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Case Report: Nodding Syndrome, Western Uganda, 1994

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Abstract. Nodding syndrome (NS) is a poorly understood condition, which was delineated in 2008 as a new epilepsy syndrome. So far, confirmed cases of NS have been observed in three circumscribed African areas: southern Tanzania, southern Sudan, and northern Uganda. Case–control studies have provided evidence of an association between NS and infection with *Onchocerca volvulus*, but the causation of NS is still not fully clarified. We report a case of a 15-year old boy with head nodding seizures and other characteristic features of NS from an onchocerciasis endemic area in western Uganda, with no contiguity to the hitherto known areas. We suggest that the existence of NS should be systematically investigated in other areas.

INTRODUCTION

Patients with head nodding movements as a feature of an epileptic disorder were observed as early as 1960 by Louise Jilek-Aall in a southern Tanzanian community with a highly elevated epilepsy prevalence.[1] On the basis of comprehensive clinical, electroencephalographic and brain imaging investigations this condition was summarized as a distinct epileptic syndrome in 2005.[2] During the past decade, increasing numbers of patients affected with the nodding syndrome (NS) were also reported from South Sudan[3,4] and northern Uganda[5–8] (Figure 1). It is accepted that patients with head nodding seizures combined with a number of other characteristic symptoms living in these three areas are affected by the same disease, NS. A case definition for NS was agreed upon at an international conference in Kampala, Uganda, 2012.[9,10]

With the help of the present case report we examine the question of whether NS also exists in western Uganda, an area with no contiguity to those mentioned above, and we give an overview on the present state of knowledge on the phenomenon of head nodding.

CASE REPORT

In May 1994, a 15-year-old boy was identified as suffering from epilepsy during a population wide survey in the Kabende parish, located in Kabarole District, western Uganda.[11] This parish of 4,743 inhabitants is situated in the Itwara onchocerciasis focus, with a prevalence of microfilaria (mf) carriers ranging from 15% to 85% in the 10–20 years age group of its 13 villages in 1994.[11] A detailed description of the epidemiology of onchocerciasis and epilepsy in Kabende parish can be found in our previous publications,[11–14] and detailed maps of the entire Itwara focus are presented by Garms and others.[15] All patients who were registered in the survey underwent a thorough clinical assessment.[14] The information given in this article is based on the original records of the initial cross-sectional survey[11,14] and of the subsequent follow-up of this cohort over a total period of 7 years.[12,16–18]

The patient was seen at his home because he was considered too weak to reach the central place of the parish on his own. He had been born in his residential village after an uncomplicated pregnancy and grew and developed normally up to the age of 7 years. At this age, he started experiencing episodes of about 10 minutes duration when he suddenly did not respond to his surroundings and his head moved repetitively forwards and backwards. Such episodes were known to the local community with the term "nateera omutwe" (head nodding). About 1 year later, these episodes were regularly followed by generalized tonic–clonic seizures (GTCS). After getting sick, the growth of the boy slowed down and his cognitive development changed for the worse to the point that he lost his ability to speak. When seen in 1994, he still could take food with his hands, but his parents said that, before a seizure was about to happen, he frequently refused to eat for about half an hour. Living in an onchocerciasis endemic area, he had received treatment with ivermectin 12 months before the present examination. In the patient's village, Rwesenene, with 290 inhabitants, there were nine patients diagnosed with epilepsy in 1994,[11] and three of these also gave an account of head nodding. During the cross-sectional epilepsy survey in 1994,[11] a total of 10 patients with this seizure type were found in the villages of Kabende parish,[14] and 5 additional patients were seen with a subsequent prospective study on epilepsy incidence.[12,14] In accordance with the findings in the patient of this report, all these patients had been healthy at birth and had experienced the first seizure at a median age of 8 years (range: 3–14 years).

On examination, severe wasting and stunting was found (height 110 cm; z-score –7.3 of NCHS height-for-age standard).[19] The boy was unable to understand what was said and his facial expression was generally reduced. He was weak and unable to stand upright without support. Muscle reflexes were normal and no focal neurologic deficit was noted. Genital development was at an infantile stage. Below the right iliac crest, a hard lump was palpable, consistent with an onchocercal nodule. A skin biopsy revealed the presence of microfilaria of *Onchocerca volvulus*.

Treatment with phenobarbitone (PHB) was started[16,17] and over the following 2 years a slow but steady improvement was observed: seizures were less frequent and his physical and mental condition improved (Table 1). However, in October 1996, the seizures worsened and eventually went on without interruption until the patient died 1 month later. In a

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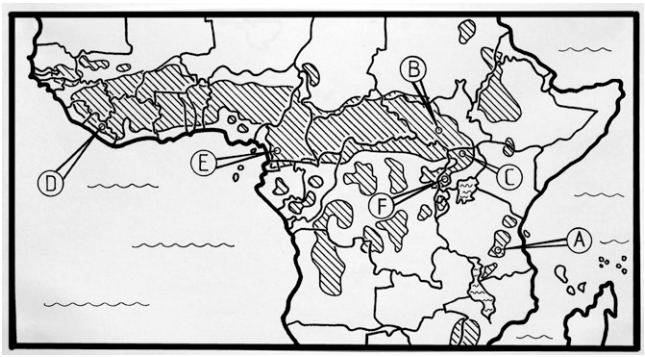

FIGURE 1. Map of sub-Sahara Africa indicating areas from where patients with confirmed nodding syndrome (NS), or head nodding seizures without confirmation of NS (HN), were reported. (**A**) Tanzania: NS; (**B**) southern Sudan: NS; (**C**) northern Uganda: NS; (**D**) Liberia: HN; (**E**) Cameroon: HN; (**F**) western Uganda: present report. Onchocerciasis endemic areas are marked by hatching.

verbal autopsy in May 1998,[18] his father said that, as long as he had been able to eat, he was given the PHB tablets daily as prescribed.

DISCUSSION

The 2012 Kampala case definition differentiates between suspected, probable, and confirmed cases of NS (Table 2).[9,10] To classify a patient as a possible case, two major criteria are listed as mandatory: 1) Ages 3–18 at onset of head nodding, and 2) nodding frequency 5–20 times/min. With regard to the suggested criterion of nodding frequency, this appears difficult to be reliably ascertained because the symptom in question (head nodding seizures) only exceptionally can be observed at the time of examination. This constitutes a general problem in epileptology which in the more equipped facilities of the industrialized countries is overcome with examining the patient by use of long-term electroencephalography combined with synchronous video monitoring. In the areas where patients with NS are found, this technique is not available and it might be questioned if it is appropriate to include this criterion as mandatory in the 2012 Kampala definition. Despite this limitation, we consider it likely that the frequency of the head nodding movements in the presented patient, as well as in the other patients found in Kabende, were actually in the range given by the 2012 Kampala definition. This frequency is corresponding well with the descriptions that we obtained in our frequent caretaker interviews, and also with the direct observation of a head nodding seizure in one other patient, which was reported in our previous publication.[14] This patient showed slow head movements, which were well compatible with the required frequency of 5–20 times/min.

Taking into account the mentioned considerations, we think that the patient presented in our report is consistent with a "probable" case of NS. Because his head nodding episodes were not observed by a trained health worker nor were

TABLE 1
A 15-year-old boy with nodding syndrome, western Uganda, 1994. Timeline, sequence of events

Date	Observation/activity	Source of information	Relevant findings (patient history, clinical findings, therapy, follow-up)
1979–1986	Birth, childhood	Parents report in May 1994	1979: normal pregnancy and birth in Rwesenene village, Kabende Parish, western Uganda, onchocerciasis endemic area, normal growth and development up to the age of 7 years
1986	Start of HN	Parents report in May 1994	No obvious external causation, accompanied with delayed growth, and progressive mental deterioration
1991	–	Parents report in May 1994	Received treatment with an antiepileptic drug over some weeks, probably PHB, with some improvement of his general condition but no effect on seizures. Stopped because of lacking supply
May 1994	Clinical assessment	Parents, G.A., C.K.	Stunting, wasting, weakness, scars from falling, cognitive impairment, onchocercal nodule, positive skin biopsy for Mf. Seizure frequency: 1–10/day. Start PHB at 60 mg/day
June 1994	Follow-up	Parents, G.A., C.K.	Reduced seizure frequency (none over several days). Improved strength, appetite and activity, slightly increased sleepiness. Dose PHB increased to 90 mg/day, recommendation to reduce to 60 mg/day if the sleepiness increases
December 1994	Follow-up	Father, W.B., C.K.	Seizure frequency further decreased (none over 3 months, now again 1/week); seizure duration reduced (generalized tonic), no more HN seizures. Strength further improved, can walk some steps. Still not understanding, not talking. Dosage PHB unchanged 90 mg/day
June 1995	Follow-up	Father, W.B., C.K.	Seizure frequency increased (one seizure every 1–2 days), short duration, immediate recovery. Mental improvement: can make parents understand that he is hungry, is reacting to his name. Strength and appetite better. PHB unchanged 90 mg/day.
February 1996	Follow-up	Father, W.B., C.K.	Seizures unchanged. Further mental improvement, still not able to speak. No tiredness. PHB increased to 120 mg/day. Recommendation to reduce again if sleepiness increases
August 1996	Follow-up	W.B.	Seen at home to receive drug provisions (W.B.). Noted: "Seen at home, he is well and comfortable," no details on seizures or physical condition
October 1996	Death	–	–
May 1998	Verbal autopsy	Father, G.A., C.K.	Increase of seizures over several weeks without obvious cause. Death with continuing seizures. No fever or other sign of illness. PHB treatment not interrupted
August 2013	Consent for publication	Parents, D.K.	Home visit (D.K.) to parents of the patient. Explanation of intended publication. Parents' consent obtained

C.K. = Christoph Kaiser; D.K. = Donozio Kisembo, student in Public Health, Mountains of the Moon University, Fort Portal, Uganda (born in Kabende Parish); G.A. = George Asaba; Mf = microfilaria of *Onchocerca volvulus*; PHB = phenobarbitone; HN = head nodding; W.B. = William Byaruhunga, village health worker, Kabende Parish.

TABLE 2
Case definition characteristics and criteria for NS,[9,10] applied to the presented case

Case definition criteria (Kampala, 2012)		Present case report (western Uganda, 1994)
Suspected case: reported head nodding in a previously healthy person (repetitive involuntary drops of the head toward the chest on ≥ 2 occasions)		+
Probable case: suspected case with at least 2 major and 1 minor criteria		
Major criteria	Age 3–18 years at onset of head nodding	+
	Nodding frequency 5–20 times/min	[+]
Minor criteria	Other neurologic abnormalities	+
	Clustering in space and time with similar cases	+
	Triggering by eating or cold weather	[+]
	Delayed sexual or physical development	+
	Psychiatric manifestations	n.r.
Confirmed case: probable case with documented head nodding episodes		
	Observed and recorded by a trained health-care worker	n.r.
	Videotaped head nodding episode	n.r.
	Video/EEG/EMG documenting head nodding as atonic seizure	n.r.

+ = criterion recorded as present; [+] = criterion likely to be present although not explicitly recorded (see discussion for details); EEG = electroencephalogram; EMG = electromyogram; n.r. = not recorded; NS = nodding syndrome.

the seizures documented by Video/EEG/EMG, in the strict sense of the Kampala case definition[10] the diagnosis cannot be considered as confirmed. However, the overall constellation of the patient's history, symptoms and signs appears typical of NS to such an extent that we consider this report as strong evidence that NS effectively existed in Kabende parish in 1994. This area in the Kabarole District of western Uganda has no contiguity with the known areas of NS, in particular with the focus in northern Uganda,[5–8] which is located several 100 km away (Figure 1). Kabende parish would thus be the fourth location where NS has been confirmed.

In 2003, the first report published from southern Sudan about children with head nodding mentioned that seizures were frequently precipitated when the patients were offered food.[3] As a particularly striking example of this observation a patient was described who reliably started head nodding at the sight of a local maize dish but did not react when offered a western candy bar.[3,4] The occurrence of this peculiar finding was confirmed in case series from northern Uganda[5,7] and Tanzania.[2] The study during which the patient of this report was examined was conducted 10 years before the publication of the mentioned report from southern Sudan,[3,11] and we were not aware beforehand of food as a possible provoking factor. Although we did not systematically search for such a relation, the parents of the presented patient gave an explicit statement that "the patient refused eating before a seizure was about to happen." It is not clear if this corresponds to the presentation of food as an actual provoking factor in our patient, or rather to a general state of reduced alertness in the prodromal stage of a seizure. Among those 10 patients found with head nodding seizures during our survey in 1994,[11,14] we met one more patient who's caretaker gave a spontaneous statement that head nodding started "after the patient saw anything hot, for example food or tea." This may be seen as indication that in our study area food is a provoking factor with a similar frequency to that reported from Mahenge, Tanzania, where this was mentioned in 9 out of 62 consecutive patients seen in an ambulatory clinic.[2]

Seizures with head nodding movements similar to those seen in NS were observed at least in two more African areas (Figure 1): 1) In 1981–1982, in a community with a high prevalence of epilepsy in the Grand Bassa County, Liberia, a type of seizure with characteristic rhythmic dorsoventral movements was observed in numerous patients[20,21] and the similarity to the earlier descriptions of Louise Jilek-Aall[1] was recognized. 2) In 2004, a team of several pediatric neurologists working in the littoral province of Cameroon made a detailed clinical assessment of 19 patients with epilepsy found in a village of 181 inhabitants.[22] Four of these patients were reported to have a seizure type with several repeated head nodding movements. The authors explicitly pointed out the resemblance of these seizures with those described in western Uganda,[14] the area of this report, and southern Tanzania.[1] The high prevalence of epilepsy, the age distribution in the population, and the age of seizure onset in this Cameroonian village also show a striking similarity with the situation in Kabende,[11] and with available data from other areas affected with NS.[4,6,23]

Like all other patients found with head nodding seizures in Kabende parish, the patient presented in this report was also affected by another seizure type, in his case GTCS, with head nodding preceding the onset of GTCS. This was also found to be the typical sequence observed in series of clinical cases from the areas with confirmed cases of NS.[1,2,5,7,24] A recently published follow-up study of those patients examined with the initial assessment leading to the conceptualization of NS in southern Tanzania[2] found that 4 years later head nodding seizures had disappeared in half of those patients who initially had been suffering from head nodding in addition to other seizures, mainly GTCS, although in most cases GTCS had continued.[24] This course was also observed with the patient in our report. We were also told by other patients interviewed in Kabende that head nodding had disappeared with the onset of a second seizure type or some time later, even if they had not received antiepileptic drug treatment (AED).

Following the start of therapy with PHB, we observed a marked reduction in the frequency of GTCS with seizure-free episodes of up to 3 months, and head nodding seizures stopped completely. To some extent the patient's general condition and mental capacity also improved. However, lasting seizure control was not achieved and over time seizure frequency increased again. We think that this can be considered as a beneficial, though limited effect of therapy with PHB in this patient. A similar experience with treatment with PHB was reported from southern Tanzania where a significant reduction in seizure frequency has been observed in most patients but full control was achieved only in a few.[24,25] In Tanzania, besides PHB patients also received treatment with other AEDs (phenytoine or carbamazepine) as monotherapy or in combination.

No clear difference was noted between the varying regimens, although this was not systematically studied.[24] On the basis of some theoretical considerations, sodium valproate (VPA) was proposed as an AED that might be most appropriate for controlling the presumably myoclonic movements of head nodding seizures.[26] However, only limited data on the use of VPA in NS are available[7,27] and these do not indicate the greater efficacy of VPA over the alternative AEDs already mentioned. In view of the possibly severe adverse effects of VPA,[28–30] the high cost and its difficult availability in rural Africa, it might be reconsidered to abide by the general WHO recommendation to use PHB as the first-line drug,[31,32] especially in patients with coexisting head nodding and convulsive seizures. Controlled comparative studies of different candidate AEDs should be undertaken to improve therapeutic efficiency.

The etiology and the pathogenesis of NS has not been fully clarified. A great number of possible causes were examined with case–control studies in South Sudan[33,34] and northern Uganda[6] including nutritional factors, possible environmental toxins, numerous infections (viral, bacterial, parasitic), and some genetic factors. As a common result of these studies, an association was found between onchocerciasis and NS whereas results on other possible factors were negative or inconsistent. Over the past two decades, numerous studies throughout endemic areas of sub-Sahara Africa have also demonstrated a strong relationship between onchocerciasis and epilepsy in general.[35,36] A possible connection with onchocerciasis is also supported by the fact that NS so far has been found exclusively in onchocerciasis endemic areas. Clinical investigations including magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) studies could not demonstrate the presence of the parasite in the brain of patients with NS or patients with other seizure types.[2,5,7,37] However, microfilaria (mf) of *O. volvulus* were found in the CSF of patients, particularly following antifilarial treatment.[38] It may be conceived that mf are present at the time of seizure onset but, spontaneously or as a result of antiparasitic treatment, disappear from the intracerebral space whereas the epileptogenic lesion prevails.[39] It also cannot be excluded that epilepsy in patients with *O. volvulus* infection can be induced by immunological mechanisms,[40,41] by extracerebral factors leading to a disturbance of the blood–brain barrier,[42] or by a, so far unidentified, coexisting neurotropic factor found connected with *O. volvulus* transmission.[36,43,44]

In summary, this report provides strong evidence that NS exists beyond the so far known endemic areas in Tanzania, South Sudan, and northern Uganda. Neurological investigations focusing on detecting cases of NS in other onchocerciasis endemic areas would be helpful in confirming this finding. This would further support existing evidence on the close, possibly causal, connection between onchocerciasis and NS, and epilepsy in general. We think that the many unclear questions of NS etiology would be best addressed with more longitudinal studies. These could provide a basis for allowing the adaptation and negotiation of research questions and programs with the affected communities. Under the difficult conditions for health-care provision in the NS affected areas, this could also help patients under study to receive continuing and long-term access to AEDs and to qualified health workers.[45] Because children affected with NS constitute a particularly vulnerable group and their families are not able to cope with the disease on their own, connecting NS research with long-term epilepsy care is also an ethical necessity. Possibly, such projects could be realized by cooperation between research institutions and humanitarian programs. Should it turn out that NS indeed is causally connected to infection with *O. volvulus*, the most effective measure to reduce its burden would probably be to intensify the approved and effective control measures against onchocerciasis in the affected communities.[46]

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REFERENCES

1. Aall-Jilek LM, 1965. Epilepsy in the Wapagoro tribe in Tanganyika. *Acta Psychiatr Scand 41:* 57–86.
2. Winkler AS, Friedrich K, König R, Meindl M, Helbok R, Unterberger I, Gotwald T, Dharsee J, Velicheti S, Kidunda A, Jilek-Aall L, Matuja W, Schmutzhard E, 2008. The head nodding syndrome—clinical classification and possible causes. *Epilepsia 49:* 2008–2015.
3. Lacey M, 2003. Nodding disease: mystery of southern Sudan. *Lancet Neurol 2:* 714.
4. Tumwine JK, Vandemaele K, Chungong S, Richer M, Anker M, Ayana Y, Opoka ML, Klaucke DN, Quarello A, Spencer PS, 2012. Clinical and epidemiological characteristics of nodding syndrome in Mundry County, southern Sudan. *Afr Health Sci 12:* 242–248.
5. Sejvar JJ, Kakooza AM, Foltz JL, Makumbi I, Atai-Omoruta AD, Malimbo M, Ndyomugyenyi R, Alexander LN, Abang B, Downing RG, Ehrenberg A, Guilliams K, Helmers S, Melstrom P, Olara D, Perlman S, Ratto J, Trevathan E, Winkler AS, Dowell SF, Lwamafa DKW, 2013. Clinical, neurological and electro-physiological features of nodding syndrome, Uganda: an observational case series. *Lancet Neurol 12:* 166–174.
6. Foltz JL, Makumbi I, Sejvar JJ, Malimbo M, Ndyomugyenyi R, Atai-Omoruto AD, Alexander LN, Abang B, Melstrom P, Kakooza AM, Olara D, Downing RG, Nutman TB, Dowell SF, Lwamafa DKW, 2013. An epidemiologic investigation of potential risk factors for nodding syndrome in Kitgum District, Uganda. *PLoS ONE 8:* e66419.
7. Idro R, Opoka RO, Aanyu HT, Kakooza-Mwesige A, Piloya-Were T, Namusoke H, Musoke SB, Nalugya J, Bangirana P, Mwaka AD, White S, Chong K, Atai-Omoruto AD, Mworozi E, Nankunda J, Kiguli S, Aceng JR, Tumwine JK, 2013. Nodding syndrome in Ugandan children—clinical features, brain imaging and complications: a case series. *BMJ Open 3:* e002540.
8. 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.
9. Dowell SF, Sejvar JJ, Riek L, Vandemaele KAH, Lamunu M, Kuesel AC, Schmutzhard E, Matuja W, Bunga S, Foltz J, Nutman TB, Winkler AS, Mbonye AK, 2013. Nodding syndrome. *Emerg Infect Dis 19:* 1374–1384.

10. World Health Organization, 2012. *International Scientific Meeting on Nodding Syndrome, Kampala, Uganda, 30 July–1 August 2012*. Available at: http://www.who.int/neglected_diseases/Nodding_syndrom_Kampala_Report_2012.pdf. Accessed November 8, 2014.
11. 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.
12. Kaiser C, Asaba G, Leichsenring M, Kabagambe G, 1998. High incidence of epilepsy related to onchocerciasis in west Uganda. *Epilepsy Res 30:* 247–251.
13. Kaiser C, Rubaale T, Tukesiga E, Kipp W, Kabagambe G, Okech Ojony J, George Asaba G, 2011. Association between onchocerciasis and epilepsy in the Itwara hyperendemic focus, west Uganda: controlling for time and intensity of exposure. *Am J Trop Med Hyg 85:* 225–228.
14. 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.
15. 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.
16. 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.
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*. Thesis, Master of Science in Community Health and Health Management in Developing Countries. Heidelberg, Germany: Institute of Tropical Hygiene and Public Health, University of Heidelberg.
18. 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.
19. National Center for Health Statistics, 1977. *NCHS Growth Curves for Children: Birth–18 Years*. DHEW publication no. (PHS) 78-1650. Rockville, MD: U.S. Department of Health Education and Welfare. Available at: http://www.cdc.gov/nchs/data/series/sr_11/sr11_165.pdf. Accessed November 8, 2014.
20. Van der Waals FW, Goudsmit J, Gajdusek DC, 1983. See-ee: clinical characteristics of highly prevalent seizure disorders in the Gbawein and Wroughbarh clan region of Grand Bassa County, Liberia. *Neuroepidemiology 2:* 35–44.
21. Gerrits C, 1984. Contextual Meaning of "Sii," epilepsy, in a part of Grand Bassa County, Liberia. *Liberian Stud J 10:* 55–66.
22. Prischich F, De Rinaldis M, Bruno F, Egeo G, Santori C, Zappaterreno A, Fattouch J, Di Bonaventura C, Bada J, Russo G, Pizzuti A, Cardona F, Sa'a, Vullo V, Giallonardo AT, D'Erasmo E, Pellicia A, Vanacore N, 2008. High prevalence of epilepsy in a village in the Littoral Province of Cameroon. *Epilepsy Res 82:* 200–210.
23. Rwiza HT, Kilonzo GP, Haule J, Matuja WBP, Mteza I, Mbena P, Kilima PM, Mwaluko G, Mwang'ombola R, Mwaijande F, Rweyemamu G, Matowo A, Jillek-Aall LM, 1992. Prevalence and incidence of epilepsy in Ulanga, a rural Tanzanian district: a community-based study. *Epilepsia 33:* 1051–1056.
24. Winkler AS, Wallner B, Friedrich K, Pfausler B, Unterberger I, Matuja W, Jilek-Aall L, Schmutzhard E, 2014. A longitudinal study on nodding syndrome—a new African epilepsy disorder. *Epilepsia 55:* 86–93.
25. Winkler AS, Friedrich K, Meindl M, Kidunda A, Nassri A, Jillek-Aall L, Matuja W, Schmutzhard E, 2010. Clinical characteristics of people with head nodding in southern Tanzania. *Trop Doct 40:* 173–175.
26. Idro R, Musubire KA, Byamah Mutamba B, Namusoke H, Muron J, Abbo C, Oriyabuzu R, Ssekyewa J, Okor C, Mwaka D, Ssebadukka P, Makumbi I, Opar B, Aceng JR, Mbonye AK, 2013. Proposed guidelines for the management of nodding syndrome. *Afr Health Sci 13:* 219–232.
27. Idro R, Namusoke H, Abbo C, Mutamba BB, Kakooza-Mwesige A, Opoka RO, Musubire AK, Mwaka AD, Opar BT, 2014. Patients with nodding syndrome in Uganda improve with symptomatic treatment: a cross-sectional study. *BMJ Open 4:* e006476.
28. Scheffner D, König S, Rauterberg-Ruland I, Kochen W, Hofmann WJ, Unkelbach S, 1988. Fatal liver failure in 16 children with valproate therapy. *Epilepsia 29:* 530–542.
29. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD Study Group, 2013. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol 12:* 244–252.
30. Star K, Edwards IR, Choonara I, 2014. Valproic acid and fatalities in children: a review of individual case safety reports in VigiBase. *PLoS ONE 9:* e108970.
31. Zhang LL, Zeng LN, Li YP, 2011. Side effects of phenobarbital in epilepsy: a systematic review. *Epileptic Disord 13:* 349–365.
32. Yasiry Z, Shorvon SD, 2012. How phenobarbital revolutionized epilepsy therapy: the story of phenobarbital in epilepsy in the last 100 years. *Epilepsia 53 (Suppl 8):* 26–39.
33. Spencer PS, Vandermaele K, Richer M, Palmer VS, Chungong S, Anker M, Ayana Y, Opoka ML, Klaucke BN, Quarello A, Tumwine JK, 2013. Nodding syndrome in Mundri county, South Sudan: environmental, nutritional and infectious factors. *Afr Health Sci 13:* 183–204.
34. Centers for Disease Control and Prevention, 2012. Nodding syndrome—South Sudan, 2011. *MMWR 61:* 52–53.
35. Pion SDS, Kaiser C, Boutros-Toni F, Cournil A, Taylor MM, Meredith SEO, Stufe A, Bertocchi I, Kipp W, Preux P-M, Boussinesq M, 2009. Epilepsy in onchocerciasis endemic areas: systematic review and meta-analysis of population-based surveys. *PLoS Negl Trop Dis 3:* e461.
36. 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.
37. König R, Nassri A, Meindl M, Matuja W, Kidunda AR, Siegmund V, Bretzel G, Löscher T, Jillek-Aall L, Schmutzhard E, Winkler AS, 2010. The role of *Onchocerca volvulus* in the development of epilepsy in a rural area of Tanzania. *Parasitology 137:* 1559–1568.
38. Duke BO, Vincelette J, Moore PJ, 1976. Microfilaria in the cerebral fluid, and neurological complications, during treatment of onchocerciasis with diethylcarbamazine. *Tropenmed Parasitol 27:* 123–132.
39. Kaiser C, Pion S, Boussinesq M, 2009. Head nodding syndrome and river blindness: a parasitological perspective. *Epilepsia 50:* 2325–2326.
40. Nabbout R, 2012. Autoimmune and inflammatory epilepsies. *Epilepsia 53 (Suppl 4):* 58–62.
41. Johnson T, Tyagi R, Lee PR, Lee M, Johnson KR, Kowalak J, Medynets M, Hategan A, Nutman TB, Sejvar J, Makumbi I, Aceng JR, Dowell, Nath A, 2014. Detection of auto-antibodies to leiomodin-1 in patients with nodding syndrome. *J Neuroimmunol 275:* 103.
42. Marchi N, Granata T, Ghosh C, Janigro D, 2012. Blood-brain barrier dysfunction and epilepsy: pathophysiologic role and therapeutic approaches. *Epilepsia 53:* 1877–1886.
43. Colebunders R, Hendy A, Nanyunja M, Wamala JF, Van Oijen M, 2014. Nodding syndrome—a new hypothesis and new direction for research. *Int J Infect Dis 27:* 74–77.
44. Colebunders R, Post R, O'Neill S, Haesaert G, Opar B, Lakwo T, Laudisoit A, Hendy A, 2015. Nodding syndrome since 2012: recent progress, challenges and recommendations for future research. *Trop Med Int Health 20:* 194–200.
45. Buchmann K, 2014. 'These nodding people': experiences of having a child with nodding syndrome in postconflict northern Uganda. *Epilepsy Behav 42:* 71–77.
46. Coffeng LE, Stolk WA, Zoure HG, Veerman JL, Agblewonu KB, Murdoch ME, Noma M, Fobi G, Richardus JH, Bundy DA, Habbema D, de Vlas SJ, Amazigo UV, 2013. African Programme for Onchocerciasis Control 1995–2015: model-estimated health impact and cost. *PLoS Negl Trop Dis 7:* e2032.