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Onchocerciasis-Associated Epilepsy with Head Nodding Seizures—Nodding Syndrome: A Case Series of 15 Patients from Western Uganda, 1994

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Abstract. Nodding syndrome (NS) is an encephalopathy characterized by the core symptom of epileptic head nodding seizures, affecting children at the age between 3 and 18 years in distinct areas of tropical Africa. A consistent correlation with onchocerciasis was found, but so far, the causation of NS has not been fully clarified. With a systematic analysis of features of a cohort of epilepsy patients examined in the Itwara onchocerciasis focus of western Uganda in 1994, we provide evidence that NS actually occurred in this area at this time, and we demonstrate a correlation between prevalence of NS and that of onchocerciasis in different villages. Following the elimination of onchocerciasis by community-directed treatment with ivermectin and ground larviciding, our data provide a baseline to examine the question whether NS will disappear once its putative cause has been removed.

INTRODUCTION

In 1994, an investigation was carried out to clarify the background of the frequent occurrence of epilepsy in an area of Kabarole district in western Uganda.[1–3] During the survey, detailed interviews were conducted about the history of the disease and the exact description of the epileptic seizures. This revealed a number of patients with a particular form of seizures characterized by slow dorsoventral head movements, called head nodding or "nateera omutwe" in the local Rutooro language.[4,5] It was recognized that the head nodding seizures encountered in the study area of Kabende parish were very similar in their appearance with those in a report from an isolated area of the Mahenge mountains in Tanzania of the early 1960s,[4,6] but the significance of this observation was not immediately clear.

Over the first decade of the millennium, large numbers of patients with a previously unknown condition comprising head nodding seizures were reported from areas in South Sudan[7,8] and northern Uganda.[9–11] When patients from these areas were studied in more detail and the result of these investigations were compared with the findings of patients with head nodding from Tanzania, it was concluded that the patients of all these three areas were affected by the same disease, then designated as "head nodding syndrome (NS)"[12] or "Nodding syndrome."[13] A widely accepted definition of NS was drawn up in an international conference in Kampala, Uganda, 2012.[14]

Recently, we have published a detailed case report,[5] indicating that the mentioned patients seen with head nodding in Kabende parish in 1994[4] were actually affected by NS. With the present article, we extend our analysis to the complete series of all patients identified in the study area between 1994 and 1996. We also give an estimate of the prevalence of the condition in the study area in 1994, and we investigate the spatial relationship with onchocerciasis endemicity.

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METHODS

Kabende parish of Kabarole district, western Uganda, is located at the edge of the Itwara forest, an area known as endemic for onchocerciasis.[15,16] With a complete house-to-house census carried out in 1994, the overall population of Kabende was 4,743,[3] and a survey for onchocerciasis in a sample of children and adolescents aged 10–19 years found the prevalence of skin microfilaria to range between 15 and 85% in the 13 villages of the parish.[3] Detailed information on the epidemiology of onchocerciasis in the Itwara focus is also available from the publications of Fischer et al.[15] and Garms et al.[16]

All patients with the mention of head nodding seizures in their assessment form during the initial epilepsy prevalence survey in March–June 1994,[3] or during the follow-up from July 1994–February 1996,[17–19] were included in the present analysis. A copy of the standardized assessment form used throughout the survey and the follow-up is given as supporting information (Supplemental Information). The original records were reviewed for details of the individual patient's history, seizure semiology, and physical examination. Based on the recorded height and weight measurements, height-for-age *z*-scores (HAZs) and *z*-scores for body-mass-index were calculated by use of the standards of the U.S. Centers of Disease Control and Prevention.[20] Generally, an HAZ of more than 2.0 standard deviations below the standard median is considered to indicate stunted growth.[20] To ensure that in the present analysis only patients with substantial growth deficit were classified as stunted, we set a threshold of an HAZ of less than –3.0 as indication of short stature. Signs of pubertal development of the patients had been systematically noted in the original records according to the classification of Marshall and Tanner.[21,22] We considered puberty as delayed, if no secondary sexual characteristics were noted in girls at 14 years and in boys at 15 years of age.[23]

The extracted information was systematically examined on the presence or absence of the criteria of the NS definition of Kampala 2012 in the individual patients.[14] The number of patients with head nodding seizures living in Kabende parish from March to June 1994 was determined for each of the different 13 villages. Population numbers were available from

TABLE 1

Features of epileptic seizures in patients with reported HN (nateera omutwe) identified in Kabende parish, western Uganda, March 1994–February 1996

Patient number (Gender/ Age at examination)	Seizure onset and semiology of head nodding seizures (nateera omutwe)
Patients identified during initial epilepsy prevalence survey March–June 1994 (see refs. 3 and 4)	
1. (♂/14 years)	Onset at age 13 years (5 months ago) with HN only: not responding if talked to and slowly nodding his head for about 1 minute, without falling. Sometimes just sitting without movements and not responding for several minutes. Since recently (date not specified) also has other seizures: Suddenly falling down, not responsive, limbs stiff, and slowly moving for 3 minutes. Then sits up but does not respond for 1 hour. Frequency of GS: 1×/week
2. (♂/11 years)	Onset at age 8 years, only HN over 5 minutes. At times, triggered by looking at hot food or tea. During HN, looking at a person when spoken to but not reacting otherwise. No other movements, not falling. Confused after HN (time not specified). Since 14 month other seizures (GS): starting with a scream and immediately falling, moves all limbs at the same time for about 2 minutes, then reacting again and moving normally, but confused for about 1 day. Frequency of HN: 3×/days until 3 month ago. Head nodding disappeared shortly after the start of GS. Had received AED sometime after onset of HN and before the start of GS (drug and dosage not specified) over 3 month with no effect on HN. Frequency of GS: 1×/week
3. (♀/14 years)	Onset of HN at age of 8 years. Thought to be brought about by cold. Shortly before an attack, complains of dizziness and headache. Then HN starts and she does not respond for about 30 minutes. When standing at the start of an attack, refuses to be seated. During the seizure, moving hands as if grasping something. Besides HN, has also episodes of confusion and acts as if picking things from the ground. Has never fallen. Frequency of HN and confusion states: 1×/day
4. (♂/14 years)	Onset at age 5 years with only HN episodes of about 2-minute duration without falling (frequency of HN not specified). Three months later other seizures (GS): falling with a scream, no response, rapid respiration, and clonic movements of all limbs over 2 minutes, then flaccid with no reaction for almost 1 hour, and then recovering. Head nodding disappeared after the onset of GS (time not specified). Had received AED (drug not specified) over 1 year until 1 year before examination with good control of GS. Frequency of GS: 1–2×/days
5. (♀/8 years)	Onset at age 6 years, 1–2×/days with series of five to six consecutive HN movements over about 3 minutes. Can respond when called upon. Separately from HN, also has episodes of non-responding over 3–4 minutes without moving. Has never fallen. Frequency of HN: 2×/days
6. (♀/14 years)	Onset at age 9 years with HN over 2 minutes, followed by falling down and lying flaccidly on the ground (duration not specified). One year later seizures changed: falling down with a scream, clonic movements for 5 minutes, then resting on the ground with groaning but no response, waking up with confusion, and sometimes wants to run away. Head nodding disappeared with onset of GS. Had received AED (unspecified) for 2 month, ~2 years ago, with good response on GS (no more HN at this time). Frequency of GS 3–4×/days, more on cold days
7.° (♀/12 years)	Onset at age 3 years with episodes of single or repeated HN movements, every 2–3 days, without falling. Three years later, seizures changed: initial scream and falling, clonic movements for 10 minutes, then waking up confused, and running away. Head nodding disappeared after GS had started (time not specified). Never had received AED. Frequency of GS: up to 10×/days, sometimes on and off through the night
8. (♂/15 years)	Onset at age 7 years with HN only and nonresponse for 10 minutes. About 1 year later, HN regularly followed by falling and clonic movements for 5 minutes and then sleeping for 2 hours. Sometimes has seizures on and off for several hours. Food is refused before a seizure is coming. Frequency of GS: 1–3×/days
9. (♀/12 years)	At onset (age 8 years), HN only, without response when talked to. Since 1 year other seizures: initial shouting, falling, and clonic movements (time not specified) followed by sleep for 1 hour. At time of examination, still has HN separately from GS, about 3–4×/days. Frequency of GS: 3×/week
10. (♀/15 years)	Onset 4 months ago, HN and not reacting when talked to, followed by falling and clonic movements of all limbs (duration not specified). Then getting up again and is confused for 30 minutes. Generalized seizure always preceded by HN, frequency 2×/week
Patients identified during follow-up July1994–February 1996 (see refs. 18 and 19)	
11. (♀/14 years)	Examined 12/1994. Onset with only HN~ 1,5 years earlier (~07/1993). Since 12 months change of seizures: falling without warning, breathing like a machine, no movements, limbs flaccid, wakes up after 30 minutes, and is normal again. Head nodding disappeared after the onset of GS (time not specified). Had received AED (phenobarbitone, 60 mg/day) soon after the onset of HN with no effect (only HN at this time). Increasing frequency of GS, now 1×/day
12. (♀/12 years)	Examined 06/1995. Onset about 5 years earlier (1990) with only HN. Later (time not specified) change of seizures: now starting with HN, followed by confusion ("behaves as if picking imaginary objects from the ground"), may return to normal at this stage or is falling, and moving arms and legs at the same time. Afterwards confused. Duration about 15 minutes. Frequency 2–3×/week at time of examination
13. (♂/12 years)	Examined 06/1995. Onset in 03/1995 with HN, from the beginning followed by falling and clonic movements. Sometimes, only HN without subsequent GS. Duration 10–15 minutes. Frequency 4×/week. (Note: episode of HN observed; see ref. 4)
14. (♂/14 years)	Examined 06/1995. Onset 4 years ago (~06/1991), only HN until time of examination. No response during HN episode. Did never fall. Falling asleep after HN. Duration about 5 minutes. Frequency 1×/day
15. (♀/13 years)	Examined 02/1996. Onset 7 month ago (04/1995), only HN. Afterwards complaining of headache, then falling asleep. Duration of some seconds. Frequency 2×/week

AED = antiepileptic drug; HN = head nodding; GS = generalized seizure.

the previously mentioned house-to-house survey of 1994.[3] Prevalence was calculated for the parish as a whole, for subzones of onchocerciasis endemicity levels, and for appropriate age groups. Differences between rates were tested with the Fisher's exact test.

All data presented in this article were collected from March 1994 to February 1996 as an activity of the Basic Health Services of Kabarole district in cooperation with the University Children's Hospital, Heidelberg. The study protocol of 1994 had been approved by the Ethical Committee of the University of Heidelberg, Germany. Before enrollment to the study, the accompanying caregivers of the patients had given their informed consent. The earlier publications based on these assessments were concerned with epilepsy in general,[3,4,17–19] whereas we now focus on the subset of patients with head nodding seizures. No additional investigations on humans were carried out.

RESULTS

Ten of 61 patients diagnosed with epilepsy during the prevalence survey of March–June 1994 gave an account of

TABLE 2

Anamnestic information and clinical findings in patients with reported head nodding (nateera omutwe), identified in Kabende parish, western Uganda, March 1994–February 1996

Patient number age/gender	Height (cm) height-for-age*/BMI* (*z*-scores)	Anamnestic information	Clinical findings	Skin snip for *Onchocerca volvulus*
Patients identified during initial epilepsy prevalence survey March – June 1994 (see refs. 3 and 4)				
1. ♂/14 years	146.5 cm –2.17/–2.02	Always healthy, until HN started 5 months ago, still attending school (primary two)	1 O.n.† otherwise normal examination, good communication. TS staging‡: G3	Positive
2. ♂/11 years	116 cm–4.16/–0.87	Born healthy. Episode of malnutrition at age of 1 year, full recovery. Growth failure and mental retardation from the age of 7 years (onset HN). Never in school	Stunting, itching skin rash, mental impairment, speaks some single words, disturbed coordination. TS staging‡: G1	Positive
3. ♀/14 years	149 cm–1.75/–1.97	Normal development until the onset of HN (age 8 years). Left school at primary two and was a good pupil	Impaired cognition, slow movements, otherwise normal. TS staging‡: B3/P3	Positive
4. ♂/14 years	152.5 cm –1.47/+0.79	Healthy and normal cognitive development up to the start of HN at the age of 6 years. Never in school	Apathetic, Slow movements, general weakness, unable to cooperate in neurological examination. 1 O.n.† TS staging‡: G3	Positive
5. ♀/8 years	121 cm–1.20/+0.29	Normal birth and development until HN started 2 years ago. Left school because of HN	During examination abruptly changing between proper comprehension/ confusion. Otherwise normal. TS staging‡: B1/P1	Positive
6. ♀/14 years	141 cm–2.97/–2.92	Normal development up to primary two (good pupil), dropped out when HN started	Wasting, impaired communication (single words), and coordination. 1 O.n.† TS staging‡: B3/P2	Positive
7. ♀/12 years/	116 cm–4.64/–2.16	Normal development up to age of 3 years (Start HN). Growth failure and mental decline thereafter	Apathetic, stunting, scars from burns, and thickened dark skin. 1 O.n.† TS staging‡: B1/P1	Positive
8. ♂/15 years§	110 cm–6.10/–9.4	Normal speech and cognition until the age of 7 years. With the onset of HN progressing deterioration	Apathetic, stunting, wasting, unable to stand, infantile genitalia, and 1 O.n. TS staging‡: G1	Positive
9. ♀/12 years	135 cm–1.97/–1.6	Normal development before HN onset at the age of 8 years. Had to leave school 7 months ago	No details of examination available (left place before being examined)	n.d.
10. ♂/15 years	156 cm–1.72/–0.77	Normal development until now, onset of HN 3 months ago, and was taken out of school for working (cattle keeping)	Normal examination. 1 O.n. TS staging‡ n.d.	Negative
Patients identified during follow-up July 1994–February 1996 (see refs. 18 and 19)				
11. ♀/15 years	n.d.	Normal mental and physical development until now. Never in school, no reason given	Normal examination. TS staging§ B3/n.d.	n.d.
12. ♀/12 years	144 cm–1.01/–0.99	Normal mental and physical development until now. Still attending school, primary four	Normal examination. TS staging§ B3/n.d.	n.d.
13. ♂/12 years	148 cm–0.18/–0.43	Normal mental and physical development until now. Left school in primary three because of seizures 3 month ago	Papular, thickened, dark, and itching skin changes. 1 O.n.‡ Otherwise normal examination. TS staging§ n.d.	n.d.
14. ♂/13 years	143 cm–1.78/–1.87	Normal development until 1 year ago when impairment started, had to leave school at primary one	Papular, thickened, dark, and itching skin changes. Mental impairment, drooling. TS staging§ n.d.	n.d.
15. ♀/13 years	136 cm–3.04/+0.34	Healthy at birth, normal mental development until now. Attending school in primary three. Start of growth failure unclear	TS staging§ B1/P1. Otherwise normal	n.d.

BMI = body mass index; n.d. = not done.
* *z*-scores for height-for-age and BMI based on 2000 CDC child growth standard (ref. 20).
† O.n. = palpable onchocerciasis nodule.
‡ TS = tanner maturity stages for breast (B1/infantile–B5) and pubic hair (P1–P5) for girls, and male genital maturity stages (G1-5) (refs. 21 and 22).
§ Details of patient published as case report (ref. 5).

head nodding seizures in their history,[3] and so did another five of 30 epilepsy patients identified during the follow-up period of July 1994–February 1996 (Tables 1 and 2).[4,18,19]

All these patients had in common that they had been born healthy and before the onset of head nodding had passed through an initial phase of healthy development. Head nodding had started at a median age of 8 years (range: 3–14 years) and in 11 of 15 cases had been the only symptom at the start of the illness. Four patients stated that head nodding and another seizure type had started at the same time and eight subsequently also developed other seizure types. In the later stage of the disease, head nodding disappeared in five cases (patient no. 2, 4, 6, 7, and 11) but was still going on in 10 patients at the time of examination. Four patients were found to be of clearly short stature (patient no. 2, 7, 8, and 15), one of whom was also considered to have delayed pubertal development (patient no. 8). Seven patients were severely mentally impaired (patient no. 2–4, 6–8, and 14). Delay of growth and mental decline were said to have started in all affected cases only after the onset of head nodding. When, case by case, the definition of NS was applied to the 15 patients of this series, it was found that all would fulfill the criteria of a probable case, with the limitation that "nodding frequency per minute" could not be verified from the patient records (Table 3).

All but one patient were living in a village directly bordering the Sogohi or the Nyakibuguta River (Figure 1). Twelve cases had been living in the study area at the time of the survey in March–June 1994 and were included in an analysis of prevalence of epilepsy patients with head nodding seizures during this time. The prevalence of the condition for the entire parish was found at 2.5 cases per 1,000 population, corresponding to 6.3 cases per 1,000 in the age between 5 and 19 years (Table 4). The prevalence of head nodding cases was found to increase with the level of onchocerciasis endemicity and was significantly higher in the villages of highest endemicity (Figure 1, Zone 4) if compared with villages of lower endemicity (8/478 versus 4/1,436; age group of 5–19 years; $P = 0.003$; Table 4).

DISCUSSION

We have carried out an analysis of a series of 15 patients with a peculiar form of epileptic seizures with slow head nodding movements, identified in an area hyperendemic of onchocerciasis in western Uganda, 1994. We found a consistent pattern of previously healthy children falling ill with the initial symptom of head nodding seizures at an age between 3 and 14 years, followed in many by other seizures and mental impairment, in some also by failure of growth or delayed puberty. These findings indicate that the patients presented in this article were actually affected by NS, which has been defined as a distinct medical entity occurring in three known areas of tropical Africa: southern Tanzania, South Sudan, and northern Uganda.[13,14] The Kabende parish in western Uganda, where the patients of the present article were found, has no contiguity with the mentioned areas and, thus, would be the fourth location with confirmed occurrence of NS.

When applying the consented definition of NS to the symptoms and signs found in our patients, we found it difficult to decide with reasonable certainty if the criterion of "nodding frequency 5–20 times/minute" had been present in an individual patient or not. In the 2012 Kampala consensus conference,[14] this criterion was set as mandatory to classify a patient as a probable case. Although the clinical workup of our investigation of 1994 did not include an explicit assessment

TABLE 3

Case definition of nodding syndrome according to Kampala 2012 consensus, applied to patients with head nodding seizures (nateera omutwe) identified in Kabende parish, western Uganda, March 1994–February 1996

	Patients identified in Kabende parish, western Uganda, 1994-1996														
	Patient number														
Case definition criteria (Kampala 2012 consensus)	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.
Suspected case: reported head nodding in a previously healthy person															
Repetitive involuntary drops of the head on ≥ 2 occasions	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Previously healthy	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Probable case: suspected case with at least two major and one minor criteria															
Major criteria:															
Age 3–18 years at the onset of head nodding	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nodding frequency 5–20 times/minute	[+]	[+]	[+]	[+]	[+]	[+]	[+]	[+]	[+]	[+]	[+]	[+]	[+]	[+]	[+]
Minor criteria:															
Other neurologic abnormalities	+	+	+	+	−	+	+	+	−	+	−	−	−	+	−
Clustering in space and time with similar cases	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Triggered by eating or cold water	−	+	+	−	−	−	−	+	−	−	−	−	−	−	−
Delayed sexual or physical development	−	+	−	−	−	−	+	+	−	−	−	−	−	−	+
Psychiatric manifestations	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Confirmed case: probable case with documented head nodding episodes															
Observed and recorded by a trained health-care worker	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Videotaped head nodding episode	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Video/electroencephalogram/electromyogram documenting head nodding as atonic seizure	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−

+ = criterion recorded; [+] = criterion likely to be present but not explicitly recorded; − = criterion not recorded/not present.

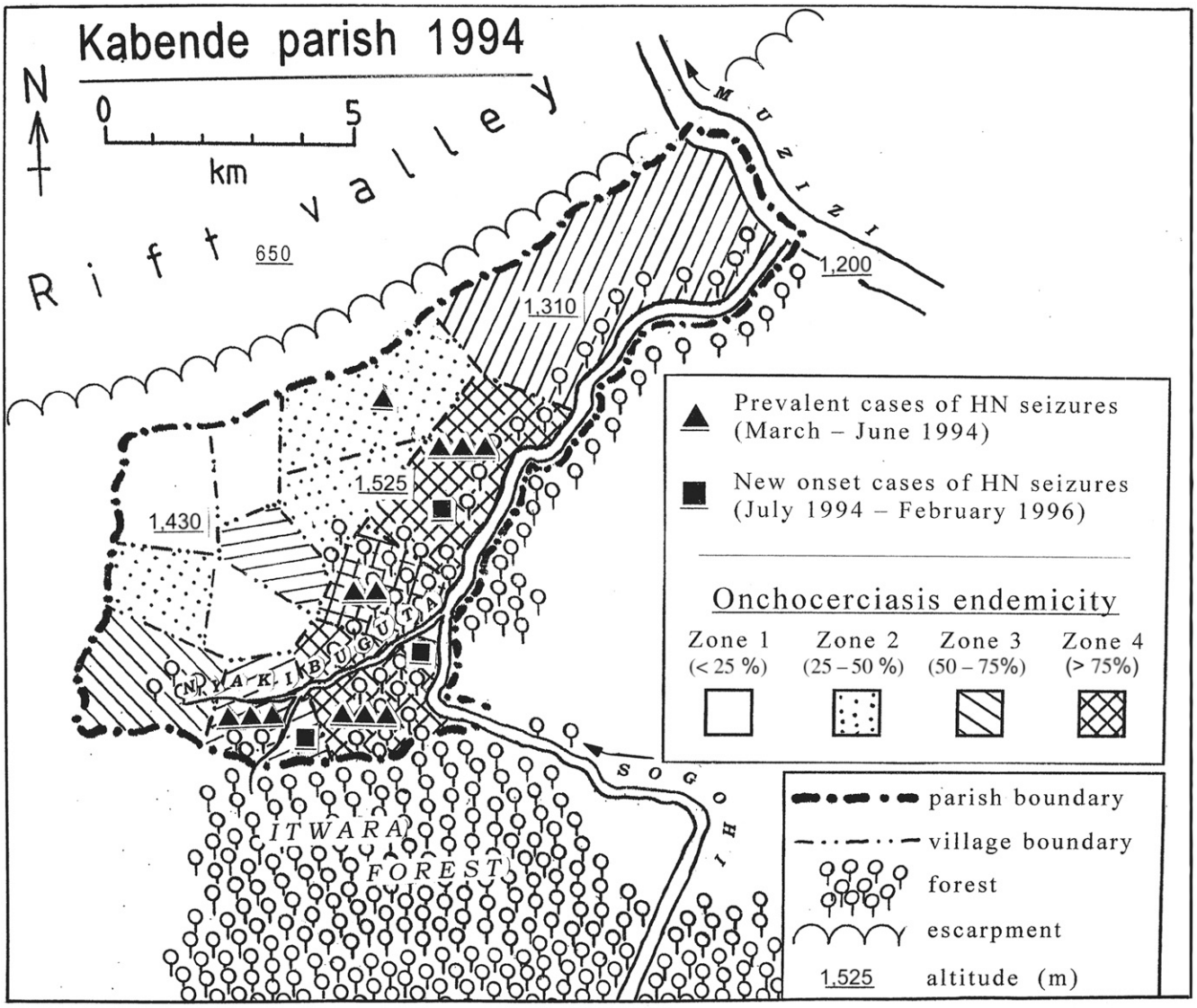

FIGURE 1. Map of Kabende parish in Kabarole district, western Uganda, 1994. Prevalence of onchocerciasis ranged from < 25% to > 75% in the 13 villages of the parish. Epilepsy patients with head nodding seizures (HN seizures) were found living mainly in villages of high onchocerciasis endemicity, located close to the vector-breeding sites at the Nyakibuguta and Sogohi rivers.

of this criterion, we think that the frequency of the head movements were likely to be in the range suggested by the 2012 Kampala definition[14] because respondents in Kabende usually described them as slow movements. The assumed frequency of nodding is also in line with the direct observation of a seizure in one patient, which was described in a previous publication.[4] So far, after its formulation in Kampala 2012, only one attempt was made to systematically use the definition of NS as a diagnostic tool in an epidemiological survey.[14,24] In this, Iyengar et al.,[24] in a study on a large population in northern Uganda, found that as many as 31% of the respondents asked about nodding frequency gave a reply of "don't know." Consequently, this question was dropped for the valuation of patients as a probable case.[14,24] We suggest that in a possible revision of the NS definition, this criterion should be changed with the aim to more adequately assess the quality of head nodding moves as a slow, non-abrupt movement that is to be differentiated from jittering, jerks, or cloni. Until then, we agree with others[25] that studies on NS should apply the Kampala 2012 definition[14] as a reference frame for the clinical assessment of suspected cases.

Before our epilepsy survey in March–June 1994, the research team was not aware of the existence of patients with head nodding seizures in Kabende parish, although the condition of "nateera omutwe" was known to the local population. This was only detected in the course of the investigation. Therefore, a specific question about head nodding as a feature of epileptic seizures could not be included in the initial house-to-house screening process focusing on the local term for convulsive seizure,[3] nor could this be done in the diagnostic examination form. It is likely that a number of patients with head nodding escaped to our attention especially during the start of the survey, and patients affected by isolated head nodding seizures without concomitant convulsive seizures were systematically missed. Probably, more patients would have been identified if we had earlier been aware about the occurrence of head nodding in the area and about the locally used term. We consider that knowing this "right word"[26] for NS

TABLE 4

Occurrence of cases with epilepsy and head HN in Kabende parish, March–June 1994, and prevalence by age and endemicity of onchocerciasis (zone 1–4)

Age group (years)	Population/number of cases with HN*; HN* prevalence (per 1,000 population)					Chi-square test‡ (zones 1–3 vs. zone 4)
	Zone 1 (< 25%)†	Zone 2 (25–50%)†	Zone 3 (50–75%)†	Zone 4 (> 75%)†	All zones	
> 20	481/0; 0	410/0; 0	480/0; 0	451/0; 0	1.822/0; 0	NA§
15–19	132/0; 0	115/0; 0	132/1; 7.6	126/2; 15.8	505/3; 5.9	$P = 0.155$
10–14	159/0; 0	143/1; 7.0	163/2; 12.3	158/5; 31.6	623/8; 12.8	$P = 0.025$
5–9	205/0; 0	177/0; 0	210/0; 0	194/1; 5.2	786/1; 1.3	$P = 0.247$
< 5	261/0; 0	240/0; 0	266/0; 0	240/0; 0	1.007/0; 0	NA§
5–19	496/0; 0	435/1; 2.2	505/3; 5.9	478/8; 16.7	1.914/12; 6.3	$P = 0.003$
All ages	1.238/0; 0	1.085/1; 2.2	1.251/3; 2.4	1.169/8; 6.8	4.743/12; 2.5	$P = 0.003$

* HN = epilepsy with head nodding seizures.
† Prevalence of microfilaria found in a random sample of 10–19-year-old inhabitants of 13 villages of Kabende parish (for details, see ref. 3).
‡ Difference between zones of low (zone 1–3) and high (zone 4) onchocerciasis endemicity tested for significance with Fisher's exact test.
§ NA = not applicable (no case of HN found in age group).

("nateera omutwe" in Kabende; "kifafa cha kusinzia"[27] or "amesinzia kichwa"[28] in Tanzania-Mahenge; "lucluc," "yengo wic," or "two luj" in northern Uganda[27]; and "adravu legnaro" in South Sudan[29]) is of importance not only for case finding but also for the diagnostic process and possible therapeutic decisions. It is also needed for communication between affected communities, medical personal, and researchers on local and medical concepts about the nodding phenomenon, and for developing workable plans for interventions.

In view of the mentioned restrictions in case finding, we think that the number of 15 patients found in Kabende, and the prevalence of 6.3 per 1,000 population in the age group between 5 and 19 years, are minimum estimates. Despite substantial differences in the assessment process, this result is similar to that of the previously mentioned investigation of Iyengar et al.[24] of 6.8% in the age between 5 and 18 years in the districts of Kitgum, Lamwo, and Pader of northern Uganda. Using a different case definition and sampling procedure, an earlier assessment of NS in northern Uganda found that the prevalence in 13 parishes of Kitgum district ranged widely from 0.6 to 46 cases per 1,000 population in the age between 5 and 15 years.[10] There is evidence that cases of NS in northern Uganda are mainly found in villages along riversides.[27,30–32] For instance, 82 patients were identified in the village of Tumangu, situated at the banks of the river Pager, in 2014.[33]

In accordance with the situation in northern Uganda, we found in our investigations that patients with head nodding seizures were unevenly distributed throughout the study area of Kabende parish in western Uganda. The prevalence was significantly higher in those villages also having a high endemicity of onchocerciasis and situated immediately along the Nyakibuguta and Sogohi rivers, known as breeding sites of onchocerciasis vector flies.[16,34] This coincides with our earlier observation of a close correlation between onchocerciasis and convulsive epilepsy in general,[3] and is giving evidence that the spatial affinity towards onchocerciasis also refers to the subset of epilepsy with head nodding seizures - NS. The correlation between the prevalence of onchocerciasis and that of convulsive epilepsy[35–37] and the clustering of epilepsy in proximity to rivers harbouring *Onchocerca volvulus*–breeding sites[38,39] has also been found in other areas of tropical Africa. Moreover, a close association was demonstrated in case–control studies on the relationship between epilepsy or NS on the one side and onchocerciasis on the other side.[8,10,40] The possible pathological mechanism by which infection with *O. volvulus* could induce an epileptogenic brain lesion has not been fully clarified. Imaging studies and analysis of cerebrospinal fluid (CSF) have failed to demonstrate the different stages of *O. volvulus* in the central nervous system of NS patients.[9,12,29,41,42] Recently, autoimmune antibodies displaying toxic properties in a neuron cell assay were detected in the CSF of cases studied from South Sudan and northern Uganda.[43] Although an immunopathogenic model could provide a plausible explanation for the complex pattern of dysfunction observed in NS, these findings need to be confirmed.[44–46]

The present case series is completing our previous case report of NS from western Uganda,[5] confirming that this severe and debilitating condition is not confined to the hitherto confirmed areas of Tanzania, South Sudan, and northern Uganda. We suggest that the existence of NS should be systematically searched for in other *O. volvulus*–endemic areas. Our findings are in line with widely growing evidence that onchocerciasis, in addition to the known manifestations at the skin and the eye, is causing devastating and in many cases lethal brain disease.[3,5,8,10,35,38–40,43,46–51] This is reenforcing the urgency to persevere and intensify onchocerciasis control measures which have been shown to be feasible and efficient.[52] In this field, Uganda can be considered as an exemplary model having achieved elimination of onchocerciasis in several foci, including the Itwara focus.[15,53] This is providing an opportunity to test the hypothesis that the removal of the putative cause of NS will lead to the disappearance of the condition in the area. This would provide additional evidence that NS is specifically linked to onchocerciasis.

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REFERENCES

1. Ovuga E, Kipp W, Mungherera M, Kasoro S, 1992. Epilepsy and retarded growth in a hyperendemic focus of onchocerciasis in rural western Uganda. *East Afr Med J 69:* 554–556.
2. Kipp W, Kasoro S, Burnham G, 1994. Onchocerciasis and epilepsy in Uganda. *Lancet 343:* 183–184.
3. Kaiser C, Kipp W, Asaba G, Mugisa C, Kabagambe G, Rating D, Leichsenring L, 1996. The prevalence of epilepsy follows the distribution of onchocerciasis in a west Ugandan focus. *Bull World Health Organ 74:* 361–367.
4. Kaiser C, Benninger C, Asaba G, Mugisa C, Kabagambe G, Kipp W, Rating D, 2000. Clinical and electro-clinical classification of epileptic seizures in west Uganda. *Bull Soc Pathol Exot 93:* 255–259.
5. Kaiser C, Rubaale T, Tukesiga E, Kipp W, Asaba G, 2015. Case report: nodding syndrome, western Uganda, 1994. *Am J Trop Med Hyg 93:* 198–202.
6. Aall-Jilek LM, 1965. Epilepsy in the Wapagoro tribe in Tanganyika. *Acta Psychiatr Scand 41:* 57–86.
7. Lacey M, 2003. Nodding disease: mystery of southern Sudan. *Lancet Neurol 2:* 714.
8. Spencer PS et al., 2013. Nodding syndrome in Mundri county, South Sudan: environmental, nutritional and infectious factors. *Afr Health Sci 13:* 183–204.
9. Idro R et al., 2014. Nodding syndrome in Ugandan children–clinical features, brain imaging and complications: a case series. *BMJ Open 3:* e002540.
10. Foltz JL et al., 2013. An epidemiologic investigation of potential risk factors for nodding syndrome in Kitgum District, Uganda. *PLoS One 8:* e66419.
11. Van Bemmel K, Derluyn I, Stroeken K, 2014. Nodding syndrome or disease? On the conceptualization of an illness-in-the-making. *Ethn Health 19:* 100–118.
12. Winkler AS et al., 2015. The head nodding syndrome—clinical classification and possible causes. *Epilepsia 49:* 2008–2015.
13. Dowell SF et al., 2013. Nodding syndrome. *Emerg Infect Dis 19:* 1374–1384.
14. World Health Organisation, 2012. *International Scientific Meeting on Nodding Syndrome, Kampala, Uganda*. Available at: http://www.who.int/neglected_diseases/diseases/Nodding_syndrom_Kampala_Report_2012.pdf. Accessed April 10, 2018.
15. Fischer P, Kipp W, Bamuhiga J, Binta-Kahwa J, Kiefer A, Büttner DW, 1993. Parasitological and clinical characterization of *Simulium neavei*-transmitted onchocerciasis in western Uganda. *Trop Med Parasitol 44:* 311–321.
16. Garms R, Lakwo TL, Ndyomugyenyi R, Kipp W, Rubaale T, Tukesiga E, Katamanywa J, Post RJ, Amazigo UV, 2009. The elimination of the vector *Simulium neavei* from the Itwara onchocerciasis focus in Uganda by ground larviciding. *Acta Trop 111:* 203–210.
17. Kaiser C, 1998. *Introducing Anti-Epileptic Treatment into Primary Health Care: A Case Study in an Area of High Epilepsy Prevalence in Kabarole District, West Uganda*. MSc Thesis, Institute of Tropical Hygiene and Public Health, University of Heidelberg, Heidelberg, Germany.
18. Kaiser C, Asaba G, Leichsenring M, Kabagambe G, 1998. High incidence of epilepsy related to onchocerciasis in west Uganda. *Epilepsy Res 30:* 247–251.
19. Kaiser C, Asaba G, Mugisa C, Kipp W, Kasoro S, Rubaale T, Kabagambe G, 1998. Antiepileptic drug treatment in rural Africa: involving the community. *Trop Doct 28:* 73–77.
20. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Mei Z, Wei R, Curtin LR, Roche AF, Johnson CL, 2002. 2000 CDC growth charts for the United States: methods and development. *Vital Health Stat 11:* 1–190.
21. Marshall WA, Tanner JM, 1969. Variations in pattern of pubertal changes in girls. *Arch Dis Child 235:* 291–303.
22. Marshall WA, Tanner JM, 1970. Variations in the pattern of pubertal changes in boys. *Arch Dis Child 239:* 13–23.
23. Abreu AP, Kaiser UB, 2016. Pubertal development and regulation. *Lancet Diabetes Endocrinol 4:* 254–264.
24. Iyengar PJ et al.; Centers for Disease Control and Prevention (CDC), 2014. Prevalence of nodding syndrome–Uganda 2012–2013. *MMWR Morb Mortal Wkly Rep 63:* 603–606.
25. Schmutzhard E, Winkler AS, 2016. Nodding syndrome–a critical note and a plea to join forces. *Trop Med Int Health 20:* 201–204.
26. Burnham G, 2003. The right word. *Lancet 361:* 456.
27. Van Bemmel K, Van der Weegen K, 2017. Universal classifications, national approaches and specific situations: a comparative study on the conceptualization of nodding syndrome in Uganda and Tanzania. *Anthropol Med 30:* 1–20.
28. Jilek WG, Jilek-Aall LM, 1970. The problem of epilepsy in rural Africa: 'Kifafa' in a Tanzanian tribe. *Transcult Psychiatry 7:* 43–48.
29. Tumwine JK, Vandemaele K, Chungong S, Richer M, Anker M, Ayana Y, Opoka ML, Klaucke DN, Quarello A, Spencer PS, 2012. Clinical and epidemiologic characteristics of nodding syndrome in Mundri county, southern Sudan. *Afr Health Sci 12:* 242–248.
30. Anonymous , 2009. *Nodding Disease or "River Epilepsy." Integrated Regional Information Network (IRIN), Kitgum*. Press release 10 August 2009. Available at: http://www.irinnews.org/report/85646/uganda-nodding-disease-or-river-epilepsy. Accessed April 10, 2018.
31. Kitara DL, Oh J, Mwaka AD, 2013. Nodding syndrome in Uganda—a disease cluster: an epidemiological dilemma. *Pac J Med Sci 11:* 21–33.
32. Colebunders R et al., 2016. Nodding syndrome and epilepsy in onchocerciasis endemic regions: comparing preliminary observations from South Sudan and the Democratic Republic of the Congo with data from Uganda. *BMC Res Notes 9:* 182.
33. Spencer PS et al.; other Members of the Oregon-Uganda Nodding Syndrome Research Team, 2016. Environmental, dietary and case-control study of nodding syndrome in Uganda: a post-measles brain disorder triggered by malnutrition? *J Neurol Sci 369:* 191–203.
34. Mpagi J, Katamanywa J, Garms R, 2001. Dispersal range of *Simulium neavei* in an onchocerciasis focus of western Uganda. *Med Vet Entomol 14:* 95–99.
35. Pion SDS et al., 2009. Epilepsy in onchocerciasis endemic areas: systematic review and meta-analysis of population-based surveys. *PLoS Negl Trop Dis 3:* e461.
36. Levick B et al., 2017. High prevalence of epilepsy in onchocerciasis endemic regions in the Democratic Republic of the Congo. *PLoS Negl Trop Dis 11:* e0005732.
37. Ngugi AK et al.; SEEDS Group, 2013. Prevalence of active convulsive epilepsy in sub-Saharan Africa and associated risk factors: cross-sectional and case-control studies. *Lancet Neurol 12:* 253–263.
38. Boussinesq M, Pion SD, Demanga-Ngangue , Kamgno J, 2002. Relationship between onchocerciasis and epilepsy: a matched case-control study in the Mbam Valley, Republic of Cameroon. *Trans R Soc Trop Med Hyg 96:* 537–541.
39. Colebunders R et al., 2016. Prevalence of river epilepsy in the Orientale Province in the Democratic Republic of the Congo. *PLoS Negl Trop Dis 10:* e0004478.
40. Kaiser C, Pion SDS, Boussinesq M, 2013. Case-control studies on the relationship between onchocerciasis and epilepsy: systematic review and meta-analysis. *PLoS Negl Trop Dis 7:* e2147.
41. König R et al., 2010. The role of *Onchocerca volvulus* in the development of epilepsy in a rural area of Tanzania. *Parasitology 137:* 1559–1568.
42. Sejvar JJ et al., 2013. Clinical, neurological, and electrophysiological features of nodding syndrome in Kitgum, Uganda: an observational case series. *Lancet Neurol 12:* 166–174.
43. Johnson TP et al., 2017. Nodding syndrome may be an autoimmune reaction to the parasitic worm *Onchocerca volvulus*. *Sci Transl Med 9:* eaaf6953.
44. Spencer PS, Schmutzhard E, Winkler AS, 2017. Nodding syndrome in the spotlight–placing recent findings in perspective. *Trends Parasitol 33:* 490–492.

45. Kakooza-Mwesige A, 2017. Unravelling the mysterious onchocerciasis-nodding syndrome link: new developments and future challenges. *Ann Transl Med 5:* 486.
46. Kaiser C, Pion SDS, 2017. River blindness goes beyond the eye: autoimmune antibodies, cross-reactive with *Onchocerca volvulus* antigen, detected in brain of patients with nodding syndrome. *Ann Transl Med 5:* 459.
47. Kaiser C, Asaba G, Kasoro S, Rubaale T, Kabagambe G, Mbabazi M, 2007. Mortality from epilepsy in an onchocerciasis-endemic area in west Uganda. *Trans R Soc Trop Med Hyg 101:* 48–55.
48. Kipp W, Burnham G, Bamuhiiga J, Leichsenring M, 1996. The Nakalanga syndrome in Kabarole district, western Uganda. *Am J Trop Med Hyg 54:* 80–83.
49. Föger K, Gora-Stahlberg G, Sejvar J, Ovuga E, Jilek-Aall L, Schmutzhard E, Kaiser C, Winkler AS, 2017. Nakalanga syndrome: clinical characteristics, potential causes, and its relationship with recently described nodding syndrome. *PLoS Negl Trop Dis 11:* e0005201.
50. Colebunders R, Suykerbuyk P, Jacob ST, van Oijen M, 2017. Nodding syndrome, other forms of epilepsy, and the Nakalanga syndrome most likely directly or indirectly caused by *Onchocerca volvulus*. *J Neurol Sci 372:* 439–440.
51. Chesnais CB, Njamnshi AK, Zoung-Kanyi Bissek A-C, Tatah GY, Nana-Djeunga HC, Kamgno J, Colebunders R, Boussinesq M, 2018. First evidence by a cohort study in Cameroon that onchocerciasis does induce epilepsy [Abstract at the first International Workshop on Onchocerciasis-Associated Epilepsy, Antwerp, Belgium, 2017]. *Infect Dis Poverty 7:* 23. Available at: https://www.uantwerpen.be/en/conferences/oae-2017/. Accessed May 23, 2018.
52. Coffeng LE et al., 2013. African programme for onchocerciasis control 1995–2015: model-estimated health impact and cost. *PLoS Negl Trop Dis 7:* e2032.
53. Katabarwa MN et al., 2018. After 70 years of fighting an age-old scourge, onchocerciasis in Uganda, the end is in sight. *Int Health 10 (Suppl 1):* 79–88.