions in Africa where onchocerciasis is poorly controlled.⁷

A meta-analysis of case-control studies from countries in West, Central, and East Africa strongly supported this association.⁸ Another meta-analysis showed that with a 10% increase in the prevalence of onchocerciasis in a population, the epilepsy prevalence increases by 0.4%.⁹ More recently, two cohort studies in Cameroon have demonstrated the temporal relationship between onchocerciasis and epilepsy, with a dose effect.^{10,11} A study in 2018 in Kabarole, western Uganda, a

Key Points

- Epilepsy is highly prevalent in Sanaga-Mbam region in Cameroon with 47.6% of the persons with epilepsy (PWE) meeting OAE criteria.
- An EEG pattern characterized by bifrontotemporal spikes and waves was present in 75% of PWE.
- Most PWE presented with severe cognitive impairment involving frontal and temporal lobe cognition.
- Onchocerciasis might impact the frontal and temporal regions of the brain, leading to epilepsy and cognitive disorders.

previously onchocerciasis-endemic area in which, an epilepsy prevalence of 30 per 1000 people had been documented in 1994, showed that since onchocerciasis was eliminated in 2004, no new cases of nodding syndrome appeared and that the epilepsy prevalence had dropped to 12 per 1000 people.¹²

Although epidemiological studies highlight the link between onchocerciasis and epilepsy, the pathophysiological mechanisms explaining this association are not yet elucidated. In 2017, the term “onchocerciasis-associated epilepsy” (OAE) was proposed to describe different forms of epilepsy occurring in onchocerciasis-endemic regions.

Recently, updated criteria for OAE have been proposed (all 5 criteria must be met).¹³

1. History of ≥ 2 unprovoked seizures, at least 24 h apart (International League Against Epilepsy (ILAE) definition of epilepsy)

2. Onset of epilepsy between 3 and 18 years of age
3. Normal psychomotor development prior to epilepsy onset
4. No obvious cause of epilepsy identified in the individual during the 5 years preceding seizure onset, such as perinatal brain insult, head trauma, or previous infection of the CNS.
5. At least 3 years of residence in an onchocerciasis-endemic village with high epilepsy prevalence and frequent household clustering of persons with epilepsy.

The best known clinical presentation of OAE is "nodding syndrome" (NS), a condition reported in South Sudan,¹⁴ Uganda,¹⁵ Tanzania,¹⁶ the Democratic Republic of Congo,¹⁷ Cameroon,¹⁸ and Liberia.¹⁹ NS was first described in 1960 in the Mahenge district of Tanzania.²⁰ Between the year 2000 and 2009, reported NS cases increased in Uganda reaching up to 6000, yielding a prevalence of 12-46 per 1000 children aged from 5 to 15.¹⁵ Typical NS seizures present as repetitive episodes of neck atonia (nodding seizures) lasting a few minutes with or without impairment of consciousness. This epileptic encephalopathy always begins in childhood between the ages of 5 and 15 years, and is often associated with progressive cognitive impairment (CI); almost always in Uganda and South Sudan and only in half of children in Tanzania.²¹⁻²³ In a later phase of the disease, generalized motor tonic-clonic seizures (GTCS) and nonmotor (absence) seizures may occur. In most cases, the evolution is marked by a progressive degradation although a few cases of spontaneous improvement have been reported.²² Highly characteristic electroencephalographic (EEG) abnormalities have been found in almost half of NS cases, consisting of interictal slowing activity that can be diffuse or focal with 1.5- to 2-Hz spikes and waves, similar to the EEG pattern seen in Lennox-Gastaut syndrome.²³

In Cameroon, epilepsy surveys have been conducted in villages located along the Mbam River valley,²⁴ an area where onchocerciasis is highly endemic because of the many breeding sites for black flies that transmit the filarial parasite causing onchocerciasis, *Onchocerca volvulus*. Another study performed in Kelleng, a village located near the Sanaga River (the Mbam river is the main tributary of the latter), reported a prevalence of epilepsy of 105 per 1000.²⁵ A case-control study including 72 persons with epilepsy (PWE) and 72 controls in the Mbam valley showed a significant association between onchocerciasis and epilepsy with strong household clustering.⁵ Recent studies in the Mbam valley showed that 93.2% of PWE met the criteria for OAE and that there was a temporal association between infection with *O. volvulus* and the development of epilepsy in this area.^{10,11,18,26} However, not much is known about the electrophysiological and neuropsychological findings in persons with OAE.

We therefore conducted a clinical, neuropsychological, and electrophysiological study on a large sample of PWE in the Ntui area, located between the Sanaga and Mbam river valleys in order to: (1) investigate the clinical and EEG manifestations of epilepsy; (2) characterize the cognitive profiles of PWE; and (3) determine the prevalence of OAE and its related EEG features.

2 | METHODS

2.1 | Study setting and population

This study was conducted in a dispensary specialized in epilepsy treatment and care in Ntui, a small town in the Centre Region, Cameroon, where about 4000 persons with presumed epilepsy were followed up. During the months preceding the study, presumed PWE who came for follow-up visits at the dispensary were informed about the possibility to participate in the research project. A total of 187 patients voluntarily registered to participate and were seen by the investigators during a research mission at the dispensary from January 26 to 29, 2018. Study participants were examined by four teams, led by neurologists (three French and one Cameroonian).

2.2 | Epilepsy diagnosis and clinical description

Participants who reported two or more unprovoked seizures at least 24 h apart were considered as presumed epilepsy cases, in line with the ILAE definition.²⁷ The neurologists performed a clinical examination and applied a standardized questionnaire that included questions concerning epilepsy characteristics (age at epilepsy onset, seizure frequency, neurological symptoms, antiseizure medication used, history of prematurity, history of neonatal distress, and history of nodding seizures). This clinical process allowed the neurologists to confirm or reject the diagnosis of epilepsy. Furthermore, the OAE criteria were used to categorize PWE as OAE or non-OAE cases.

The type of seizure was determined in two ways:

1. Recognition by the caregivers of video recordings showing typical seizures (generalized motor tonic-clonic seizures (GTCS), generalized nonmotor seizures (absences), focal seizures, and psychogenic nonepileptic seizures (PNES)). One video sample for each type of seizure was randomly shown to the caregivers. They had to choose which sample was most representative of the type of seizures of the patient.

2. Medical history providing a detailed description of the type of seizure, the prodromal features, and the postictal phase.

2.3 | Electroencephalographic profiles

All persons with a confirmed diagnosis of epilepsy were scheduled for a 20-min EEG with 11 channels. The rating of EEG abnormalities was done by one single neurologist (DP) according to a 5-level score: 1: normal, 2: bifrontotemporal spikes and waves, 3: bifrontotemporal spike and waves and diffuse slow waves, 4: diffuse slow waves, and 5: others including typical pattern of syndromic or focal epilepsy. Once done, PWE with “bifrontotemporal spike and waves” and “bifrontotemporal spike and waves and diffuse slow waves” profiles were regrouped in one category, which was called “specific EEG.” The categories “diffuse slow waves” and “others” were considered as nonspecific.

2.4 | Neurocognitive assessment

First, we assessed speech and psychomotor development prior to epilepsy onset based on the information provided by caregivers and available medical records. Two components were tested to evaluate psychomotor development: age at which the participant walked (normal: ≤ 2 years old) and age of speech acquisition (normal: < 5 years old). Second, a series of nonverbal tests was used to explore different cognitive functions in order to evaluate the neuropsychological features associated with epilepsy.

We began by evaluating the global cognition level, using Raven's matrix test. Then, we specifically assessed three major cognitive functions using appropriate neuropsychological tests: episodic memory using a 5-figure test (free and cued immediate and delayed recall),²⁸ working memory using the Corsi block-tapping test (direct and indirect visual span),²⁹ and frontal functions using the Frontal Assessment Battery (FAB) nonverbal subtests (Go-no-go, prehension behaviour, conflicting instructions, motor series).³⁰ For these neurocognitive tests, only adult subjects (≥ 18 years) were included.

2.5 | Parasitological assessment

After the clinical examination, consenting participants were directed to a separate room where Ov16 IgG4 rapid diagnostic tests (Standard Diagnostics, Gyeonggi-do, South Korea) were performed to identify those with antibodies demonstrating a past or present infection with *O. volvulus*. Briefly, PWE were aseptically finger-pricked and a drop of blood

transferred from their finger to the rapid test plate. The test results were available within 20 min.

2.6 | Data analysis

We performed an exhaustive description of the study population followed by data analysis with bivariate analyses using adequate tests (Fisher's exact test for binary variables, Mann-Whitney test for continuous variables, and Cuzick's trend test for categorical variables). EEG results were described according to the 5-level score described above. Once the variable “specific EEG” was constructed, we performed a multivariable logistic regression model including the following 13 variables: age (in four balanced categories [< 20 , 20–25, 26–30, and > 30 years]), sex, school level (primary vs secondary), history of prematurity (yes vs no), age of onset of epilepsy (before 15 years vs after 15 years), duration of the epilepsy (< 20 years vs more than 20 years), motor development (normal vs abnormal, see below), Ov16 result (negative vs positive), seizure frequency (at last one seizure per day, at last one seizure per month, and at last one seizure per year), history of nodding seizures (yes vs no), OAE criteria met (yes vs no), history of ivermectin intake (yes vs no, ivermectin is widely distributed in the area to combat onchocerciasis), and type of antiepileptic drug (phenobarbital, carbamazepine, or both). The “motor development” variable was constructed using the speech and walking development assessment, and was defined as: “abnormal” if one of these two were abnormal and “normal” if both were normal. We first performed a saturated model including all the variables and then a stepwise backward elimination of the less significant variable with, for the final model, a tolerance at a P -value at .200 since the sample size was relatively small. Lastly, we studied the four neurocognitive test results (5-word test, Raven's test, Corsi's cube test, and FAB subtests); each one examined separately. We compared the crude scores for each variable using adequate statistical tests. Then, we performed for each one of these neurocognitive tests, a multivariable linear regression model (as above, first with a saturated model and then a stepwise backward elimination). All the missing data were categorized as such to conserve our initial sample. All statistical analyses were computed with Stata® (version 15.1; StataCorp).

3 | RESULTS

3.1 | Study population

Of the 187 participants with presumed epilepsy, 144 had the epilepsy diagnosis confirmed by the neurologists. In addition, in 6 persons with EEG findings compatible with an epilepsy but who had not been considered as PWE based

on the medical examination alone (no history of seizure/no sufficient data to confirm the epilepsy diagnosis), the diagnosis was reconsidered, taking the EEG findings into consideration. Hence, our overall study population included 150 PWE. The average age was 26.1 years, with a standard deviation (SD) 8.6. Twenty-six participants (17.3%) were adults, and 88 (58.7%) were males. The complete description of the study population is presented in Table 1. Average age of onset of epilepsy was 11.9 years (SD 6.1). Nineteen (12.7%) PWE had a history of nodding seizures, and 69 (46.0%) individuals met the OAE criteria. No Nakalanga features, notably stunted growth and lack of external signs of sexual development, were observed in the study population.

Fifty-one of the 106 PWE who underwent the Ov16 antibody test (48.1%) were found positive. Ov16-positive individuals were significantly younger than the negatives (23.8 SD 7.7 vs 28.5 SD 7.9; Wilcoxon rank-sum test, P -value = .002), and 74.1%, 57.7%, 27.3%, and 32.3% were positive in the 4-19, 20-25, 26-30, and >30 years old groups, respectively ($\chi^2 = 15.194$, degree of freedom [df] = 3, P -value = .002). Male patients were more often positive to Ov16 (59.4%) than female patients (31.0%). Fifty-one of the 106 PWE who underwent the Ov16 antibody test (48.1%) were found positive. Ov16-positive individuals were significantly younger than the negatives (23.8 SD 7.7 vs 28.5 SD 7.9; Wilcoxon rank-sum test, P -value = .002), and 74.1%, 57.7%, 27.3%, and 32.3% were positive in the 4-19, 20-25, 26-30, and >30 years old groups, respectively ($\chi^2 = 15.194$, degree of freedom [df] = 3, P -value = .002). Male patients were more often positive to Ov16 (59.4%) than female patients (31.0%; $\chi^2 = 8.206$, $df = 1$, P -value = .004).

3.2 | Neurological and EEG patterns

Among the 150 PWE, only 91 had EEG examinations done due to logistical challenges; in 55 (60.4%) of them, the EEG was normal. Bifrontotemporal spikes and waves (1.5-2 Hz), (example in Figure 1: EEG : bifrontotemporal spike and waves) were identified in 21 subjects (23.1%); in 5 (5.5%), there were bifrontotemporal spikes and waves and diffuse slow waves (1.5-2 Hz, example in Figure S1); in one (1.1%), diffuse slow waves (Figure S2); and in 9 (9.9%), more common epileptic abnormalities such as 3-Hz spikes and waves (idiopathic epilepsy) and temporal or occipital spikes. Table 2 shows the descriptive characteristics of the five EEG patterns.

Table 3 shows the bivariate analysis using the “specific EEG” variable as the dependent variable ($N = 81$, including 55 with normal EEG and 21 + 5 with “specific EEG”). A multivariable logistic regression model showed that prematurity and having an onset of epilepsy before 15 years old

were associated with “specific EEG” category (considering a P -value threshold of 0.200; Table 4). None of the onchocerciasis variables (Ov16 positivity and OAE) was associated with this “specific EEG” profile.

3.3 | Neurocognitive assessment: bivariate analyses

Thirty-four (22.7%) of the 150 PWE had a history of an abnormal motor development. We performed 62 neurocognitive tests among the adult population. Table 5 shows the mean score for each test and the results of bivariate analyses. For Raven's test, only school level (mean scores: 4.2 vs 6.4, for primary and secondary levels, respectively) and meeting the OAE criteria (mean scores: 4.5 vs 4.3, for non-OAE vs OAE, respectively) showed significantly different scores between categories. The same two variables showed significant differences for the 5-drawing test (scores of 4.6 and 6.9 for subjects having reached the primary and secondary levels; and 6.1 and 4.1 for those without and with OAE). For Corsi and FAB tests, female patients performed poorer than male patients (Table 5), and individuals with secondary education had a higher Corsi score than those who did not go beyond primary school.

3.4 | Neurocognitive assessment: multivariable models

For Raven's test (Table S1), being younger than 20 years was associated with significantly higher scores; similarly, participants who reached secondary school level had higher scores compared with their counterparts with only primary education (adjusted $\beta = 1.89$, P -value = .028). Older age of epilepsy onset and meeting the OAE criteria were both associated with lower scores at Raven's test (Table S1).

Regarding the 5-drawing test (Table S2), the results and trends were similar to those obtained with Raven's test.

For the Corsi test (Table S3), the results were similar for school level, age, age of onset of epilepsy, and duration of the disease. However, we did not find significant associations between the Corsi test scores and the presence of OAE or “specific EEG.”

Regarding the FAB test (Table S4), neither age nor education level was significantly associated with the score. A late onset of epilepsy, an abnormal motor development, and a “specific EEG” were significantly associated with a lower FAB score (adjusted $\beta = -3.39$, -3.67 , and -1.80 ; P -values <.001, .001, and .014; respectively). Individuals with OAE had also significantly lower FAB scores (adjusted $\beta = -5.41$, P -value <.001). However, Ov16 positivity was not associated with any abnormality of these cognitive tests.

TABLE 1 Description of the study population (N = 150): sociodemographic, motor development, and parasitological and neurological characteristics

Variable		Number and percentages
Sociodemographic characteristics		
Age	Mean and standard deviation	26.1 (8.6)
	Median and interquartile range	25 (30-31)
	Range	4-52
Sex	Male	88 (58.7)
	Female	62 (41.3)
School	Primary	118 (78.7)
	Secondary	27 (18.0)
	MD	5 (3.3)
Prematurity	No	95 (63.3)
	Yes	8 (5.3)
	MD	47 (31.3)
Neonatal distress	No	122 (81.3)
	Yes	6 (4.0)
	MD	22 (14.7)
Motor development		
Walking development	Normal	95 (63.3)
	Abnormal	26 (17.3)
	MD	29 (19.3)
Speech development	Normal	92 (61.3)
	Abnormal	32 (21.3)
	MD	26 (17.3)
Parasitological characteristics		
Ov16	No	55 (36.7)
	Yes	51 (34.0)
	MD	44 (29.3)
Seizure characteristics		
Generalized motor tonic-clonic seizure	No	3 (2.0)
	Yes	108 (72.0)
	MD	39 (26.0)
Generalized nonmotor seizure (absence)	No	74 (49.3)
	Yes	21 (14.0)
	MD	55 (36.7)
Focal seizure	No	95 (63.3)
	Yes	7 (4.7)
	MD	48 (32.0)
Focal-to-bilateral tonic-clonic seizure	No	84 (56.0)
	Yes	20 (13.3)
	MD	46 (30.7)
Nodding seizure	No	93 (62.0)
	Yes	19 (12.7)
	MD	38 (25.3)

(Continues)

TABLE 1 (Continued)

Variable		Number and percentages
OAE	No	43 (28.7)
	Yes	69 (46.0)
	MD	38 (25.3)
Seizure frequency	Daily	23 (15.3)
	Monthly	50 (33.3)
	Annually	32 (21.3)
	MD	45 (30.0)
Age of onset ^a	Mean and standard deviation	11.9 (6.1)
	Median and Interquartile range	12 (8-15)
	Range	1-41
History of treatments		
Ivermectin intake	No	43 (28.7)
	Yes	96 (64.0)
	MD	11 (7.3)
Type of drug	Phenobarbital	49 (32.7)
	Carbamazepine	76 (50.7)
	Both	12 (8.0)
	MD	13 (8.7)

Abbreviation: MD, missing data.

^aSix missing data.

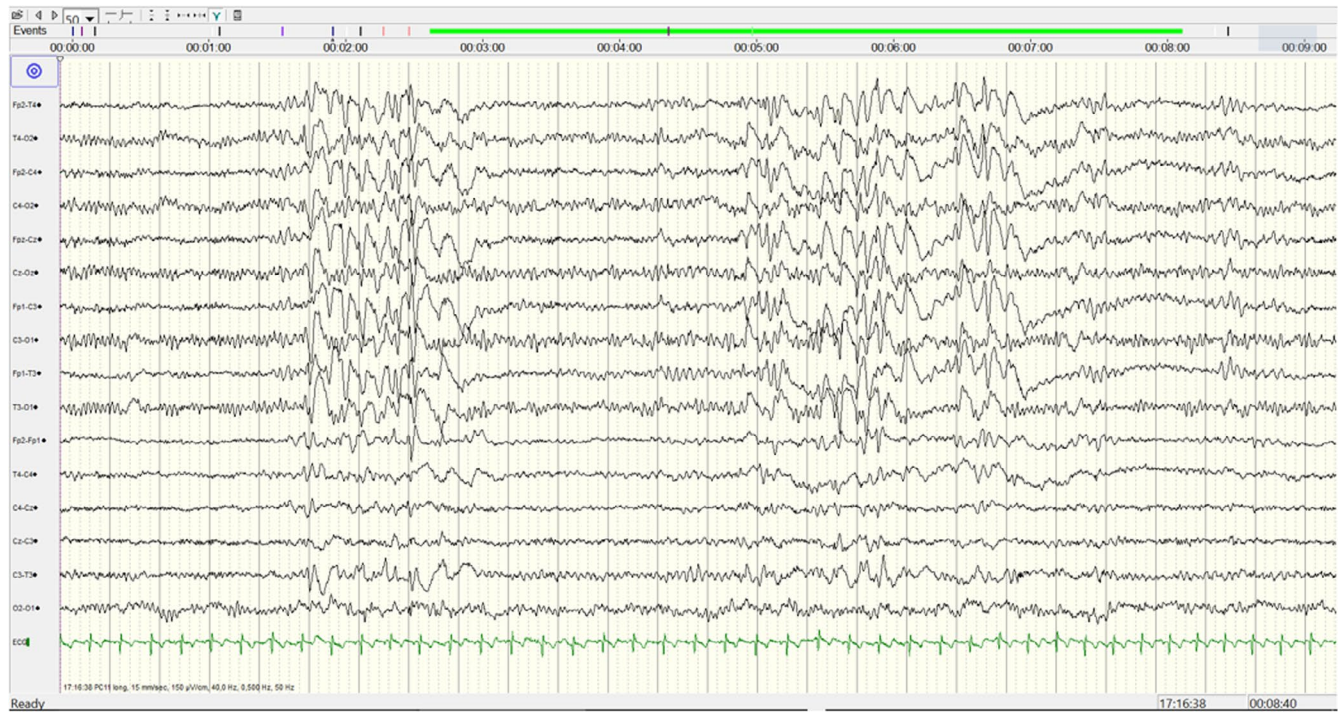


FIGURE 1 EEG: bifrontotemporal spike and wave pattern

TABLE 2 Bivariate analysis with respect to the electroencephalogram results (N = 91)

Variable		Normal	Bifrontotemporal spike and waves	Bifrontotemporal spike	Bifrontotemporal spike and waves and diffuse slow waves	Diffuse slow waves	Other	P-value
Age (y)	Mean (SD)	28.0 (8.2)	25.7 (7.8)		25.6 (7.4)	30 (NA)	21.8 (8.9)	.271
Sex	Male	33 (61.1)	12 (22.2)		2 (3.7)	0	7 (13.0)	.496
	Female	22 (59.5)	9 (24.3)		3 (8.1)	1 (2.7)	2 (5.4)	
Educational level	Primary	41 (59.2)	14 (20.3)		5 (7.3)	1 (1.4)	8 (11.6)	.632
	Secondary	13 (68.4)	5 (26.3)		0	0	1 (5.3)	
	MD	1 (33.3)	2 (66.7)		0	0	0	
Prematurity	No	40 (61.5)	14 (21.5)		5 (7.7)	0	6 (9.2)	.184
	Yes	1 (20.0)	3 (60.0)		0	0	1 (20.0)	
	MD	14 (66.7)	4 (19.1)		0	1 (4.8)	2 (9.5)	
Age of onset of epilepsy (y)	Mean (SD)	13.3 (7.2)	9.8 (3.7)		9.6 (5.5)	12 (NA)	11.4 (5.4)	.311
Duration of the epilepsy (years)	Mean (SD)	14.9 (9.1)	16.1 (9.2)		16.0 (5.1)	18 (NA)	10.3 (5.9)	.411
Neonatal distress	No	50 (60.2)	18 (21.7)		5 (6.0)	1 (1.2)	9 (10.8)	.930
	Yes	2 (66.7)	1 (33.3)		0	0	0	
	MD	3 (60.0)	2 (40.0)		0	0	0	
Motor development	Normal	37 (62.7)	12 (20.3)		4 (6.8)	1 (1.7)	5 (8.5)	
	Abnormal	13 (54.2)	7 (29.2)		1 (4.2)	0	3 (12.5)	.961
	MD							
Ov16	No	28 (60.9)	10 (21.7)		4 (8.7)	1 (2.2)	3 (6.5)	.762
	Yes	23 (59.0)	9 (23.1)		1 (2.6)	0	6 (15.3)	
	MD	4 (66.7)	2 (33.3)		0	0	0	
Seizure frequency	Daily	10 (62.5)	3 (18.8)		1 (6.3)	0	2 (12.5)	.911
	Monthly	17 (50.0)	11 (32.3)		2 (5.9)	1 (2.9)	3 (8.8)	
	Annually	13 (61.9)	5 (23.8)		1 (4.8)	0	2 (9.5)	
	MD	15 (75.0)	2 (10.0)		1 (5.0)	0	2 (10.0)	
Nodding seizures	No	39 (60.9)	14 (21.9)		3 (4.7)	0	8 (12.5)	.356
	Yes	8 (57.1)	4 (28.6)		0	1 (7.1)	1 (7.1)	
	MD	8 (61.5)	21 (23.1)		5 (5.5)	1 (1.1)	9 (9.9)	
(Continues)								

TABLE 2 (Continued)

Variable	Normal	Bifrontotemporal spike and waves	Bifrontotemporal spike	Bifrontotemporal spike and waves and diffuse slow waves	Diffuse slow waves	Other	P-value
OAE							.736
No	19 (63.3)	7 (23.3)		2 (6.7)	0	2 (6.7)	
Yes	30 (63.8)	10 (21.3)		3 (6.4)	1 (2.1)	3 (6.4)	
MD	6 (42.9)	4 (28.6)		0	0	4 (28.6)	
Ivermectin intake							.518
No	10 (45.4)	7 (31.8)		3 (13.6)	0	2 (9.1)	
Yes	40 (63.5)	13 (20.6)		2 (3.2)	1 (1.6)	7 (11.1)	
MD	5 (83.3)	1 (16.7)		0	0	0	
Type of drug							.919
Phenobarbital	18 (69.2)	5 (19.2)		2 (7.7)	0	1 (3.8)	
Carbamazepine	27 (52.9)	13 (25.5)		3 (5.9)	1 (2.0)	7 (13.7)	
Both	6 (75.0)	1 (12.5)		0	0	1 (12.5)	
MD	4 (66.7)	2 (33.3)		0	0	0	

Abbreviation: y, years old; OAE, onchocerciasis-associated epilepsy; only 91 electroencephalograms were performed.

4 | DISCUSSION

This study is to our knowledge the first to report both EEG patterns and nonverbal neuropsychometric test performance in PWE in the Sanaga-Mbam region of Cameroon, a hyperendemic onchocerciasis area with high epilepsy prevalence.^{5,18,24} We detected a specific EEG pattern consisting of bifrontotemporal slow waves and/or 1.5- to 2-Hz spikes and waves among 36 (72.2%) PWE with abnormal EEGs and related cognitive deficits mostly in frontal cognition. Interestingly, a case-control study conducted in 2017 in Bilomo, a village in the Mbam valley using a verbal and non-verbal neuropsychological battery, demonstrated a higher prevalence of cognitive impairment in PWE than in controls, particularly a significant decrease in executive function and verbal fluency,³¹ suggesting underlying frontal and temporal dysfunction.

Of the 144 participants with clinically confirmed epilepsy, 69 (46.0%) met the OAE criteria. Persons with OAE may present with multiple seizure types, largely dominated by GTCS (72%). These results may be biased by the fact that GTCS are more striking and easier to recognize than nodding seizures. The prevalence of NS differs according to the onchocerciasis-endemic areas, and in our study, about 13% of participants reported nodding seizures. This is a low prevalence of nodding seizures compared with what was observed in certain onchocerciasis-endemic villages in northern Uganda and South Sudan,^{4,32} suggesting that the OAE clinical presentation varies in different regions, with nodding seizures being a relatively rare presentation of OAE in Sanaga valley. In a study in South Sudan, NS was shown to be associated with a high level of onchocerciasis infection than other persons with OAE.³³ Therefore, differences in the clinical spectrum of OAE in different areas may be related to differences in the level of *O. volvulus* transmission.

Almost all subjects were treated with antiseizure medication (97.5%), which is a higher percentage than in other reports in the Mbam valley of Cameroon where only 61% of the PWE are treated.²⁶ The low treatment gap in our study is most likely due to the fact that PWE were recruited in a clinic specialized in epilepsy treatment, in contrast to PWE identified during community-based surveys. This is one of several non-physician-run epilepsy clinics established in this rural area by Cameroonian neurologists between 2000 and 2005.³⁴ Forty-three subjects declared they took antiseizure medication in association with traditional medicine, but this number might be underestimated. The two main antiseizure medication (ASM) used were carbamazepine (50.7%) and phenobarbital (32.7%). Despite this, epilepsy was generally uncontrolled, with at least one seizure per day in 20.6% of PWE, while 48.4% of PWE had seizures monthly and another 30.9% experienced seizures annually (not every month).

TABLE 3 Bivariate analysis with respect to the electroencephalogram results focusing on specific EEG pattern (N = 81)

Variable		Normal	Abnormal ^a	P-value	P-value (MD excluded)
Age (y)	Mean (SD)	28.0 (8.2)	25.7 (7.6)	.147	.147
Sex	Male	33 (70.2)	14 (29.8)	.636	.636
	Female	22 (64.7)	12 (35.3)		
Educational level	Primary	41 (68.3)	19 (31.7)		.475
	Secondary	13 (72.2)	5 (27.8)		
	MD	1 (33.3)	2 (66.7)		
Prematurity	No	40 (67.8)	19 (32.2)	.129	.118
	Yes	1 (25.0)	3 (75.0)		
	MD	14 (77.8)	4 (22.2)		
Age of onset of epilepsy (y)	Mean (SD)	13.3 (7.2)	9.8 (4.0)	.041	.061
Duration of the epilepsy (years)	Mean (SD)	14.9 (9.1)	16.0 (8.4)	.549	.662
Neonatal distress	No	50 (68.5)	23 (31.5)	.843	.999
	Yes	2 (66.7)	1 (33.3)		
	MD	3 (60.0)	2 (40.0)		
Motor development	Normal	37 (69.8)	16 (30.2)	.865	.586
	Abnormal	13 (61.9)	8 (38.1)		
	MD	5 (71.4)	2 (28.6)		
Ov16	No	28 (66.7)	14 (33.3)	.935	.808
	Yes	23 (69.7)	10 (30.3)		
	MD	4 (66.7)	2 (33.3)		
Seizure frequency	Daily	10 (71.4)	4 (28.6)	.292	.657
	Monthly	17 (56.7)	13 (43.3)		
	Annually	13 (68.4)	6 (31.6)		
	MD	15 (83.3)	3 (16.7)		
Nodding seizures	No	39 (69.6)	17 (30.4)	.875	.999
	Yes	8 (66.7)	4 (33.3)		
	MD	8 (61.5)	5 (38.5)		
OAE	No	19 (67.9)	9 (32.1)	.842	.999
	Yes	30 (69.8)	13 (30.2)		
	MD	6 (60.0)	4 (40.0)		
Ivermectin intake	No	10 (50.0)	10 (50.0)	.141	.096
	Yes	40 (72.7)	42 (27.3)		
	MD	5 (83.3)	1 (16.7)		
Type of drug	Phenobarbital	18 (72.0)	7 (28.0)	.680	.460
	Carbamazepine	27 (62.8)	16 (37.2)		
	Both	6 (85.7)	1 (14.3)		
	MD	4 (66.7)	2 (33.3)		

Note: N = 81.

^aType 2 and 3 put together and 4 and 5 excluded from the analyses (10 participants excluded).

Possible explanations for the poor seizure control may be related to low adherence to treatment and/or quality of the ASM, but this requires further investigation.

The first most important result of this study was the detection of a specific EEG pattern characterized by bifrontal 1.5- to 2-Hz spike and waves, with or without diffuse slow waves,

TABLE 4 Multivariable analysis with respect to the electroencephalogram^a results

Variable		Full multivariable model			Final multivariable model		
		Adjusted OR	CI 95%	P-value	Adjusted OR	CI 95%	P-value
Age (y) (Ref: <20 y)	20-25	0.28	0.03-2.46	.250			
	26-30	0.33	0.03-3.35	.346			
	>30	0.14	0.01-4.06	.255			
Sex (Ref: male)	Female	0.90	0.17-4.67	.898			
Educational level (Ref: Primary)	Secondary	0.61	0.09-3.85	.598			
Prematurity (Ref: no)	Yes	8.11	0.23-284.09	.249	5.25	0.50-54.77	.165
Age of onset of epilepsy (y) (Ref: <15 y)	>15	0.05	0.01-2.17	.121	0.27	0.06-1.34	.110
Duration of the epilepsy (years) (Ref: <20 y)	>20	0.74	0.04-14.42	.844			
Motor development (Ref: normal)	Abnormal	0.08	0.01-4.05	.210			
Ov16 (Ref: no)	Yes	0.41	0.07-2.49	.333			
Seizure frequency (Ref: daily)	Monthly	2.57	0.43-15.45	.301			
	Annually	1.17	0.14-10.21	.884			
Nodding seizures (Ref: no)	Yes	1.27	0.18-8.99	.810			
OAE (Ref: no)	Yes	0.10	0.01-2.98	.186			
Ivermectin intake (Ref: no)	Yes	0.42	0.09-4.05	.269			
Type of drug (Ref: phenobarbital)	Carbamazepine	1.49	0.25-8.85	.663			
	Both	0.17	0.01-5.35	.312			

Note: N = 81.

^aType 2 and 3 put together and 4 and 5 excluded from the analyses (10 participants excluded).

very similar to that described in a series of 21 patients with NS in South Sudan²³. In a study of 20 patients with NS in Uganda, a similar EEG pattern was observed but two asymptomatic siblings and one unrelated community control also presented abnormal epileptiform abnormalities.³⁵ In another study conducted on 65 patients with NS in Tanzania, only 11 (44%) showed generalized slowing of the EEG and only 6 of these patients showed spike-and-wave abnormalities.²² Furthermore, in a study performed in an onchocerciasis-endemic area in the Democratic Republic of Congo (DRC) and which enrolled 82 PWE and 29 persons without epilepsy (PWOE), the investigators also described bifrontally predominant generalized spike-and-wave discharges in 11 PWE and in one PWOE.³⁶ This EEG pattern may also appear in *Onchocerca volvulus*-infected persons before the onset of epilepsy or without development of epilepsy, thus explaining why this EEG pattern was found in some asymptomatic subjects in these studies. It has been observed that in places where NS is highly prevalent (such as Sudan or Uganda), EEG studies usually reveal the same EEG patterns as in our study. In areas where the prevalence of NS is lower (eg, Tanzania or Cameroon), a majority of EEGs are normal,

perhaps relating to a lesser degree of severity of the disease. Nevertheless, when the EEG is abnormal, the pattern is most often characteristic.

The second important finding of our study is the confirmation of the finding of severe CI in PWE in the Mbam valley by Njamnshi et al.³¹ who reported 92.5% reduction of performance in executive function tests and 100% impairment of verbal fluency. In our study participants, 66% had severe frontal CI, while 29% showed severe global CI and 28% had severe episodic memory impairment. The disparities may be explained by the differences in psychometric tests used in the two studies but frontal and temporal CI appears to be a constant feature, and this corresponds to the specific EEG findings. CI might thus be a consequence of repeated seizures, and this is consistent with the fact that EEG abnormalities are mainly in the frontal and temporal lobe. However, the role of ASM and onchocerciasis infection in CI in our study subjects cannot be ruled out, especially given that the case-control study in Bilomo³¹ reported CI in controls, although the issue of using culturally sensitive neuropsychological tests remains to be resolved. ASM might have contributed to CI as phenobarbital use was associated with a lower cognitive score

TABLE 5 Neurocognitive assessment

Variable		Raven's matrices	P-value	Drawing	P-value	Corsi's block	P-value	FAB test	P-value
Total		4.5 (2.5)		4.9 (2.7)		3.1 (1.6)		2.4 (2.9)	
Age (y)	18-23	4.3 (2.0)	.863	4.8 (2.4)	.963	3.2 (1.4)	.292	2.6 (2.9)	.624
	24-28	4.2 (2.3)		4.7 (2.6)	.640	2.6 (1.3)		1.8 (2.6)	
	29-32	4.6 (3.3)		5.0 (3.4)		2.9 (2.0)		2.5 (2.7)	
	>32	5.0 (2.6)		5.2 (2.7)		3.5 (1.7)		2.9 (3.3)	
Sexe	Male	4.9 (2.5)	.069	5.4 (2.7)	.067	3.4 (1.5)	.022	3.0 (3.0)	.020
	Female	3.9 (2.5)		4.3 (2.6)		2.6 (1.7)		1.7 (2.5)	
School	Primary	4.2 (2.4)	.007	4.6 (2.6)	.004	2.9 (1.6)	.017	2.3 (2.8)	.249
	Secondary	6.4 (2.4)		6.9 (2.4)		4.0 (1.6)		3.4 (3.2)	
	MD	3.0 (2.8)		3.0 (2.8)		2.5 (0.7)		1.5 (1.7)	
Prematurity	No	4.8 (2.6)	.641	5.2 (2.9)	.674	3.0 (1.7)	.480	2.6 (2.9)	.865
	Yes	4.4 (2.2)		4.8 (2.6)		2.8 (1.5)		2.7 (2.3)	
	MD	3.8 (2.1)		3.9 (2.1)		3.3 (1.3)		2.0 (3.1)	
Age of onset (y)	<8	4.0 (2.2)	.151	4.4 (2.6)	.170	2.9 (2.0)	.810	2.4 (2.6)	.916
	9-12	4.3 (2.7)		4.6 (2.9)		3.1 (1.4)		2.5 (2.7)	
	13-15	5.7 (1.6)		6.3 (1.9)		3.3 (1.3)		3.0 (3.5)	
	>15	4.5 (2.9)		4.9 (3.1)		3.1 (1.8)		2.3 (3.1)	
Duration (years)	<10	5.3 (2.2)	.155	5.8 (2.4)	.137	3.5 (1.4)	.175	3.0 (3.4)	.599
	11-15	4.5 (2.5)		5.1 (2.7)		3.1 (1.6)		2.6 (2.8)	
	16-20	3.4 (2.7)		3.7 (2.9)		2.5 (1.3)		1.7 (2.0)	
	>20	4.7 (2.6)		4.9 (2.7)		3.1 (1.9)		2.5 (3.0)	
EEG	Normal	4.8 (2.5)	.366	5.2 (2.6)	.366	3.2 (1.7)	.347	3.6 (3.1)	.140
	Abnormal	4.2 (2.8)		4.5 (3.1)		2.7 (1.7)		2.4 (2.5)	
Neonatal distress	No	4.5 (2.6)	.969	4.9 (2.8)	.887	3.1 (1.6)	.304	2.5 (2.8)	.525
	Yes	4.3 (0.6)		5.0 (1.0)		2.0 (2.0)		4.0 (4.6)	
	MD	5.6 (0.9)		5.6 (0.9)		3.8 (0.8)		1.9 (3.2)	
Motor development	Normal	4.2 (2.7)	.127	4.6 (2.9)	.137	3.1 (1.6)	.866	2.6 (2.9)	.859
	Abnormal	5.2 (2.3)		5.6 (2.5)		3.2 (1.6)		2.8 (3.0)	
	MD	5.1 (1.1)		5.3 (1.1)		3.0 (1.9)		1.6 (2.7)	
Ov16	No	5.6 (2.3)	.757	4.9 (2.6)	.813	2.9 (1.7)	.437	2.8 (2.9)	.639
	Yes	3.7 (2.6)		4.7 (2.8)		3.3 (1.5)		3.1 (2.9)	
	MD	5.1 (1.3)		5.9 (3.0)		3.1 (1.5)		1.0 (2.3)	
Seizure frequency	Daily	4.3 (2.5)	.636	4.6 (2.7)	.646	2.8 (1.6)	.814	3.1 (2.7)	.334
	Monthly	4.1 (2.5)		4.4 (2.7)		2.9 (1.6)		2.2 (2.4)	
	Annually	4.6 (2.2)		5.2 (2.5)		3.0 (1.6)		2.0 (2.8)	
	MD	5.2 (2.9)		5.6 (3.1)		3.8 (1.5)		2.6 (3.5)	
Nodding seizures	No	4.2 (2.5)	.528	4.7 (2.7)	.507	2.9 (1.6)	.554	2.5 (2.8)	.421
	Yes	4.9 (2.5)		5.3 (2.5)		3.2 (1.5)		3.0 (2.7)	
	MD	5.3 (2.8)		5.5 (3.0)		3.6 (1.9)		2.1 (3.2)	
OAE	No	4.5 (2.5)	.004	6.1 (2.5)	.005	3.5 (1.5)	.126	3.4 (3.2)	.115
	Yes	4.3 (2.5)		4.1 (2.9)		2.8 (1.6)		2.3 (2.7)	
	MD	5.6 (2.9)		5.4 (1.5)		3.2 (1.8)		1.1 (2.5)	

(Continues)

TABLE 5 (Continued)

Variable		Raven's matrices	P-value	Drawing	P-value	Corsi's block	P-value	FAB test	P-value
Ivermectin intake	No	4.4 (2.6)	.595	4.9 (2.8)	.884	2.7 (1.9)	.160	2.1 (2.7)	.566
	Yes	4.6 (2.6)		4.9 (2.8)		3.2 (1.4)		2.5 (3.0)	
	MD	4.6 (2.1)		4.6 (2.1)		3.6 (1.3)		3.6 (3.0)	
Type of drug	Phenobarbital	4.6 (2.7)	.607	4.8 (2.9)	.517	3.1 (1.8)	.827	1.9 (3.1)	.169
	Carbamazepine	4.7 (2.4)		5.1 (2.6)		3.3 (1.5)		2.7 (2.7)	
	Both	3.6 (2.5)		3.9 (2.6)		2.6 (1.5)		3.3 (3.3)	
	MD	4.1 (3.0)		4.9 (3.2)		2.0 (1.8)		2.1 (2.9)	

Note: N = 81.

than carbamazepine, suggesting a potentiation of the cognitive disorders by phenobarbital, known for its long-term side effects on attention mechanisms.³⁷

In our current study, the results obtained with the global cognitive test such as Raven's test, and memory tests such as the five-figure test and Corsi's test suggest that late-onset epilepsy is associated with more cognitive deficiency, further supporting the argument that it may be the epileptic seizures (and not a neurodevelopmental disorder) that induce the observed cognitive deficits. We observed that having epilepsy for a longer duration and meeting the OAE criteria were both associated with a low score on Raven's test (hence poorer cognitive performance). This further suggests that frequent recurrent seizures, most likely caused by OAE during childhood, may be the main cause of cognitive deficits among the participants. Conversely, Ov16 seropositivity was associated with none of our outcomes, including in the bivariate analyses (especially before adjustment on OAE variable). One possible explanation is that the Ov16 results can reflect a past or current exposure to *O. volvulus*, and does not inform on the past individual microfilarial density (a key quantitative factor for the development of OAE). It is interesting to note that the FAB, a frontal cognitive test, was associated with abnormalities on EEG and OAE status, suggesting a relationship between repeated frontal lobe aggression and impaired cognition. This is consistent with previous findings of Tau deposits in the temporal and frontal lobes of persons with OAE, probably secondary to seizures or trauma.³⁸ Magnetic resonance imaging studies performed in Uganda and Tanzania showed evidence of generalized atrophy more than inflammatory lesions in persons with NS.^{22,39} Two postmortem studies, recently published, describe the histological findings in the brains of persons with OAE, including NS. In a first study on four persons with NS,³⁸ Tau depositions were observed in all individuals, mainly in the cortical regions. The most severe changes were present in the prefrontal cortex, and the superior and middle frontal gyri. In a second postmortem study of four persons with NS and five with another form of OAE, the histological examination of the brains revealed general

cortical neuronal loss in the cerebrum, with atrophy, and loss of Purkinje cells and granular cells in the cerebellum. The hippocampus was spared in most cases. Gliotic lesions were observed in all cases, favoring the mesencephalon and cortical regions.⁴⁰

Epilepsy and cognitive impairment have a dramatic psychosocial impact leading, among other consequences, to frequent school dropout as revealed the fact that 81.3% of participants had only primary school level of education. School dropout could also be a consequence of the diagnosis of epilepsy in children, which led them to be forced out of school because of stigma, which has been well characterized in the study area,⁴¹ leading to cognitive impairment due to low education. Indeed, attending secondary school was associated with higher score on Raven's test.

Until now, the pathophysiology of OAE remains incompletely understood, but strong epidemiological data suggest a causal relationship between onchocerciasis and epilepsy.^{7,10,11}

Our study has several limitations. Due to the nonexhaustive nature of clinical reports, and the lack of access to other investigations besides EEGs, we were unable to rule out other causes of epilepsy such as neurocysticercosis or genetic epilepsy.

Among the limitations that must be noted in this study is the fact that we did not include any control population. The OAE case definition is a tool for epidemiological studies to estimate the burden of disease and to identify areas of high onchocerciasis transmission.⁴² However, this definition does not imply that the epilepsy is caused by onchocerciasis. Without additional laboratory and imaging investigations, other etiologies of epilepsy cannot be excluded. Besides, we were sometimes unable to obtain complete information about the seizure history of participants, particularly in case the PWE's close relatives were unavailable to answer specific questions. Indeed, the EEG acquisition parameters (20 min, 11 electrodes) constitute the limits of their interpretability. Thus, further investigations are warranted to confirm our results by performing EEGs of higher spatial and temporal resolution in a larger number of PWE, adding a control population, and using normalized neuropsychological tests that

take into account the level of education and are culturally sensitive. Ideally, such a population should be followed up and EEGs repeatedly performed.

In conclusion, we detected a specific EEG pattern in PWE in an onchocerciasis-endemic area in Cameroon, suggesting that this epilepsy could be related to a frontal and temporal disease process.

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CONFLICT OF INTEREST

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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