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Environmental, dietary and case-control study of Nodding Syndrome in Uganda: A post-measles brain disorder triggered by malnutrition?

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ABSTRACT

Nodding Syndrome (NS) is an epileptic encephalopathy characterized by involuntary vertical head nodding, other types of seizures, and progressive neurological deficits. The etiology of the east African NS epidemic is unknown. In March 2014, we conducted a case-control study of medical, nutritional and other risk factors associated with NS among children (aged 5–18 years) of Kitgum District, northern Uganda (Acholiland). Data on food availability, rainfall, and prevalent disease temporally related to the NS epidemic were also analyzed. In NS Cases, the mean age of reported head nodding onset was 7.6 years (range 1–17 years). The epidemiologic curve of NS incidence spanned 2000–2013, with peaks in 2003 and 2008. Month of onset of head nodding was non-uniform, with all-year-aggregated peaks in April and June when food availability was low. Families with one or more NS Cases had been significantly more dependent on emergency food and, immediately prior to head nodding onset in the child, subsistence on moldy plant materials, specifically moldy maize. Medical history revealed a single significant association with NS, namely prior measles infection. NS is compared with the post-measles disorder subacute sclerosing panencephalitis, with clinical expression triggered by factors associated with poor nutrition.

1. Introduction

Nodding Syndrome (NS) is an idiopathic brain disorder of children and adolescents in parts of east Africa [1]. The disorder was first recognized in Tanzania where it has been extant for decades among impoverished residents (Wapogoro) of the Mahenge mountains [2–4]. For the past 20–25 years, epidemics of NS have occurred in conflict zones of South Sudan (among the Moru) and in northern Uganda (Acholi) where community disruption has required emergency supplies of food, medicine and seed for planting [5–9]. Preliminary case-control studies led by the World Health Organization in 2002 [5,8] and the U.S Centers for Disease Control and Prevention (CDC) in 2012 found that South/Sudanese children with NS were small for age, stunted, reproductively undeveloped, infected with nematodes (notably *Onchocerca volvulus*, *OV*, in skin but not cerebrospinal fluid by PCR), dependent on home-grown food, and had a history of infant hunger in the first 2 years of life [1,4,10]. Several Moru families had more than one NS-affected child, disease usually starting with vertical nodding (atonic seizure, 10–20/min, elicited most commonly by food but also by cold) in awake and initially responsive children, and evolving over 2–5 years to more frequent nodding and whole-body convulsions, leading to severe wasting, mental retardation, burns, stigmatization, social isolation

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and death [5,8,10]. The epidemic of NS in then-southern Sudan's Western Equatoria Province began in 1991 and peaked in 1998–2001, and affected both male and female children aged 2–19 years (age 9–12 maximally), with onset between 5 and 13 years, with a peak at age 9 [5,8].

In northern Uganda (Acholiland), reports of NS began to appear in 1997 [7,9], with the first recorded cases in Kitgum District in 1998 (Fig. 1). Cases rapidly increased annually beginning in 2001, with peaks in 2003–2005 and 2008, 5–6 years after peaks in the number of wartime conflicts and deaths. Additionally, peaks of NS followed peak influxes 5–7 years earlier of households into internal displacement camps [9]. The 2013 estimated number of probable Ugandan NS Cases was 1687 (95% confidence interval [CI] = 1463–1912), for a prevalence of 6.8 (CI = 5.9–7.7) per 1000 children aged 5–18 years in the three most heavily impacted districts of Kitgum, Lamwo and Pader [11]. Kitgum District, the location of the present study, experienced a NS epidemic between 2000 and 2011 [7,9,12]. A December 2009 study in west Kitgum District, led by the U.S. Centers for Disease Control and Prevention (CDC), estimated a prevalence of 12 (0.6 to 46 cases) per 1000 five- to 15-year-old children [7]. Factors associated with NS in the CDC-led case-control study included a positive *OV* serology, exposure to munitions (later defined as 'gun raids'), and consumption of "crushed roots" used in traditional medicine [7]. The plant species and therapeutic intent were not stated but, in Uganda, the crushed roots of *Cryptolepis sanguinolenta* (Lindl.) Schltr. traditionally are used for treatment of snakebites, hernia and measles [13], the latter representing a potential link with findings reported here.

In March 2014, we conducted a case-control study to evaluate the medical history, environmental exposures and current health of adolescents with NS in Tumangu, southwest of Kitgum Town. We also investigated the temporal onset of head nodding in relation to residence, climate, harvest patterns, food availability, and infectious disease. In contrast to the 2009 CDC-led study, we found evidence of seasonal variation in NS onset and association of NS with prior acute measles infection and consumption of fungus-contaminated plant food immediately before onset of head nodding. Preliminary findings have been reported elsewhere [14,15].

2. Methods

2.1. Setting

The study was set in Tumangu Village, Lamit Parish, Labongo Akwang Sub-County, Kitgum District in northern Uganda (Fig. 1). An isolated, largely rural community, Kitgum District has high levels of poverty, inadequate water and sanitation, and significant disease burden. Child and maternal mortality rates in 2007 were higher than in most parts of Uganda [16]. Between 1987 and 2006/2008, this region was a civil war zone involving the Lords Resistance Army (LRA), the Sudan People's Liberation Army, and the Ugandan Peoples Defence Force. The civil war resulted in human atrocities, including rape, abduction of children, confiscation of livestock, killing of unarmed civilians, and destruction of granaries, schools, hospitals, and bore holes. Beginning in 1996, Acholi civilians were moved into internally displaced peoples' (IDP) camps where many families became dependent on emergency food supplies. Camp life was associated with malnutrition, social breakdown, a rising incidence of mental health disorders and alcoholism. The camps also became breeding grounds for cholera, measles, HIV/AIDS and other preventable diseases. In 2008, following the expulsion of the LRA, the Acholi people began to return to their villages and rebuild their society [17]. After NS was recognized in Acholiland, Uganda registered affected children, established government Screening and Treatment Centers [18] and distributed anticonvulsants and nutritional supplementation to affected children [19].

Fig. 1. Map of Uganda showing Kitgum District; the approximate location of Tumangu Village is marked with a spot. The capital city of Kampala (box) is ~8 h by road from Kitgum, which abuts South Sudan.

2.2. Ethics statement

Study and instrument design were approved by the Institutional Review Board (IRB) of Oregon Health & Science University, Portland, Oregon, USA, in concert with the Research and Ethics Committee of the School of Health Sciences of Makerere University, Kampala, Uganda. The university-approved research plan was reviewed and approved by the Uganda National Council for Science and Technology, the Office of the President of Uganda, and the Chairman, Local Council III, Kitgum District, northern Uganda. The research team worked closely with the Tumangu Village Health Team Leader in carrying out the study in the open air at a central collecting point (large mango tree) in the village.

Parents and or guardians (caregivers) of children gave informed consent on behalf of all child participants. Informed consent for the interview was administered orally and data collected by 5 Ugandan medical students who spoke with household caretakers in the Acholi language under the supervision of an academic physician (D.L.K.) who was born and nurtured near Kitgum Town. IRB-approved oral consent was employed because the caregivers could not read the documents. Oral consent was documented by placement of an inked thumbprint on the consent forms. Caretakers of children were paid for their time the equivalent of U.S. $10.00 in local currency. One copy of the set of executed consent forms was deposited with the Department of Food Technology and Nutrition, College of Agricultural and Environmental Sciences, Makerere University, Kampala, Uganda.

2.3. Case-control study design

NS Cases ($n = 50$) and Community Controls ($N = 50$) were 5 to 18 years of age. NS Cases were defined according to an international consensus definition [6]. Community Controls (CC) drawn from NS-free households in the same community had no history of head nodding or other seizures, including febrile seizures. Randomly selected NS and CC were individually screened and examined by the research team. Each NS and CC was matched both by age ($n = 50$ pairs) and, whenever possible, by both age and sex ($n = 42$ pairs). In addition to the NS Cases included in the study, data were collected for age of onset and year/month of onset (when available) of head nodding in other children with documented NS in households with NS Cases.

2.3.1. Study instrument

A questionnaire directed to parents or caregivers requested a listing of family members, including those with and without NS, and the year and month of the first sign of head nodding in all children with NS in the household. A detailed history of food use by the family was obtained

for the time period immediately before the NS Case first began visible head nodding, or for an equivalent time period for Community Controls, including: the type of food items, quality of major food items, and the relative dietary importance of these items. Additional survey questions for NS and CC included birthdate of the child and prior place(s) of residence. The child's past medical history (prior diseases, history of vaccination) and current health status were reported by the caregiver or parents and described by the absence or presence of the medical condition and clinical manifestations of illness.

2.3.2. Anthropometric data

Each child was measured clothed and barefoot for height and body weight. Weight was measured using a calibrated digital scale. Height was measured using a vertical stadiometer.

2.3.3. Data extraction and analyses

Information was extracted from questionnaires independently by two research team members who then compared the data for consistency and resolved any inconsistencies by mutual agreement and in consultation with the Study Director. Conditional logistic regression was used to screen 57 potential explanatory variables (9 continuous, 3 ordinal and 45 dichotomous) for association with NS. *p*-Values were derived from likelihood ratio (LR) tests and 95% confidence intervals for the odds ratio(s) found by inverting the LR test. Likelihood-based methods were chosen over standard Wald tests/confidence intervals because they exhibit better performance in small samples when asymptotic (Wald) inference may be less reliable. Formal adjustment for multiple testing was not done, as the investigation sought to identify associations of interest rather than test a pre-specified list of targets. Instead, the method of Schweder and Spjøtvoll [20] was used to identify the most promising associations in the collection of all variables considered.

2.4. Environment, food security, and vaccine-preventable disease

Ecological analyses were performed on information drawn from publicly available electronic records. These data included region-specific annual rainfall; ambient temperature; crop planting and harvesting patterns; measures of food security, and emergency food supplies provided by the World Food Programme [21]. The WHO Vaccine Preventable Diseases Monitoring System and data from Doctors Without Borders sourced information on infectious disease in East Africa, notably measles, and vaccination campaigns [22–27].

3. Results

3.1. Nodding Syndrome: year and month of onset

In addition to the 50 NS Cases, 33 other household NS cases were identified, all of whom were reported in households with a NS case. For both NS sets and for the total NS subjects ($n = 83$), year of reported onset of heading nodding spanned 2000–2013, with incidence increasing markedly from 2001 and declining after 2008 (Fig. 2).

When data from 2000 to 2013 were aggregated, the mean month of reported onset of head nodding was similar in the NS Cases (known in 43), other household children with NS (known in 25) and, therefore, the combination of the two (Fig. 3). Combined, NS Cases and other children with NS showed a significant all-year nonrandom distribution of onset throughout the year, with peaks in April and June and no correlation with monthly rainfall.

3.2. Crop production

Using publicly available data from governmental and non-governmental sources, we evaluated the possible impact of environmental factors, specifically food security [21] and crop harvest patterns [24],

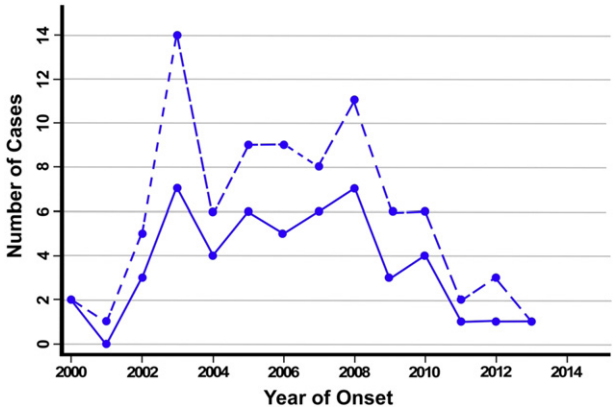

Fig. 2. Semi-bimodal epidemic curve of Nodding Syndrome. For NS Cases enrolled in the NS-CC Case-Control study (solid line; $n = 50$ NS), reported onset of head nodding peaked in 2003 and 2008 ($n = 7$ each), though the incidence was only marginally higher than that in 2005 and 2007 ($n = 6$). For NS Cases plus other household NS Cases (dashed line; $n = 83$), NS onset also peaked in 2003 ($n = 14$) and 2008 ($n = 11$). In both analyses, onset incidence began to decrease after 2008.

during the time of NS onset as reported in our survey questionnaire. While families resided in IDP camps and were provided with emergency food supplies, local cultivation of food crops was sometimes possible during their internment. Analysis of the planting and harvest times for 10 essential staple foods showed the peak months (April/June) of reported head nodding onset corresponded to times when planting was underway or completed for most crops (Fig. 4). The end of the harvest times for sorghum (August), cassava (August), sweet potato (October) and maize (November) suggested that stocks would have been low in April the following year, the month when onset of head nodding first peaked.

Months of reported low crop production by displaced families (March to July) corresponded to periods when feeding the family reportedly was most difficult (Fig. 5). Food storage in IDP camps was poor and prone to wetting and spoilage in the form of mold growth [21].

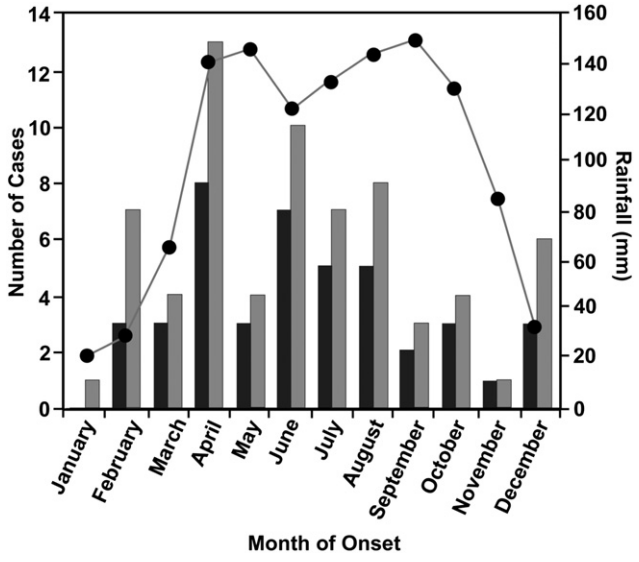

Fig. 3. Reported month of onset of head nodding was non-uniform, with all-year aggregated peaks (2000−2013) that were unrelated to the monthly rainfall pattern in Kitgum (2003−2012). For NS Cases (solid black bars) plus other household NS Cases (patterned bar) ($n = 43 + 25$, respectively), reported NS-onset peaks showed a non-uniform distribution throughout the year ($\chi^2 = 26.131$, df $= 11$, $p < 0.01$). Month of head nodding onset was reported in the 2014 Tumangu survey questionnaire. Rainfall data (filled circles) were collected from the Kitgum District Five Year Plan [28].

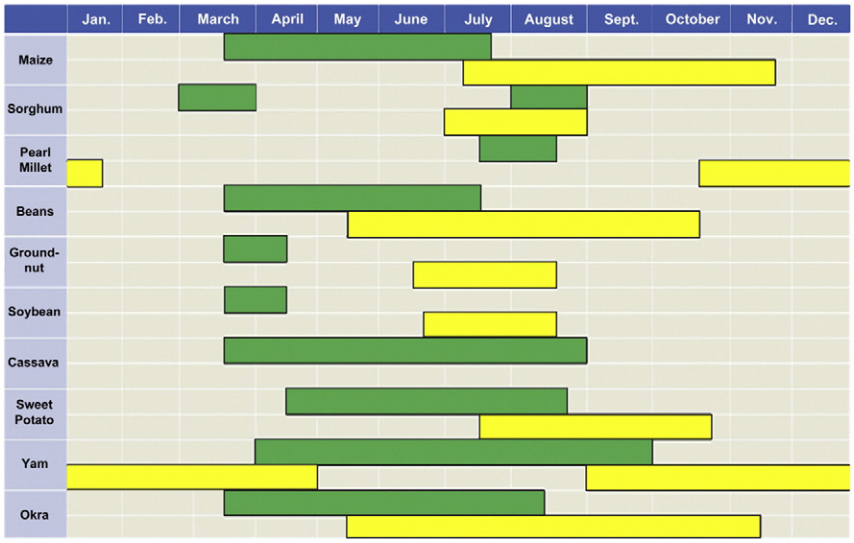

Fig. 4. Harvest patterns for staple foods in northern Uganda. Planting periods (green bars) and harvest periods (yellow bars) for 10 essential staple plant foods in northern Uganda showed an extremely limited number of crops harvested between January and May. Data source: United Nations Food and Agriculture Organization [24].

3.3. Nodding Syndrome Cases vs. Community Controls

3.3.1. Demography and residence

All NS Cases met the consensus definition for NS except for one subject who had onset of head nodding (one year-old) outside the defined age range. NS Cases and CC were similar in age, sex, and family size (Table 1). Males with NS non-significantly predominated over females with NS. Of the 50 NS Cases, the average age when head nodding in the child was first noted by the caregiver was 7.6 years. NS-affected families of up to 8 members had up to 6 (NS Case + 5 other NS-affected) children with Nodding Syndrome.

The child's current body weight showed the strongest association with NS (est. OR = 0.93; 95% CI: 0.87–0.98 per each additional kg, $p = 0.005$) and was the only NS-associated demographic characteristic. Age of the child ($p = 0.091$), weight at birth ($p = 0.865$; $n = 18$ matched pairs), sex ($p = 0.477$) and number of people per household (family size; $p = 0.390$) were not associated with NS. Both NS and CC were equally likely to have lived in an IDP camp ($p = 0.53$), and there was no correlation between prior IDP residence location and NS.

3.3.2. Dietary history and association with NS

Three food-related variables were significantly more frequent for NS than CC: (a) the family consumed emergency food delivered by the World Food Programme (est. OR = 4.00; 95% CI: 1.27–17.6, $p = 0.016$) and, immediately prior to onset of head nodding, (b) the family used maize, including moldy maize (est. OR = 4.00; 95% CI: 1.00–26.5, $p = 0.50$) and (c) used moldy maize for consumption (est. OR = 4.33; 95% CI: 1.40–18.9, $p = 0.009$) (Table 2 and Supplementary Fig. S1) (*vide infra*). The maize consumed reportedly smelled bad and induced diarrhea and vomiting. Use of other common items for food,

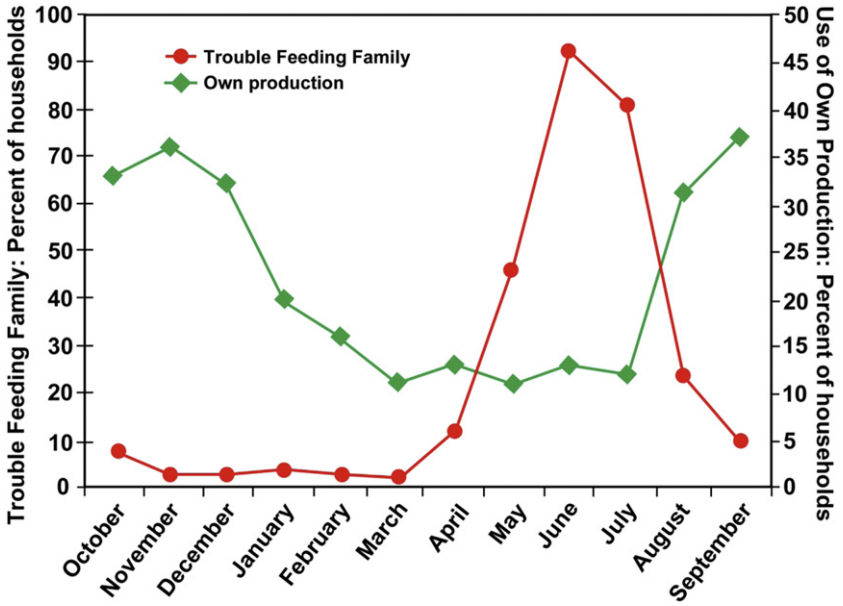

Fig. 5. Food shortages were associated with periods of low crop production. Displaced people in Kitgum District reported months during which they encountered difficulties feeding their families (dots) during periods of low crop production (diamonds). Data were taken from the WFP Food Security Report of Ugandan camps for internally displaced persons [21].

Table 1
Demographic characteristics of Cases of Nodding Syndrome (NS) and Community Controls.

Characteristics	NS Cases	Community Controls	*p*-Value
Total subjects	50	50	
Age (years). Mean ± SD (range)	15.6 ± 1.5 (12–18)	15.4 ± 1.8 (12–18)	0.091
Sex (M:F)	1.4:1	1.6:1	0.477
Family size. Mean ± SD	8.3 ± 3.2	7.8 ± 2.7	0.58
Age at onset of head nodding. Mean ± SD	7.6 ± 3.1	—	—
Number of other NS Cases in household. Mean (range)	1.6 (1–5)	—	—

including moldy plants, showed no significant difference between NS and CC (Table 2).

3.3.3. Medical history and clinical findings

The only difference between NS and CC in the medical history was a caregiver's report of acute measles infection prior to onset of NS (est. OR = 6.00; 95% CI: 1.03–113, $p = 0.047$). Current body weight was significantly lower in NS vs. CC. (Table 3).

NS children were under treatment with sodium valproate, and five subjects reported no head nodding at the time of examination. Six NS Cases reportedly had a history (age unknown) of convulsions associated with fever years before onset of head nodding. Clinical manifestations

Table 2
Dietary factors immediately before onset of head nodding in Nodding Syndrome vs. equivalent time period for Community Controls. Food quality was scored on a Likert scale of 1–5.

Factors	N	OR (95% CI)	χ^2 (df)	*p*-Value
Dietary importance				
Importance of maize in diet	48		χ^2 (2) = 0.51	
# 1 (ref)		1.0		
# 2		0.60 (0.123–2.44)		0.777
# 3		1.00 (0.120–8.33)		
Importance of sorghum in diet	48		χ^2 (2) = 2.00	0.368
# 1 (ref)		1.00		
# 2		0.57 (0.228–1.33)		
# 3		0.29 (0.012 to 3.44)		
Importance of cassava in diet	45		χ^2 (2) = 0.06	0.971
# 1 (ref)		1.00		
# 2		0.91 (0.098–8.46)		
# 3		1.03 (0.122–8.70)		
Importance of bean in diet	22		χ^2 (1) = 2.94	0.086
# 1 (ref)		1.0		
# 2/3		3.50 (0.846–23.5)		
Food quality				
Quality of maize	47	1.25 (0.834–1.93)	χ^2 (1) = 1.15	0.284
Quality of cassava	43	1.58 (0.890–3.20)	χ^2 (1) = 2.38	0.123
Quality of sorghum	47	1.08 (0.755–1.54)	χ^2 (1) = 0.16	0.686
Quality of cowpeas	17	0.96 (0.522–1.73)	χ^2 (1) = 0.02	0.882
Quality of bean	21	0.81 (0.41–1. 61)	χ^2 (1) = 0.36	0.548
Foodstuff use				
Use of any cassava	50	1.5 (0.259–11.4)	χ^2 (1) = 0.20	0.654
Use of any bean	50	1.09 (0.478–2.51)	χ^2 (1) = 0.04	0.835
Use of any cowpeas	50	0.83 (0.36–1.93)	χ^2 (1) = 0.18	0.670
Use of any pearl millet	50	1.22 (0.506–3.03)	χ^2 (1) = 0.20	0.654
Use of any sweet potato	50	0.60 (0.204–1.62)	χ^2 (1) = 1.01	0.315
Use of maize for food	**50**	**4.00 (1.002–26.5)**	**χ^2 (1) = 3.85**	**0.050**
Use of moldy maize	**50**	**4.33 (1.397–18.9)**	**χ^2 (1) = 6.74**	**0.009**
Use of red sorghum	50	1.75 (0.529–6.68)	χ^2 (1) = 0.83	0.363
Use of moldy red sorghum	50	2.20 (0.800–6.98)	χ^2 (1) = 2.31	0.129
Use of white sorghum	50	1.80 (0.831–3.90)	χ^2 (1) = 2.32	0.128
Use of moldy white sorghum	50	1.90 (0.902–4.25)	χ^2 (1) = 2.84	0.092
Use of pearl millet	50	1.71 (0.690–4.61)	χ^2 (1) = 1.33	0.249
Use of moldy pearl millet	50	2.00 (0.777–5.74)	χ^2 (1) = 2.04	0.153
Use of sweet cassava	50	2.00(0.630–7.49)	χ^2 (1) = 1.36	0.244
Use of bitter cassava	50	1.00(0.534–5.29)	χ^2 (1) = 0	1
Use of moldy cassava	50	1.29 (0.479–3.60)	χ^2 (1) = 0.25	0.617
Local produce				
Household grew vegetable	50	2.50(0.539–17.4)	χ^2 (1) = 1.33	0.249
Household gathered vegetable	50	1.33(0.464–4.05)	χ^2 (1) = 0.29	0.592
Household gathered wild fruits	50	1.00(0.342–2.92)	χ^2 (1) = 0.00	1
Household gathered wild roots	50	1.29(0.479–3.60)	χ^2 (1) = 0.25	0.617
Food supplements				
Took vitamin/mineral supplements	49	1.50(0.621–3.83)	χ^2 (1) = 0.81	0.370
Ate taboo foods	50	2.00(0.390–14.4)	χ^2 (1) = 0.68	0.410
Possibly ate plants while unsupervised by adults	50	0.93 (0.431–1.99)	χ^2 (1) = 0.04	0.847
Ate sclerotia	50	1.50(0.541–4.47)	χ^2 (1) = 0.60	0.437
Ate smut	50	0.36(0.101–1.06)	χ^2 (1) = 3.40	0.065
Ate special meals	45	2.60 (0.981–8.10)	χ^2 (1) = 3.68	0.055
Ate food unfit for human consumption	47	1.00(0.459–2.18)	χ^2 (1) = 0.00	1.00
Ate deteriorated food	44	1.33(0.464–4.05)	χ^2 (1) = 0.29	0.592
Ate emergency food supplies	**47**	**4.00 (1.271–17.6)**	**χ^2 (1) = 5.78**	**0.016**
Ate emergency sorghum	32	2.40(0.890–7.54)	χ^2 (1) = 2.97	0.085
Ate (pesticide)-painted seeds	47	2.33(0.936–6.59)	χ^2 (1) = 3.29	0.070

Significant values shown in bold.

Table 3
Association between anthropomorphic data and health status in NS vs. CC.

	N	Odds ratio (95% CI)	χ^2(df)	*p*-Value
Birth weight	18	0.92 (0.332–2.47)	χ^2 (1) = 0.03	0.865
Current body weight	**49**	**0.93 (0.871–0.978)**	**χ^2 (1) = 8.04**	**0.005**
Sex	50	1.67 (0.409–8.12)	χ^2 (1) = 0.51	0.477
Age	50	2.00 (0.909–7.09)	χ^2 (1) = 2.85	0.091
Number of people in household	50	1.06 (0.927–1.23)	χ^2 (1) = 0.74	0.390
Hx of prior illness	50	1.83 (0.698–5.32)	χ^2 (1) = 1.49	0.222
Hx. of urinary infection	50	0.71 (0.308–1.60)	χ^2 (1) = 0.67	0.413
Hx. of diarrhea	50	0.80 (0.305–2.03)	χ^2 (1) = 0.22	0.637
Malaria	50	0.93 (0.431–1.99)	χ^2 (1) = 0.04	0.847
Hx. of ear/nose/throat infection	50	0.25 (0.013–1.69)	χ^2 (1) = 1.93	0.165
Hx. of measles	**50**	**6.00 (1.025–113)**	**χ^2 (1) = 3.96**	**0.047**
Hx. of chicken pox	50	0.50 (0.023–5.22)	χ^2 (1) = 0.34	0.560
Hx. of any other illness	50	1.50 (0.541–4.47)	χ^2 (1) = 0.60	0.437
Hx. of oral lesions	50	0.50 (0.023–5.22)	χ^2 (1) = 0.34	0.560
Received deworming	40	0.83 (0.352–1.93)	χ^2 (1) = 0.18	0.670
Received Ivermectin	40	1.00 (0.390–2.56)	χ^2 (1) = 0.00	1.00
Prior residence in IDP camp	50	0.67 (0.170–2.33)	χ^2 (1) = 0.40	0.526

Significant values shown in bold.

Table 4
Prevalence of clinical and behavioral features among NS Cases.

Clinical and behavioral features	*N* (%)
Clinical signs:	
Fixed gaze/staring	26 (52%)
Uncoordinated limb movements	17 (34%)
Drooling saliva (mouth open)	25 (50%)
Disorientation	27 (54%)
Episodes of loss of consciousness	19 (38%)
Localized facial or limb movements	4 (8%)
Generalized convulsions	18 (36%)
Perceptual disturbances (before/after fits)	27 (54%)
Aggressive behavior	24 (48%)
Wandering	14 (28%)
Sleep pattern:	
Normal sleep	13 (26%)
Lacks sleep	5 (10%)
Excessive sleep	23 (46%)
Bad dreams	9 (18%)
Change in appetite:	
Normal appetite	18 (36%)
Reduced appetite	14 (28%)
Increased appetite	18 (36%)
Emotion (most of the time):	
Feels normal	17 (34%)
Feels sad	22 (44%)
Feels anxious/fearful	6 (12%)
Feels excited	5 (10%)
Predominant thoughts/preoccupations:	
Normal thoughts	22 (44%)
Worried	26 (52%)
Thoughts of dying/self-harm	2 (4%)
Social interaction:	
Good	26 (52%)
Poor/no social interaction	24 (48%)
Functional deficits and injuries	
Mental impairment	30 (61%)
Visual impairment	2 (4%)
Gait ataxia	5 (10%)
Inability to walk	1 (2%)
Feeding and swallowing difficulties	1 (2%)
Behavioral difficulties	10 (20%)
Cognitive and learning difficulties	32 (64%)
Speech difficulties	11 (22%)
Difficulty with activities of daily living	11 (22%)
Injuries and burns	5 (10%)

associated with NS reported by caregivers included: altered sleep patterns (74%), including excessive sleep (46%), bad dreams (18%), and lack of sleep (10%); mental impairment (61%); disorientation (54%); fixed gaze/staring (52%); drooling saliva (50%); aggressive behavior (48%); emotional problems (56%); episodes of loss of unconsciousness (38%); uncoordinated limb movements (34%); wandering (28%); behavioral disability (20%); and localized facial or limb movements (8%). Furthermore, caregivers reported cognitive impairment (60%), ataxia (10%), visual difficulty (4%) and inability to walk (2%) among NS Cases (Table 4).

At the time of examination, subject history of reported treatment with ivermectin, antimalarials and deworming medication was similar in NS and CC. Reported vaccination was also similar (mostly >90%) for poliomyelitis, tetanus, diphtheria, pertussis and tetanus (DPT), and measles (Table 5). Whether the vaccination was recent or otherwise was not determined.

4. Discussion

4.1. Main findings

Study results show that between 2000 and 2013, the community of Tumangu village, Kitgum District, northern Uganda, experienced a semi-bimodal NS epidemic, with apparent peaks in 2003 and 2008 and all-year mean monthly maxima in April and June, the latter corresponding to a nadir in production of crops used as staple foodstuffs and peak difficulty in feeding families. Immediately prior to the first appearance of head nodding, there was a greater nutritional dependence by NS vs. CC on emergency food supplies, including moldy plant products, particularly moldy maize. NS Cases were reported to have a normal birth weight but, on examination in March 2014, exhibited a lower body weight than healthy Community Controls perhaps arising from poor nutrition and/or social neglect. On average, a child with NS had more than one and sometimes multiple NS-affected siblings suggestive of familial stressors, such as nutritional and/or infection.

Caregiver report of prior measles illness was significantly higher in children with NS vs. CC, although 2014-reported immunization rates for measles and other infectious diseases were similar (but somewhat lower in NS). These children were all born (dob: 1996–2002) during the conflict period (1996–2006/8), when food variety and quality were poor, measles immunization was absent (until 2002/3) and, consequently, acute measles infection rates were very high (1998–2002, vide infra). Immunization for infectious diseases must have occurred during or after the tail end of the conflict (circa 2006). Below, we examine the hypothesis that the etiology of NS arises from an interaction between early-age measles infection and malnutrition.

Table 5
2014 vaccination status, nutritional supplements, and anti-parasitic medications.

	Group	Proportion received
Polio	NS Cases	93%
	Community Controls	96%
Tetanus	NS Cases	51%
	Community Controls	59%
Measles	NS Cases	95%
	Community Controls	98%
DTP	NS Cases	95%
	Community Controls	98%
Antimalarial	NS Cases	24%
	Community Controls	20%
Ivermectin	NS Cases	76%
	Community Controls	77%
Vitamin A	NS Cases	76%
	Community Controls	88%
Deworming	NS Cases	68%
	Community Controls	75%

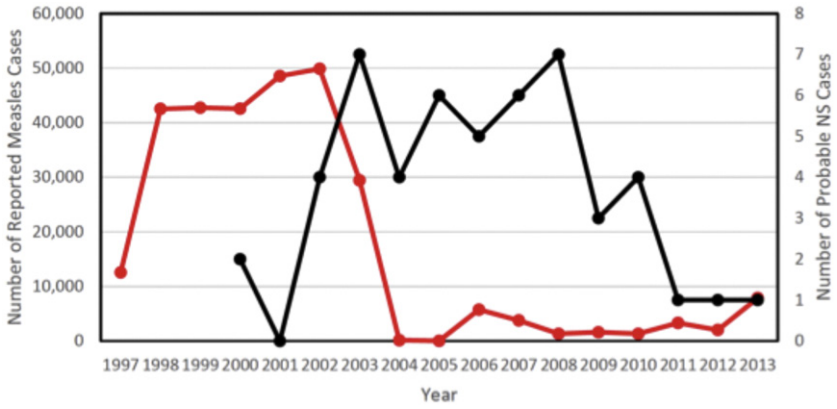

Fig. 6. Measles epidemic (Uganda) preceded the NS epidemic (Tumangu, northern Uganda). Onset peak of NS (right-side trace) from 2003 to 2008 followed the onset peak of reported measles incidence in Uganda (left-side trace) from 1998 to 2002. World Health Organization data show that measles cases in Uganda rose dramatically in 1997 through 2003 (>40,000 cases/year) when, in 2003, the United Nations called for a warfare truce to permit measles vaccination in northern Uganda, with rates dropping precipitously countrywide by 2004. Data source: WHO Vaccine Preventable Diseases: Monitoring System. 2014 Global Summary [22]. Doctors without Borders also carried out a measles-vaccination campaign (exact location unstated) in September 2004 covering 20,000 children under the age of five [23]. NS incidence data were taken from March 2014 Tumangu survey.

4.2. Measles virus and Nodding Syndrome

Age-matched NS and CC subjects showed a single significant difference in medical history, namely a caregiver's report of prior measles infection OR 6.0 (95% CI 1.025–113, $p = 0.047$). Five years earlier (December 2009) in west Kitgum, a CDC-led case-control study of NS [7] comprising 49 cases (55% males, mean age 11.6 years) *unmatched* for age to 49 village controls (44% males, mean age 8.5 years, $p > 0.001$), found that self-reported measles was also significantly higher among NS Cases (OR 4.0, CI 1.1–14.2); however, the association with measles was lost when subjects were matched for age post hoc [7].[5]

Given that two independent studies of NS in Kitgum District have identified a case association with prior measles infection, it is imperative to consider the possibility that NS is a type of post-measles brain disorder of which several are known. Measles is endemic in Uganda, more common in children under age 5, with higher mortality rates among immunocompromised and malnourished subjects. Measles is a major cause of infant death in populations lacking immunization. In Uganda, the acute measles incidence was very high between 1998 (~45,000 cases) and 2002 (~50,000 cases), dropping precipitously thereafter to baseline levels, with small elevations in 2006 and 2013 (Fig. 6). The geographical distribution of these cases is uncertain, but the marked reduction of cases from 2002 onward accords with the vaccination campaign undertaken in northern Uganda towards the cessation of regional hostilities. By 2011, regional measles vaccination coverage across Acholiland was reported to be 90% (2/3rd of whom held vaccination cards) among 9- to 59-month-old children, above the national target of 85% [30]. This accords with present data showing similarly high reported vaccination percentages for NS (95%) and CC (98%). However, for future studies, it should be noted that a survey conducted by the Uganda Ministry of Health and World Health Organization in the first 6 months of 2005 revealed that a considerable proportion of children in Kitgum District (34.5%) and Pader District (19.9%), two heavily NS-affected populations of Acholiland, had no written evidence of measles vaccination [31].

4.3. Nodding Syndrome: a post-measles brain infection?

4.3.1. Comparative epidemiology of measles-NS and measles-SSPE

Among those who survive measles infection as infants, ~3 of every 10 cases experience complications that may include the tardive brain disorder subacute sclerosing panencephalitis (SSPE) [32]. SSPE is a rare but well studied progressive 'slow viral' disease caused by persistent brain infection with defective measles virions that most often surfaces clinically 6–8 years after an acute measles illness [33]. SSPE usually affects children aged 5–13 years, sometimes involving males more than females. By comparison, the mean age of onset of NS in Tumangu village was 7.6 ± 3.1 years, and both this and the preceding CDC study included a preponderance (55%) of males among the randomly selected NS Cases [7]. Thus, NS and SSPE affect children of similar proportionate sex and age.

The incidence of NS in Tumangu peaked 5–6 years (2003–2008) after the peak incidence of measles (1998–2002), and the post-immunization drop to near zero cases of measles (2004) preceded by 7 years a precipitous drop in cases of NS (Fig. 6). By comparison, the mean period from acute measles infection to SSPE onset (latency) is 4–10 years [34–36]. In Israel in the 1960–1970s, peaks for the incidence of measles and SSPE were separated by 7–9 years. Measles vaccination begun in 1967 resulted in a dramatic reduction of SSPE and increased onset age from 7 years in 1966 to 17 years in 1986 [35,36]. Subsequently, in Germany, the incidence peaks for cases of childhood (under 5 years) measles (1993–2001) and SSPE (2002–2009) were separated by 8–9 years [36,37]. Taken in concert, therefore, the latency period between acute measles infection and SSPE matches the temporal separation between peaks of measles and NS in Uganda.

4.3.2. Clinical features of NS vs. SSPE

There are numerous similarities in the clinical features of patients with NS and SSPE. The clinical course of NS in Ugandan children has been described [38], and later stages have been documented in longstanding Tanzanian patients [9]. Importantly, one third (11/33) of the latter subjects (and 7/50 in the present study) had a history of febrile seizures in infancy consistent with (but not specific for) acute measles infection [4]. Both NS and SSPE have an insidious afebrile onset, with behavioral changes (notably irritability) and intellectual deterioration, followed by myoclonus, typically beginning with the head [5,8,33,39,40]. Unpublished data from the World Health Organization (WHO)

[5] Multiplex Polymer Chain Reaction (PCR) analyses for 19 families of viruses, plus measles virus, performed on cerebrospinal fluid (CSF) of 16 NS cases and zero controls, was reportedly negative across the board [7,3]. Since CSF samples of 14 tested cases with "a high clinical likelihood of head nodding" and no controls were also negative for protein (normal value: 14–45 mg/dL) and low in glucose (7–1 vs. a normal value of 40–70 g/dL), the biological integrity of the CDC-study samples may have been sub-optimal. Because the study site in Kitgum District is in a remote location, lacks dry ice and refrigerated transport, it is challenging to maintain biological samples in optimum condition required for measles antibody assays according to CDC guidelines [29]. Samples collected in the CDC study were analyzed in Atlanta, GA, approximately 30 h travel time from the collection site. While we would have faced similar technical challenges, our study design did not include the collection of cerebrospinal fluid or blood for viral analyses.

study of NS in then-southern Sudan show the first reported sign among cases was usually head nodding (53/87), half of which evolved to head nodding and seizures, while the balance either began and continued with both (7/87), or began with seizures (27/87) and later added head nodding (6/27) (K. Vandermaele et al., unpublished data, 2002). Similarly, SSPE may be present with generalized seizures [41–43]. Partial seizures and generalized tonic-clonic seizures occur in both diseases.

Head nodding corresponds with atonic seizures in African children in both NS [2] and SSPE [44]. Detailed description of myoclonic head nods in a black female African child with measles virus D3 serotype-associated SSPE is described by Vardas and associates [45]. Canadian children with head drops early in SSPE are described and illustrated by Campbell and colleagues [35]. Head nodding may occur on awakening and is exacerbated by excitement in SSPE [33,46], and triggered by the sight of food, eating and cold in NS [8]. This suggests the brain is in a "proconvulsive" state in both NS and SSPE. Signs of, sleepiness, stupor, catatonia, muscle weakness, speech disturbance and sudden falls are reported in both SSPE and NS [33,38,47–49]. With the advance of SSPE, myoclonus may decrease or disappear, spasticity with pyramidal and extrapyramidal signs becomes apparent, and a few develop ataxia, dystonia and dyskinesia [33]. Similarly, ataxia, hyperreflexia and parkinsonian signs are described in longstanding cases of NS [4]. Unusually cold lower extremities have been reported in Sudanese and Ugandan children with NS [5,38] while, in advanced stages of SSPE, loss of thermoregulation causes marked core temperature fluctuations [33]. Progressive cognitive decline leading to dementia and mutism is described in both disorders [33,38,48]. Ocular and visual manifestations, including papilledema, optic atrophy and choreoretinitis, cortical blindness) affect a minority of patients with SSPE [33], mostly those with adult-onset brain disease [49]. Formal ophthalmological assessment of children with NS is awaited, the results of which would have to be considered in relation to the potential visual effects (River Blindness) of infection with *O. volvulus*. Two NS children in the present study reportedly had visual difficulty.

Magnetic resonance imaging (MRI) of brains in SSPE and NS also show overlap. Whereas many studies have documented SSPE sequentially, few MRI images are available for NS. The brain may be unremarkable initially but can progress to severe atrophy in both conditions [38,50]. In SSPE, abnormalities reflecting loss of myelin are more commonly seen bilaterally or asymmetrically in the occipital subcortical white matter than in the frontal region. Jagtap and Kambale [51] found gray as well as white matter changes in the parieto-occipital area, followed by involvement of the fronto-parietal region. By comparison, in NS brains with generalized cortical atrophy, Idro and colleagues [38] noted "a suggestion of more atrophy in the occipital lobes or the parieto-occipital regions than anteriorly". Basal ganglia, thalamus, cerebellum and brainstem are less commonly involved in SSPE [52,53]. Cerebral and cerebellar atrophy has been noted in NS [38,54].

4.3.3. Survival period and other features of NS vs. SSPE

NS is a progressive epileptic encephalopathy which, when untreated in the setting of wartime then-southern Sudan, was reported by local informants to have a ~3-year downhill course and fatal outcome (P. Spencer, unreported data). Adequate nutrition and treatment with anticonvulsants (valproic acid) greatly reduces seizure activity, markedly improves health, but fatalities occur and life expectancy of treated NS patients is unknown [1]. Some Tanzanian patients survived for 1–3 decades (mean = 12.6 years) after onset of head nodding [4]. By comparison, SSPE patients often have a rapid downhill course to death (1–3 years), with a fatal prognosis in 95% of patients. However, less aggressive forms are recognized [55], and the course of SSPE is sometimes variable and unpredictable [56]. Remission or halting of disease progression occurs spontaneously in 5% of SSPE cases. Remission may be temporary, lasting weeks to years [57,58]. A disease course beyond 5 years is unusual but a few SSPE cases survive for up to 12–14 years [59,60]. A 17 year-old Indian female who developed SSPE and underwent progressive neurological deterioration experienced a substantial spontaneous clinical and electroencephalographic remission that was maintained for at least 8 years [61]. In Colombia, two patients with SSPE returned to almost normal intellectual function after having a typical clinical course and electroencephalographic picture, and after being in a vegetative state for several weeks. Another patient recovered from a vegetative state and was left with moderate mental retardation and minimal motor sequelae. A further seven patients survived in a severe state of decortication without further progression [62]. In sum, the temporal course of SSPE and NS overlaps.

The neuropathology of NS has yet to be described but crystalline inclusions of unknown significance have been described by CDC (letter from Dr. Wun-Ju Shieh to Ruth Aceng, Uganda Director-General of Health Services) in histological sections of the pons (viewed using polarized light) of autopsied brains of 5 NS children aged 12–15 years [18,63]. The neuropathology of SSPE is stage-dependent (mild inflammation to gross atrophy) and characterized by measles antibody-positive intranuclear and intracytoplasmic eosinophilic inclusion bodies [64], and tau- and ubiquitin-positive neurofibrillary tangles [65], with typical involvement of the brainstem and elsewhere [33,49]. By transmission electron microscopy, the eosinophilic inclusions correspond to paracrystalline arrays of measles nucleocapsids [66]. There is an urgent need to determine if the crystalline inclusions of NS correspond to viral nucleocapsid inclusions.

While the foregoing epidemiological, clinical and imaging observations raise the possibility that NS is a post-measles SSPE-like disorder, demonstration of this putative association requires evidence of measles antibody in cerebrospinal fluid, a compatible electroencephalographic (EEG) picture (which is stage-dependent in SSPE), and immunocytochemical demonstration of paracrystalline neuronal and glial cell inclusions positive for the measles virus genome. It is noteworthy that oligoclonal bands in cerebrospinal fluid, typical of CNS infectious diseases including SSPE [67], have been reported in NS [68]. The few EEG observations in NS have demonstrated severely abnormal background activity with interictal diffuse slowing, as well as spike-and-wave and polyspike and wave epileptiform discharges [3,54,69,70].

4.4. Trigger and seasonality of Nodding Syndrome

The differential monthly/seasonal timing of reported onset of head nodding showed all-year mean peaks in April/June when local crop production was at its lowest (March to July) and food shortage at its peak (June). For people crowded in IDP camps of Kitgum District, there was a significant association between NS and family use of emergency food supplies (OR 4.0 CI 1.29–12.40, $p = 0.016$) and poor quality food immediately prior to the first sign of head nodding. Might such factors be related to reactivation of a putative latent brain measles virus? The interplay between the measles virus and human hosts is well studied at the population level [71] but the trigger for SSPE is unknown [72]. Measles epidemics show regular patterns that are modified by human activity, such as the seasonal crowding of children in primary schools [73]. Illustrative of seasonal differences of measles [74], April and May are the peak months for measles (H1a genotype) in Shanghai, China [75]. In the context of many less developed countries, general seasonal drivers, including agricultural cycle and associated droughts and famines, are likely to play a more significant role [76]. Perhaps these observations are relevant not only to the timing of acute infectious measles but also to the reemergence of latent measles infection in the form of SSPE and, perhaps, NS.

How measles virus in brain is reactivated to trigger progressive neurological disease years after primary measles infection is unknown [77]. The question is broadly relevant to neurotropic viruses, including those of the herpes family. Exposure to certain chlorinated solvents has been proposed to activate latent ganglionic *Herpes simplex* virus and thereby trigger trigeminal neuralgia [78]. Among herpes labialis-prone African

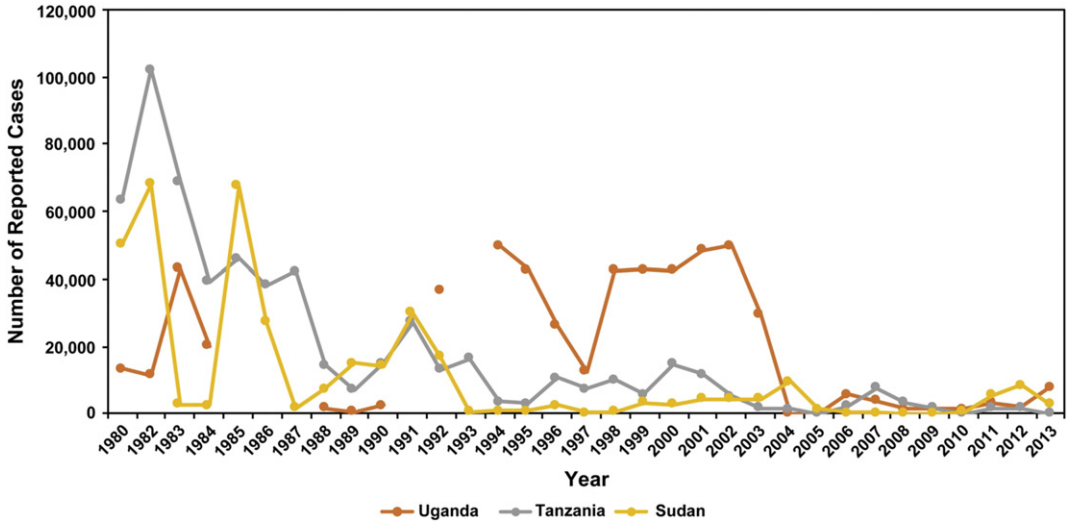

Fig. 7. Cases of measles in Uganda, Tanzania, and Sudan 1980–2013. Number of reported cases in 1980: <20,000 (Uganda), <60,000 (Sudan) and >60,000 (Tanzania). Data from country-specific WHO Vaccine-preventable Diseases Monitoring System [25–27].

dental healthcare providers, the major triggers of disease are fever-inducing infections (malaria), stress and fatigue [79]. In the case of herpes virus 4 (Epstein Barr virus, EBV), physical and psychological stressors associated with spaceflight resulted in decreased virus-specific T-cell immunity and reactivation of EBV [80]. Additionally, the mycotoxin aflatoxin B1 reactivates the EBV cycle and triggers pro-carcinogenic mechanisms that culminate in Burkitt's lymphoma [81]. Aflatoxin and other immunosuppressive mycotoxins contaminate maize in east Africa [82], exposure to aflatoxin is ubiquitous among rural Ugandans [83], and the present study found NS case association with moldy maize at onset of head nodding. Thus, it is plausible that a latent mutant measles virus sequestered in the brains of future NS Cases could have been reactivated by nutritional deprivation and/or mycotoxin-induced immunosuppression. Another risk factor associated with NS in this population is stress arising from violent wartime activities [7,9,84].

4.5. Measles and NS in east Africa

4.5.1. South Sudan

World Health Organization (WHO) measles incidence data for the NS-affected countries of Uganda [25], Tanzania [26] and Sudan [27] are shown in Fig. 7. In war-torn Sudan, where epidemic NS preceded that in northern Uganda by ~10 years, measles immunization was exceptionally low in the 1990s [85,86] and immunization supplies dropped drastically during the period of conflict. Reported cases of measles peaked in 1982 (~70,000 cases), 1985 (~70,000 cases) and 1991 (~30,000 cases) before dropping to low levels (<10,000 cases per annum) from 1992 to 2013. In then-southern Sudan, recorded cases of measles dropped from nearly 2000 to below 100 per annum between 2006–2010 and, during this period, infant and under-five mortality rates decreased from 102 to 84 and 135 to 106 per 100 live births, respectively [27,28]. The first cases of NS were reported in 1991, 6–9 years after peak incidence of measles cases countrywide, the timing of which fits with the appearance of a post-measles brain disorder akin to SSPE.[6]

[6] However, in 2002, two of us (J.T., P.S.) participated in a WHO outbreak investigation of Nodding Syndrome in southern Sudan that found a significant inverse relationship between a reported history of measles and NS [5,8]. We cannot explain this result other than to note that measles infection of infants < age 1 year (the age for high risk for post-measles brain complications) may go unrecognized [8]. Possible differences in measles vaccination history were also not obtained in the southern Sudan study [5].

The most striking yet puzzling finding of the WHO-led 2002 NS disease outbreak investigation in then-southern Sudan was the high prevalence of head nodding in the sessile Moru subsistence farmers and the complete absence of the disorder in itinerant Dinka pastoralists. An initial hypothesis focused on nutrition [87], the Dinka having access to milk, blood and meat, and their practice of prolonged infant nursing, while the Moru generally lacked livestock, hunted and gathered wild plants seasonally, and cultivated rain-fed plants grown in communal gardens which, during periods of internal displacement, likely suffered in quality, including mold infestation [8]. In the present study in neighboring northern Uganda, we found a significant temporal relationship between onset of head nodding and family dependence on moldy plant products, in particular moldy maize (*Zea mays*) which, in Uganda and other sub-Saharan countries, contains immunosuppressive aflatoxin and fumonisin mycotoxins [88–90]. While these agents might have a role in the clinical expression of NS (vide supra), it has also long been recognized that malnutrition-induced immunocompromise increases susceptibility to infectious agents, including measles paramyxovirus [91].

4.5.2. Paramyxoviridae and NS susceptibility in east Africa

4.5.2.1. Measles and related viruses. Measles in primates, distemper in canines and rinderpest in ruminants, are caused by closely related enveloped paramyxoviruses of the genus *Morbillivirus*. These viruses are highly infective, spread via the respiratory route, induce profound immune suppression, and cause large disease outbreaks with high mortality. Cross-immunity among susceptible species is known; for example, dogs that feed on rinderpest-infected meat can acquire immunity against rinderpest virus and canine distemper virus [92] and measles vaccination offers protection of dogs from canine distemper [93]. Within the *Morbillivirus* genus, measles virus is hypothesized thousands of years ago to have crossed the species barrier from cattle to primates/humans [94].

4.5.2.2. South Sudan. Rinderpest was endemic in then-southern Sudan during the time of the 2002 WHO-led NS-outbreak study. Animal health services before the war and in the period of peace (1972–1983) were not effective, such that endemic rinderpest was not controlled. Vaccination campaigns (1992–2001) reduced the number of rinderpest outbreaks from 12 in 1993 to 2 in 1998, with eradication by 2005 [95,96]. Thus, prior to the 1991 outbreak of NS, and for many years thereafter, there was a high probability the Dinka (unlike the Moru) would have

been exposed to cattle harboring or clinically affected by the rinderpest virus. Since the rinderpest virus is very closely related to the human measles virus, the Dinka could have acquired cross immunity to measles in the same way that British physician-scientist Edward Jenner, FRS (the 18th Century "Father of Immunology") noted that milkmaids who acquired cowpox (a mild disease) developed immunity to smallpox [97]. If the Dinka acquired protection from measles virus, and NS is a post-measles disorder, this would explain why Dinka children were spared NS at the time of the WHO-led disease investigation in 2002. However, rinderpest-acquired protection from measles would be expected to decline and disappear (with rinderpest eradication) by 2005; thereafter, newborn children of Dinka families would be at risk for measles infection and, thus putatively, for NS. In accord with this point, living cases of NS among Dinka people were reported at the 2nd International Conference on Nodding Syndrome held in Gulu in July 2015 [1].

4.5.2.3. Uganda. A 1990–98 survey of rinderpest identified the northeast of Uganda as a high-risk region with low seroprevalence. Risk factors for outbreaks of rinderpest included cattle raids [98] that, during the period of civil conflict, were widely practiced in Acholiland by the LRA. The resulting depletion of non-LRA members of the population (the large majority) from potential contact with cattle, especially during periods of internal displacement, would have excluded exposure to rinderpest virus and possible acquisition of cross-immunity to measles. By contrast, LRA-related children, none of whom is known to have developed NS, would have had a much higher potential exposure to cattle, including those harboring or expressing the rinderpest virus. Only one of our study members, an 18-year-old female CC, reported spending time with the LRA.

4.5.2.4. Tanzania. There is little information with which to assess risk factors for NS among the isolated Pogoro people of the Mahenge highlands in Tanzania [3]. In World War 1, Mahenge was held as a military garrison by Germany, which had zero tolerance for cattle infected by rinderpest [99]. Head nodding in this population was reported as early as 1934 [4], with the first clinical descriptions in the 1960s [2,3]. At this time, the Wapogoro were subsistence farmers who cultivated maize and millet, lacked food storage systems, and did not keep livestock [99]. Subject to periodic famine, they were plagued by a combination of malnutrition, avitaminosis, protein deficiency, severe parasitic (including *OV*) infestation, anemia and epilepsy [100]. Outbreaks of measles in the vicinity are also recorded [101]. By the turn of the century, only 65% had received measles vaccine by age one year [102], the age of acute infection that carries the maximum risk for post-measles SSPE. In sum, therefore, the NS-susceptible Pogoro people of Tanzania show parallels with the NS-susceptible Moru (vide supra) given their probable common lack of exposure to rinderpest-prone ruminants, susceptibility to measles, and dependence on rain-fed plants subject to spoilage and fungal contamination.

4.6. Nodding Syndrome and Onchocerciasis

An alternative etiologic hypothesis for NS focuses on the significant case-association with *Onchocerca volvulus (OV)*, a nematode and cause onchocerciasis, some cases of which develop visual deficits (i.e. River Blindness) [7,103]. While the current study did not evaluate this hypothesis, two of the authors (P.S, J.T.) participated in the 2002 WHO-led case-control study of NS in then-southern Sudan that first reported the NS-*OV* association [5,8]. The association was later found in the 2009 CDC study of NS in west Kitgum District [7]. *OV* is also prevalent in the longstanding focus of NS in Mahenge Tanzania [104] and speculation on the potential etiologic role in NS of infection with *OV* and/or the *OV* symbiotic bacterium *Wolbachia*, continues [18,105]. However, the *OV* hypothesis suffers from (a) the presence of active *OV*-related disease in NS-free regions of sub-Sahara, Central and South America, and in many neurologically normal controls used in case-control studies, (b) the absence of *OV* infection in a small percentage of NS Cases in Uganda [15,68], and (c) the negative results of independent PCR analyses for *OV* in the CSF of Sudanese and Tanzanian children with NS. Neurological illness (vertigo, headache and vomiting) in onchocerciasis arises from the side effects of anti-filarial drug treatment targeted at microfilariae in cerebrospinal fluid [5,106] which itself does not offer protection from head nodding. Additionally, the peaks of head nodding onset in April and June reported here do not correlate with seasonal human 'biting' activity of OV-infective black flies in nearby northeastern Uganda [105, 107].

We note that acute measles infection severely suppresses the immune system for 2–3 years [108], thereby increasing the risk for persistent all-cause opportunistic infection [108–110], such as the establishment of persistent *OV* infection. While the dermatological features of *OV* infection often contribute to the clinical picture in NS [5], we interpret *Onchocerca volvulus* to be a bystander in Nodding Syndrome, not the cause of this devastating, possibly measles-associated brain disease. Resolving this issue is important because planned treatment trials of Ugandan children are based on an hypothesis that NS is a neuroinflammatory disorder induced by *OV* or *Wolbachia* antibodies cross-reacting with host neuron surface proteins [18]. It should be noted there are many causes of neuroinflammatory disorders, including post-measles SSPE, a progressive inflammatory brain disease.

4.7. Study limitations

1. Recall bias. The case-control study results heavily depend on the accurate recall of caregivers. All caregivers were living with the NS case at the time of head-nodding onset. All CC lived in households with no NS case. One NS had no CC. Other household cases of NS were reported by the caregiver and confirmed in government case records held by the Village Health Team Leader.
2. Accuracy of the reported month of onset of head nodding. Since head nodding may be preceded by a prodromal period [6], the actual month of clinical onset of NS may have preceded the reported date of disease (head nodding) onset.
3. Duration, dosage and currency of treatment of NS Cases with anti-seizure medication were not determined. Valproic acid is usually well tolerated but serious complications (including hyperammonemic encephalopathy) may occur [111] and, if present, would have affected reported clinical signs.
4. This study was designed as an exploratory effort to generate testable etiologic hypotheses, which could possibly have led to false-positive associations in the absence of adequate statistical power.

4.8. Study strengths

This is one of the few controlled studies to evaluate the etiology of a neglected epidemic of a potentially fatal brain disease that places hundreds of thousands of individuals in Sub-Saharan Africa at-risk. The study was conducted in the community and the villages affected by NS; transportation to and from the village study site was provided for all the subjects participating in the study. This decreased the selection bias associated with differential participation of individuals with increased disabilities due to a higher burden of NS. This is the first study of NS in Uganda that evaluated the diet of subjects. Use of a structured questionnaire decreased the ascertainment bias of food and nutritional exposures.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jns.2016.08.023.

Conflict of interest

None.

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