Research Article

Aetiologies and therapies of nodding syndrome: a systematic review and meta-analysis

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Background

Nodding syndrome (NS) is a childhood epileptic disorder of unknown aetiology confined to parts of South Sudan, Uganda and the United Republic of Tanzania. Patients suffer from atonic seizures that result in characteristic head nodding, and may develop other neurological, endocrinological and psychiatric manifestations. The objective of this study was to adopt a non-judgemental approach to review the hypothesised aetiologies and therapeutic options available for NS. To explore the reported association between NS and *Onchocerca volvulus* (OV) a meta-analysis of the prevalence of OV among NS cases and controls was performed.

Methods

Systematic searching of five electronic databases yielded 26 articles that addressed potential aetiologies of NS and 12 that explored the treatment of NS.

Results

Nine articles contained data about the prevalence of OV in NS cases that was suitable for inclusion in the meta-analysis. Four broad aetiological themes were identified. 1) Nutritional associations included biomarkers of malnutrition and conflicting reports regarding the consumption of some foodstuffs. 2) Regional conflict and the associated psychological trauma have led to consideration of psychiatric aetiologies. 3) There is a strong epidemiological association between NS and *Onchocerca volvulus*. The meta-analysis in this study revealed that 68.0% (95% confidence interval (CI)=45.2-87.0) of 416 NS patients were OV+, compared to 46.6% (95% CI=16.4-78.1) of 321 controls. Heterogeneity among both cases ($I^2=95.5\%$, 95% CI=93.3-97.0) and controls ($I^2=97.1\%$, 95% CI=95.5-98.2) was high. The difference of 21.4% in OV prevalence between the pooled populations was significant ($P<0.0001$). It is thought that NS represents a form of onchocerciasis-associated epilepsy, however there are also reported associations with *Mansonella pestans* and measles virus. 4) Autoantibodies against leiomodulin-1 and the voltage-gated potassium channel have been associated with NS. Molecular mimicry between leiomodulin-1 and *O. volvulus* tropomyosin is a recently suggested aetiology. Without a clear aetiology treatment is symptomatic and patients have been shown to improve with a combination of anti-epileptic medication and supportive therapy.

Conclusions

The aetiology of NS remains unclear. The leading theory is that NS represents a form of onchocerciasis-associated epilepsy secondary to autoimmunity driven by molecular mimicry. Alternatively, it has been suggested that NS may represent a post-infectious sequelae of measles virus infection. However, each theory currently leaves some questions unanswered. It remains important to understand the aetiology of NS to better prevent or treat future outbreaks.

Nodding syndrome (NS) is a neurological condition of unknown aetiology confined to parts of the United Republic of Tanzania (URT), South Sudan and Uganda. The characteristic head nodding that gives the syndrome its name

was first recorded as a symptom of epilepsy in the URT in 1965 and retrospective analysis has found evidence for possible cases as early as 1934.^{1,2} However, it was not until

Table 1. Nodding syndrome case definition criteria. Adapted from Idro et al.⁵

A suspected case:	Reported head nodding in a previously normal person; head nodding was defined as repetitive, involuntary drops of the head to the chest on two or more occasions. This case definition is used at the community level.
A probable case is a suspected case with:	Both of the following major criteria:
	-Age at onset of nodding between 3 and 18 years old
	-Frequency of nodding 5 to 20 per minute
	Plus at least one of the following minor criteria:
	-Other neurological abnormalities (cognitive decline, school dropout due to cognitive/behavioural problems, other seizures or neurological abnormalities)
	-Clustering in space or time with similar cases
	-Triggered by food and/or cold weather
A confirmed case is a probable case plus a documented nodding episode that is:	-Stunting or wasting
	-Delayed sexual or physical development
	-Psychiatric symptoms
	Observed by a trained healthcare worker or recorded on film or on EEG/EMG.

epidemics of NS were later recorded in South Sudan and Uganda in the 1990s and 2000s that NS attracted attention.

NS primarily affects children aged 5 to 15.³ Patients experience progressive neurological, and in some cases endocrinological, dysfunction; case definition criteria are shown in [table 1](#).⁴ The extent of mortality directly associated with NS remains unclear. Anecdotal evidence has suggested that the greatest risk to NS patients may come from incidental deaths occurring during seizures.⁴ Seizures are initially atonic although other forms, including myoclonic, absence and generalised tonic-clonic seizures can manifest at later stages of the disease.⁵

A range of possible aetiologies have been suggested for NS, including associations with diet and nutrition, *Onchocera volvulus* (OV), *Mansonella pestans*, measles virus and autoantibodies as well as psychogenic causes.^{4,6–8} The most recent hypothesis is that NS may represent an autoimmune consequence of molecular mimicry between the autoantigen leiomodin-1 (LM-1) and OV tropomyosin.⁸ Despite the lack of a definitive aetiology, the term ‘onchocerciasis-associated epilepsy’ (OAE) has emerged in the literature.⁹ OAE refers to NS alongside other forms of epilepsy with postulated links to OV infection. These include Nakalanga syndrome, documented in Uganda, Burundi and Ethiopia, and other forms of epilepsy, some of which have been documented with head nodding but not confirmed as cases of NS.^{10,11} There is increasing evidence for OAE, with a recent prospective study demonstrating an association between skin microfilarial density and later risk of seizures or epilepsy.¹² With the exception of a syndrome described in Mexico in 1938,¹³ OAE has thus far only been identified in Africa. No NS cases have been reported beyond the URT, South Sudan or Uganda and no new epidemic cases have been recorded since 2013.¹⁴

Without a defined aetiology, therapeutic approaches to NS have been forced to take a symptomatic approach, with guidelines published in 2013.⁵ A comprehensive programme of pharmacological, physical, speech, language,

nutritional and mental health therapy has been shown to improve the condition of NS patients.¹⁵

Given recent developments regarding the potential aetiology of NS,⁸ and a shift towards the phrase OAE in the literature, a systematic review and critique of the proposed aetiologies and therapies of NS and a meta-analysis of the prevalence of OV among NS cases compared with controls is warranted. To maximise the evidence retrieved for non-judgemental appraisal the systematic searches in this review were conducted without restriction on intervention, comparison or study design.

METHODS

Systematic searches were conducted on 21 June 2018 using five electronic databases: EMBASE (1980–2018), Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE® (1946–2018), Global Health (1973–2018), Web of Science and BIOSIS Citation Index (1926–2018). The Web of Science Core Collection Citation Indexes searched were: Science Citation Index Expanded (1900–2018), Conference Proceedings Citation Index- Science (1990–2018), Book Citation Index— Science (2005–2018) and the Emerging Sources Citation Index (2015–2018). Each database was searched using the terms ‘nodding syndrome’ OR ‘nodding disease’ OR ‘luc?luc’, without restriction on language, study date or design. For databases that used the Ovid platform (MEDLINE, EMBASE and Global Health) each of these terms were followed by the suffix ‘.ti,ab.’, instigating a search of the title and abstract. The term ‘nodding syndrome’ was also searched as a medical subject heading. For databases accessed through the Web of Science platform, each of the three terms above were searched as topics. Additional manuscripts were identified using manual searching.^{16–20}

SELECTION OF STUDIES

Deduplication was performed using Endnote (version X8.0.1) and Zotero (version 5.0.47). All studies underwent

title and abstract screening. Studies were deemed eligible if they were available in English and explicitly addressed NS. Studies which addressed the broader field of OAE and did not explicitly examine NS were excluded. Studies deemed eligible by title and abstract screen were accessed in full-text. Presentation abstracts were deemed to exist as full-text. Thereafter articles not containing primary data regarding the aetiology or treatment of NS were excluded. Studies which could not be accessed in full-text and did not state sufficient information in the abstract were excluded. Studies reporting primary data reported elsewhere were excluded. Both title and abstract and full-text screening were performed independently by two authors (JDJ, HJS), with discrepancies resolved by agreement. To minimise bias, studies eligible for the meta-analysis contained data from which the prevalence of OV in ≥ 10 NS patients or, if available, ≥ 10 controls could be calculated. This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,²¹ and a PRISMA checklist completed (Appendix S1 in the **Online Supplementary Document**). A study protocol was not published prior to this study.

DATA EXTRACTION AND RISK OF BIAS

The following information was extracted from each eligible study: author(s), publication date and title, journal name, study location, date, design and case/control population sizes, key findings and prevalence data for meta-analysis if available. The risk of bias was assessed using the appropriate critical appraisal tool from the suite offered by the Joanna Briggs Institute.²² Pre-study randomised controlled trial (RCT) protocols were not subject to critical appraisal.

STATISTICAL ANALYSIS

A random-effects meta-analysis was performed to calculate the pooled prevalence (with 95% confidence intervals (Cis)) of OV microfilariae in skin snips taken from NS patients compared to controls. Study heterogeneity was assessed by the I^2 statistic, reported with 95% CIs, and interpreted as low ($\leq 25\%$), moderate (25–75%) and high ($\geq 75\%$).²³ All meta-analyses were conducted using the ‘meta-analysis of proportions’ function on MedCalc version 18.0 (MedCalc Software, Ostend, Belgium) which uses an arcsine square root transformation to calculate the weighted summary proportion.²⁴ The significance of proportions was compared using the MedCalc N-1 χ^2 calculator.

RESULTS

STUDY SELECTION AND CHARACTERISTICS

[Figure 1](#) illustrates the study selection process. The systematic search yielded 377 articles; five additional articles were identified from review articles and manual searches.^{16–20} The titles and abstracts of the 161 articles that remained following deduplication were screened, and a further 40 articles excluded. Of the remaining 121 articles accessed in full-text, 82 were excluded because: they were not primary literature (n=42), the full-text was inaccessible (n=21) or they did not contain relevant (n=16) or new (n=3) data. The

final 39 studies included 26 that explored potential aetiologies of NS and 13 that explored treatment of NS. Nine studies contained data suitable for meta-analysis of the prevalence of OV among NS cases and controls. These studies formed the core of the review and were supplemented by wider primary and secondary literature.

The selected articles ranged in date from 2008 to 2018 and included studies from South Sudan (n=4), Uganda (n=22), the URT (n=5), the Democratic Republic of Congo (n=1) and the United States of America (n=1). Study details and key findings are shown in [Table 2](#) and [Table 3](#) for aetiological and therapeutic perspectives respectively. The outcome of critical appraisal of the included studies and the list of studies that were excluded are included in Appendices S2 and S3 in the **Online Supplementary Document** respectively. Critical appraisal revealed a range of shortcomings in reporting across the eligible studies which, while important to highlight, were not considered to indicate bias sufficient to warrant exclusion.

THE AETIOLOGY OF NS

Appraisal of the data extracted from the 26 articles which investigated theoretical aetiologies of NS^{7,8,16,17,25–44} revealed four broad aetiological themes which form the basis of this review: metabolic, infectious, autoimmune and psychiatric associations.

METABOLIC

Many of the populations where a high incidence of NS was recorded had experienced recent conflict and food shortages and often became reliant on relief food. Aid deliveries were regularly disrupted, sometimes resulting in the delivery of mouldy food, often consumed nonetheless. A correlation was identified between the peaks in NS cases and upsurges in conflict and food shortages, with a temporal disparity of 5–7 years.³⁵ Moreover, it has been reported that there were no cases of NS in Ugandan conflict zones in which people had not been moved into internally displaced persons (IDP) camps, but instead cases appeared after the establishment of the IDP camps, supplied by relief food. This led to the hypothesis that the rise in NS cases may have been linked to the consumption of specific foodstuffs regularly supplied in the IDP camps.^{16,17,40}

Four case-control studies have provided mixed conclusions regarding the association between consumption of (spoiled) relief foods and NS.^{6,7,36,41} Tumwine and colleagues were the first to suggest an association with food, specifically serena, a type of red/brown sorghum.⁷ However, further analysis of these data confirmed no association with cassava consumption.⁴⁰ Later, Spencer and colleagues found positive associations with the consumption of maize, mouldy maize or relief food.⁴¹ Obol and colleagues also subsequently identified an association with the consumption of relief food.³⁶ However, it has been suggested that recall bias over approximately eight years, and the attribution of blame by those affected to the Ugandan government and international organisations, may have influenced the results obtained by Spencer and colleagues.⁴⁵ In contrast, Foltz and colleagues identified an association with the

Table 2. Studies examining the aetiology of nodding syndrome

Citation	Publication date	Title	Study location	Study date	Study design	Cases	Controls	Key finding(s)	Journal
43	2008	The head nodding syndrome - clinical classification and possible causes of a new epilepsy disorder	Tanzania	N/A	Cohort	62	-	90.3% had at least one relative with epilepsy. Association with OV: 31/51 SS and 12/20 PCR were OV+. CSF PCR negative (0/48).	Neurology
26	2012	Nodding syndrome - South Sudan	South Sudan	2010	Case-control	38	38	NS associated with OV+ SS. Total study figures included Maridi and Witto communities. Among the 25 Maridi matched pairs, 88% of cases vs 44% of controls were OV+. No significant OV association between the 13 Witto pairs.	Morbidity and Mortality Weekly Report
7	2012	Clinical and epidemiologic characteristics of nodding syndrome in Mundri County, southern Sudan	South Sudan	2001-02	Case-control	82	81	No association with MV: 2/13 NS patients had a history of MV vs 11/19 controls. Association with OV: 76/82 NS patients had OV+ SS vs 39/81 controls. HN triggered by food (73% of 39 cases). Association with serena (sorghum): OR=6.22; P=0.049. Association with MP: OR=3.22; P= 0.05.	African Health Sciences
6	2013	An epidemiologic investigation of potential risk factors for nodding syndrome in Kitgum District, Uganda	Uganda	2009	Case-control	49	49	No association with MV or sorghum. Serological association with OV, exposure to munitions (AOR=13.9 [1.4-135.5]), consumption of crushed cassava roots (AOR=5.4 [1.3-22.1]), visual hallucinations (AOR=13.6 [1.5-121.7]) and vitamin B6 deficiency (84% cases, 75% controls). Matched serological AORs for Ov16 and OvFAR/MSA were 3.16 (0.84-11.89) and 20.80 (1.37-316.24)	PLoS One

Citation	Publication date	Title	Study location	Study date	Study design	Cases	Controls	Key finding(s)	Journal
								respectively.	
29	2013	Nodding syndrome in Ugandan children-clinical features, brain imaging and complications: a case series	Uganda	2012	Case series	22	-	MRI and EEG findings described. 12/22 NS patients had psychiatric morbidities. A 57% reduction in total seizure burden was achieved with sodium valproate.	BMJ Open
33	2013	Nodding syndrome (NS) in Northern Uganda: a probable metabolic disorder	Uganda	2012	Case-control	101	101	NS associated with malnutrition, OV and a high anion gap.	British Journal of Medicine and Medical Research
38	2013	Clinical, neurological, and electrophysiological features of nodding syndrome in Kitgum, Uganda: an observational case series	Uganda	2009	Case series	23	-	MRI, CSF and EEG findings described. No evidence of inflammation found.	Lancet Neurology
2	2013	Nodding syndrome: origins and natural history of a longstanding epileptic disorder in sub-Saharan Africa	Tanzania	1960-71	Retrospective	150	-	Historical evidence for probable NS cases with onset between 1934 and 1962.	African Health Sciences
40	2013	Nodding syndrome in Mundri county, South Sudan: environmental, nutritional and infectious factors	South Sudan	2001/2012	Case-control			Analysis of data from Tumwine and colleagues 2012. Adds no association with cassava consumption.	African Health Sciences
44	2013	MRI findings in people with epilepsy and nodding syndrome in an area endemic for onchocerciasis: an observational study	Tanzania	N/A	Cohort	12	20	MRI findings described. Cerebral pathology associated with OV (SS/PCR). Control group was OCE patients.	African Health Sciences
27	2014	Nodding syndrome in Tanzania may not be	Tanzania	N/A	Case-control	22	8	Controls=7 healthy, 1 OCE. No evidence for NMDA or VKGC	African Health Sciences

Citation	Publication date	Title	Study location	Study date	Study design	Cases	Controls	Key finding(s)	Journal
		associated with circulating anti-NMDA- and anti-VGKC receptor antibodies or decreased pyridoxal phosphate serum levels-a pilot study						autoantibodies. No association with pyridoxal-phosphate serum levels.	
31	2014	Detection of auto-antibodies to leiomodrin-1 in patients with nodding syndrome	N/A	N/A	Case-control	19	19	Anti-LM-1 Ig was detected in the serum of 11/19 NS patients and 5/19 controls. Anti-LM-1 identified in the CSF of an unreported number of NS patients, shown to be neurotoxic <i>in vitro</i> and cross-react with OV tropomyosin. LM-1 expression shown in CNS regions comparable with reported MRI findings.	Journal of Neuroimmunology
34	2014	High anion gap metabolic acidosis among children with nodding syndrome (NS) in Northern Uganda: case series	Uganda	2012	Case series	10	-	Of the 10 probable NS cases all had hypocalcaemia, raised bicarbonate and a high anion gap suggestive of metabolic acidosis.	British Journal of Medicine and Medical Research
35	2014	Nodding syndrome in Kitgum District, Uganda: association with conflict and internal displacement	N/A	N/A	Retrospective	N/A	N/A	Retrospective analyses suggested that conflict and movement of people into IDP camps were associated with rises in NS 5-6 and 7 years later respectively.	BMJ Open
37	2014	Physical growth, puberty and hormones in adolescents with nodding syndrome; a pilot study	Uganda	N/A	Cross-sectional	10	-	Endocrinological analysis suggestive of pituitary growth and gonadal hormone axis dysfunction. 5/8 NS patients had stunting, 8/8 had a normal serum GH level, but 3/8 had low IGF1/IGFBP3. Thyroid, adrenal, parathyroid, prolactin levels were normal.	BMC Research Notes
32	2015	Nodding episodes	Uganda	N/A	Case report	1	-	Report of a 13-year-old male	British Journal of

Citation	Publication date	Title	Study location	Study date	Study design	Cases	Controls	Key finding(s)	Journal
		and high anion gap in a 13-year-old child with nodding syndrome: a case report						with probable NS and pyomastitis, as reported in Kitara 2013. Adds temporal association between an elevated anion gap and the presence of seizures.	Medicine and Medical Research
39	2015	Nodding syndrome: an epileptic disorder restricted to Africa?	N/A	2014	Case-control	50	50	Much data available in Spencer and colleagues 2016. This adds that mycotoxin analysis of plasma and urine found no difference between cases and controls.	Journal of the Neurological Sciences
30	2016	Is nodding syndrome an Onchocerca volvulus-induced neuroinflammatory disorder? Uganda's story of research in understanding the disease	N/A	2013	Case-control	31	11	Review, included as it contains data not published elsewhere. 15/31 NS patients vs 1/11 controls were anti-VGKC Ig positive.	International Journal of Infectious Diseases
36	2016	Reduced plasma concentrations of vitamin B6 and increased plasma concentrations of the neurotoxin 3-hydroxykynurenine are associated with nodding syndrome: a case control study in Gulu and Amuru districts, Northern Uganda	Uganda	2013	Case-control	66	73	Low plasma vitamin B6 (AOR=7.22, $P=0.001$), raised 3-HK (AOR=4.50, $P=0.0130$), child being cared for by mother only (AOR=5.43, $P=0.011$), child being cared for by guardian (AOR=5.90, $P=0.019$) and consumption of relief food at weaning (AOR=4.05, $P=0.021$) were associated with NS.	Pan African Medical Journal
42	2016	Nodding syndrome: 2015 international conference report and Gulu Accord	N/A	N/A	Mixed	N/A	N/A	Report from the 2015 international conference on NS. Results presented, not found elsewhere, include a case-control study ($n=39$ and 41 respectively) that associated low household income and not purifying	eNeurologicalSci

Citation	Publication date	Title	Study location	Study date	Study design	Cases	Controls	Key finding(s)	Journal
								water with NS. A cross-sectional study investigating the psychiatric and psychological features of 225 Ugandan NS patients, the majority of cases (51.6% male, 48.4% female) started HN in IDP camps between 2005-10. Psychiatric disorders included major episodic depression (25.3%), PTSD (16.4%), GAD (30.7%) and PDD (4%).	
41	2016	Environmental, dietary and case-control study of nodding syndrome in Uganda: a post-measles brain disorder triggered by malnutrition?	Uganda	2014	Case-control	50	50	Onset of NS peaked in 2003 and 2008, primarily in April and June. Eating emergency food (OR=4.0 [1.3-17.6], p=0.016), maize (OR=4.00 [1.0-26.5]), mouldy maize (OR=4.33 [1.4-18.9], p=0.009) and a history of MV (OR=6.00 [1.03-113], p=0.047) were associated with NS.	Journal of the Neurological Sciences
25	2017	Metabolic analysis of children affected with nodding syndrome in north Uganda: A pilot study	Uganda	2014	Cohort	48	-	Much data available in Denis and colleagues 2017. This study adds clinical biochemistry findings. 37/47 had low biotinidase. Mean BMI was 16.9. Mean acetyl carnitine level was low. Propionyl carnitine and butyryl carnitine levels were elevated.	Developmental Medicine and Child Neurology
17	2017	Is there a line between internal displacement; environmental and dietary factors in the onset of nodding syndrome in northern Uganda? A clinical observational study design	Uganda	2014	Cohort	48	-	Duration of stay in IDP camps and being in a family in which the firstborn had NS were strongly associated with NS.	World Journal of Pharmaceutical and Medical Research

Citation	Publication date	Title	Study location	Study date	Study design	Cases	Controls	Key finding(s)	Journal
28	2017	Nodding syndrome: multimycotoxin case-control study in Northern Uganda	Uganda	2014	Case-control	50	50	Analysis of plasma and urine samples from Spencer and colleagues 2016. Mycotoxins were detected in 14% and 12% of NS and control cases respectively; concluded the mycotoxin burden was similar.	Annals of Neurology
8	2017	Nodding syndrome may be an autoimmune reaction to the parasitic worm <i>Onchocerca volvulus</i>	N/A	N/A	Case-control	55	55	Added data for a further 36 cases and controls to the data from Johnson 2014, giving 55 matched pairs. Of the NS cases, 80% were OV+ and 52.7% were anti-LM-1 Ig+. Of the controls, 45.5% were OV+ and 30.9% were anti-LM-1 Ig+. The finding that anti-LM-1 Ig to be neurotoxic <i>in vitro</i> and cross-react with OV tropomyosin was confirmed. LM-1 expression shown in CNS regions comparable with reported MRI findings. 8/16 CSF samples from NS patients were anti-LM-1 Ig+, compared to 0/8 North American controls.	Science Translational Medicine
16	2018	Could nodding syndrome in Northern Uganda be a form of autism	Uganda	2014	Cohort	?	?	Much data available in Denis and colleagues 2017. This study conjectures that NS may be akin to ASD.	Pan African Medical Journal

3-HK - 3-hydroxykynurenine, AOR - adjusted odds ratio, ASD - autism spectrum disorder, BMI - body-mass index, CNS - central nervous system, CSF - cerebrospinal fluid, EEG - electroencephalogram, GAD - generalised anxiety disorder, GH - growth hormone, HN - head nodding, IDP - internally displaced persons, Ig - immunoglobulin, IGF1 - insulin-like growth factor 1, IGFBP3 - Insulin-like growth factor-binding protein 3, LM-1 - leiomodin-1, MP - *Mansonella pestans*, MV - measles virus, MRI - magnetic resonance imaging, NMDA - N-methyl-D-aspartate, NS - nodding syndrome, OCE - other convulsive epilepsy, OR - odds ratio, OV - *Onchocerca volvulus*, Ov16 and OvFAR/MSA are OV antigens, PCR - polymerase chain reaction, PDD - pervasive developmental disorders, PTSD - post-traumatic stress disorder, SS - skin snip, VGKC - voltage-gated potassium channel

Table 3. Studies examining therapeutic options for nodding syndrome

Citation	Publication date	Title	Study location	Study date	Study design	Cases	Controls	Key finding(s)	Journal
75	2013	Pyomyositis in Nodding syndrome (NS) patient--a case report	Uganda	N/A	Case report	1	-	Pyomyositis in a probable NS case. Seizures treated with sodium valproate.	The Pan African Medical Journal
52	2013	Neuropsychiatric perspectives on nodding syndrome in northern Uganda: a case series study and a review of the literature	Uganda	N/A	Case series	6	-	NS patients may have histories of psychological trauma, and comorbidities including PTSD, DTD and depression. Treatments included CBZ or PHB and sometimes imipramine, with mixed results.	African Health Sciences
15	2014	Patients with nodding syndrome in Uganda improve with symptomatic treatment: a cross-sectional study	Uganda	2013	Cohort	484	476	Controls were patients with OCE. Treatment according to the 2013 guidelines resulted in 25% of NS patients being seizure free. >70% had a reduced seizure frequency. Emotional and behavioural difficulties resolved in 59%. 86/484 children who had not previously been able to attend school could now do so. 83.1% achieved independence in basic self-care.	BMJ Open
76	2014	A longitudinal study on nodding syndrome--a new African epilepsy disorder	Tanzania	2009	Cohort	62	-	Longitudinal follow-up study on Winkler and colleagues 2008. HN decreased in 11, increased in 2, did not change in 4 and stopped in 15 of 32 patients treated with PHB. Of the 15, 13 still had GTCS. HN stopped in 3 patients treated with CBZ, all continued to have GTCS.	Epilepsia
78	2015	Catatonia in	Uganda	N/A	Cross-	33	-	16/33 patients met	BMC Research

Citation	Publication date	Title	Study location	Study date	Study design	Cases	Controls	Key finding(s)	Journal
		Ugandan children with nodding syndrome and effects of treatment with lorazepam: a pilot study			sectional			diagnostic criteria for catatonia. Lorazepam administration reduced the severity of catatonia symptoms in 10 of 16 patients, and by more than 50% in 6.	Notes
48	2015	Evaluation and immunomodulatory treatment at the NIH of children with nodding syndrome from northern Uganda	USA	N/A	Case series	3	-	Abstract only available. 3 related NS patients were examined. CSF from 1/3 had oligoclonal bands, another had partially identical bands in CSF and serum. Biomarkers for pyridoxine-responsive seizures were absent in all. Mt DNA was normal. 2/3 were given plasmapheresis, 1/3 was given IVIG, all were given pyridoxine. No HN episodes recorded, 1/3 had multiple seizures.	Neurology
77	2015	Neurophysiological and clinical findings on nodding syndrome in 21 South Sudanese children and a review of the literature	South Sudan	2012-13	Case series	21	-	18 probable cases, 3 confirmed. Clinical and EEG findings described. None achieved good seizure control with CBZ monotherapy (n=9) or in combination with PHB (n=9) or PHT (n=3).	Seizure-European Journal of Epilepsy
11	2015	Case report: nodding syndrome, Western Uganda, 1994	Uganda	1994	Case report	1	-	Description of NS in a 15-year-old male from an OV endemic area in an area of Western Uganda not previously associated with NS. Treatment with PHB did not achieve long-term seizure control.	American Journal of Tropical Medicine and Hygiene
72	2016	Health seeking behaviours among	Uganda	2013	Cross-sectional	249 caregivers	-	78.3% of caretakers sought help from a health	PLoS One

Citation	Publication date	Title	Study location	Study date	Study design	Cases	Controls	Key finding(s)	Journal
		caretakers of children with nodding syndrome in Pader District - Northern Uganda: a mixed methods study						facility, 50% with a delay of at least one month. 12.9% sought help from traditional healers and 8.8% self-medicated.	
73	2016	An exploration of caregiver burden for children with nodding syndrome (lucluc) in Northern Uganda	Uganda	N/A	Qualitative	54 caregivers	-	Caregivers have a high burden of care and associated emotional agony, anxiety for their patient's safety and own risk of burnout, face social isolation and stigmatisation and homicidal and suicidal ideations were recorded.	BMC Psychiatry
83	2017	Ivermectin treatment in patients With onchocerciasis-associated epilepsy: protocol of a randomized clinical trial	Democratic Republic of Congo	2017-ongoing	Randomised controlled trial protocol	N/A	N/A	Protocol for a RCT in OV+ epilepsy patients, comparing immediate and delayed (after 4 months) ivermectin treatment. All patients will receive AEDs.	JMIR research protocols
19	2018	Treatment and rehabilitation outcomes of children affected with nodding syndrome in Northern Uganda: a descriptive case series	Uganda	2012	Retrospective	32	-	13 months of nutritional and multivitamin supplementation reduced the incidences of severe or moderate wasting (9.7% to 2.6% and 19.7% to 2.6% respectively) and severe and moderate stunting (combined 54.8% to 12.8% and 7.7% respectively). AED therapy for 29 cases was detailed, although reduction in seizure frequency not clearly reported. Higher seizure frequency associated with female gender or febrile	Pan African Medical Journal

Citation	Publication date	Title	Study location	Study date	Study design	Cases	Controls	Key finding(s)	Journal
82	2018	Setting up a clinical trial for a novel disease: a case study of the doxycycline for the treatment of nodding syndrome trial - challenges, enablers and lessons learned	Uganda	2015	Randomised controlled trial protocol	115	115	illness. NS patients will be given 6 weeks of doxycycline (100mg/day) or a placebo. Primary outcome: % of patients with anti-LM-1 Ig at 24mo post-treatment.	RCT protocol (NCT02850913)

AED - anti-epileptic drug, CBZ - carbamazepine, CSF - cerebrospinal fluid, DTD - developmental trauma disorder, EEG - electroencephalogram, GTCS - generalised tonic-clonic seizure, HN - head nodding, Ig - immunoglobulin, IVIG - intravenous immunoglobulin, LM-1 - leiomodion-1, mo - month, Mt - mitochondrial, NS - nodding syndrome, OCE - other convulsive epilepsy, OV - *Onchocerca volvulus*, PHB - phenobarbitone, PHT - phenytoin, PTSD - post-traumatic stress disorder, RCT - randomised controlled trial

Figure 1. PRISMA flow diagram illustrating study selection.

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

consumption of crushed cassava roots, but did not identify strong associations with the consumption of red sorghum or spoiled relief food.⁶ Notably, the consumption of certain cyanogenic plants, including sorghum and cassava, on the background of a protein-deficient diet has been linked to outbreaks of neurotoxic disease, albeit apparently not reminiscent of NS.⁴⁰

It has also been postulated that mycotoxin-driven immunosuppression might have contributed to the NS outbreak, but mycotoxin levels have been shown to be similar between cases and controls^{28,39} and the distribution and clustering of cases does not appear to reflect an association with meals.⁴⁶

Aside from the consumption of specific foodstuffs, the disruption of food security, food shortages and associated starvation have also been linked to the aetiology of NS. Several studies have investigated the presence of biomarkers for chronic malnutrition in NS patients. Vitamin B6 deficiency is known to cause abnormal tryptophan metabolism, leading to excessive production of 3-hydroxykynurenine which is known to be neurotoxic.⁴⁷ Obol and colleagues studied 66 Ugandan cases and found that significantly lower

vitamin B6 levels and high levels of 3-hydroxykynurenine were strongly associated with the presence of NS.³⁶ In contrast, Foltz and colleague's earlier study of 42 Ugandan cases did not identify any significant association between NS and vitamin B6 deficiency.⁶ Moreover, a Tanzanian case-control study, which compared 22 NS patients to seven controls and one patient with generalised epilepsy, also failed to find an association between NS or epilepsy and vitamin B6 deficiency.²⁷ A large anion gap, indicative of metabolic acidosis, has been observed in 112 NS patients across a case report, case series and case-control study.^{32–34} However, this likely reflects the patient's nutritional state, which could explain associations with a history of residence in IDP camps.³⁴ It has also been suggested that this metabolic acidosis may reflect underlying mitochondrial dysfunction^{32–34}; however, analysis of three cases did not detect any aberrations in mitochondrial DNA.⁴⁸ The serum biotinidase and acetyl carnitine levels of 47 Ugandan NS cases were found to be abnormally low,²⁵ generating speculation that NS may represent the influence of metabolic disruption upon the central nervous system (CNS),¹⁶ as has been hypothesised for autism-spectrum disorders.^{49–51} Vitamin D

deficiency has also been noted among NS patients, and could reflect more time spent indoors due to stigmatisation, the use of anticonvulsants or an aspect of the condition itself.³⁷

PSYCHIATRIC

Many children had horrific experiences during the conflicts that ravaged parts of Uganda and South Sudan in the 1990s and 2000s, while the URT remained comparatively stable. Psychiatric aetiologies for NS have therefore been considered and a sub-classification of 'NS psychiatric' (negative EEG and EMG findings), 'NS neurological' (positive electroencephalogram [EEG] and electromyograph [EMG] findings), 'NS mixed' and 'NS atypical' was proposed.⁵² However, detailed EEG analysis of two patients has demonstrated that head nodding episodes represent atonic, not 'pseudo', seizures.³⁸ Musisi and colleagues found that many NS patients had complex psychiatric morbidities, some with a form of post-traumatic stress disorder known as developmental trauma disorder, and visual hallucinations were also reported.⁵² A 2013 case series of 22 patients by Idro and colleagues found that 12/22 had psychiatric morbidities including hallucinations (n=6), aggression (n=5) and other behavioural problems (n=4).²⁹ An association between NS and visual hallucinations was also reported in a 2009 case-control study by Foltz and colleagues, but no association was found with the abduction of a family member or auditory hallucinations.⁶ In contrast, a recent case series involving 48 NS patients found no association between NS and visual hallucinations.²⁵ Unpublished results from a 2016 cross-sectional study of 225 NS patients found that 'the majority' began head nodding in the IDP camps and also found that associated psychiatric comorbidities included depression, generalised anxiety disorder, post-traumatic stress disorder and pervasive developmental disorder.⁴² In a 2018 case series of 32 NS patients that had been resident in IDP camps, parents reported depression (50% of cases), aggression (48.1%), loss of appetite (39%) and anxiety (14.3%); 23.1% of these NS patients reported suicidal thoughts.¹⁹

It has been reported that for some patients episodes of head nodding may be spontaneous or triggered by cool temperatures, the offer of food, hyperventilation or sleep.^{29,38,53} Remarkably, head nodding has been reported to be triggered by the consumption of local, but not imported, foodstuffs.⁷ The psychological and neurological triggering of head nodding episodes requires greater investigation, and may contribute to the pathophysiological understanding.

INFECTIOUS ASSOCIATIONS

There has been a consistent epidemiological association in the literature between NS and the filarial nematode OV.^{6,10,30,43,54} An association with another filarial nematode, *Mansonella pestans* (MP), has also been reported.⁷ There are two predominant theories regarding the role of filarial infection.

The first is that OV infection indirectly leads to NS via an autoimmune aetiology (see below). Cases of NS have thus

far only been identified in areas endemic for OV.⁵⁵ Temporal, familial and geographical clustering have been observed,^{56,57} for example limited mapping of NS cases has revealed clustering around watercourses, compared with other forms of epilepsy.³⁰ Regional conflict has also caused disruption of OV elimination programmes, and may have resulted in increased prevalence.⁵⁶ Moreover, regions in which community-directed treatment with ivermectin and larviciding of major watercourses have been reinstated have experienced a substantial drop in NS cases.^{58,59}

Nine and six studies contained skin snip and/or polymerase chain reaction (PCR) data about the prevalence of OV among NS patients and non-epileptic controls respectively (Table 4). Among these studies there was limited, but conflicting, evidence about the association of ivermectin treatment with the prevalence of NS specifically.^{7,33} We found that four of the six studies that contained OV prevalence data about both NS patients and controls identified a statistically significant difference between both populations, however many of these studies used small sample sizes. To mitigate against this we performed random-effects meta-analyses to examine the prevalence of OV among NS cases and controls. Among a pooled population of 416 NS patients we found that 68.0% (95% CI=45.2-87.0) were OV+ (Figure 2). Among a pooled population of 321 control subjects 46.6% (95% CI=16.4-78.1) were OV+ (Figure 3). Both results were significant but there was a high level of heterogeneity among both cases ($I^2=95.5\%$, 95% CI=93.3-97.0) and controls ($I^2=97.1\%$, 95% CI=95.5-98.2). The difference of 21.4% in OV prevalence between the pooled populations was significant ($P<0.0001$).

Despite the strong association with the presence of microfilariae in the skin, and magnetic resonance imaging (MRI) evidence of gross neurological lesions in some NS patients, to date evidence of microfilariae in the cerebrospinal fluid (CSF) of NS patients has not been forthcoming.^{4,6,7,38,40,43} A 2010 survey of CSF from 197 Tanzanians representing healthy, OV+ epileptic, OV+ only or epilepsy only patients did not yield evidence of OV in CSF, nor was skin snip density found to differ between groups.⁶⁰ However, there is one report from 1976 of microfilariae in the CSF of 5/8 heavily infected onchocerciasis patients without recorded NS or epilepsy.⁶¹

The second theory is that OV, and potentially MP, represent opportunistic infections in patients with immunosuppressive neurotropic viral infections, such as MV.⁴¹ Conflict-related disruption of immunisation programmes contributed to a large MV epidemic in northern Uganda between 1997 and 2003, with approximately 40 – 50,000 cases per year. There were also simultaneous increases, albeit of lower magnitude, in cases in South Sudan and the URT. It has been observed that the peak in this outbreak preceded the peak in NS cases by 5–6 years.⁴¹ This led to the hypothesis that NS may represent a post-infectious sequelae of MV, much like subacute sclerosing panencephalitis (SSPE), reported to occur in 4–27.4 cases per 100,000.⁶² Clinical similarities between NS and SSPE have been reported, and the two conditions have been compared elsewhere.⁴¹ However, NS has not been reported from other countries with past or present outbreaks of MV.

Table 4. Studies with data about the prevalence of OV in NS cases and/or controls

Citation	Publication date	Location	Study date	Cases	Controls	OV+ NS patients	Total NS patients	%	95% CI	OV+ controls	Total control	%	95% CI	p
43	2008	Tanzania	N/A	62	-	43	51	84.3	71.4-93.0	-	-	-		-
26	2012	South Sudan	2010	38	38	29	38	76.3	59.8-88.6	18	38	47.4	31.0-64.2	0.010
7	2012	South Sudan	2001-02	82	81	76	82	92.7	84.8-97.3	39	81	48.1	36.9-59.5	<0.0001
6	2013	Uganda	2009	49	49	32	45	71.1	55.7-83.6	21	39	53.8	37.2-69.9	0.1034
29	2013	Uganda	2012	22	-	3	10	30.0	6.7-65.2	-	-	-		-
33	2013	Uganda	2012	101	101	16	101	15.8	9.3-24.4	0	101	0.0*	0.0-3.6	<0.0001
44	2013	Tanzania	N/A	12	20	9	12	75.0	42.8-94.5	-	-	-		-
27	2014	Tanzania	N/A	22	8	17	22	77.3	54.6-92.1	7	7	100*	59.0-100.0	0.1736
8	2017	N/A	N/A	55	55	44	55	80.0	67.0-89.6	29	55	52.7	38.8-66.3	0.0026

*Assumed 0.01 or 99.9 to permit calculation of significance. CI -confidence intervals, NS - nodding syndrome, OV - *Onchocerca volvulus*

Figure 2. Forest plot of the prevalence of OV in NS patients (n=416).

Blue boxes show effect estimates for each study; horizontal lines indicate 95% CIs. The diamond shows the pooled prevalence of OV, with the centre being the pooled estimate and tips 95% confidence intervals; NS, nodding syndrome; OV, *Onchocerca volvulus*.

Figure 3. Forest plot of the prevalence of OV in control subjects (n=321).

Blue boxes show effect estimates for each study; horizontal lines indicate 95% CIs. The diamond shows the pooled prevalence of OV, with the centre being the pooled estimate and tips 95% confidence intervals; NS, nodding syndrome; OV, *Onchocerca volvulus*.

Three case-control studies have investigated the association between MV and NS; two studies from northern Uganda and one from South Sudan.^{6,7,41} Together these three studies examined 112 cases and 118 controls for the

association of a caregiver's report of previous MV infection and NS. Spencer and colleagues reported a seemingly strong association between previous MV infection and NS, although the 95% CIs were wide (odds ratio (OR)=6.00, 95%

CI=1.03-113²²). In contrast, Foltz and colleagues found a positive, albeit weaker, association (OR=4.0, 95% CI=1.1-14.2; adjusted odds ratio (AOR)=3.3, 95% CI=0.8-13.6⁶). In a smaller study from South Sudan, Tumwine and colleagues examined 13 cases and 19 controls and found no evidence of an association (OR=0.13, 95% CI=0.02-0.76⁷). A medical history of MV infection is however open to recall bias, Foltz and colleagues used PCR to investigate the presence of MV in the CSF of 16 NS cases, all of which were negative.⁶

Immunosuppression, linked to mycotoxin exposure and malnutrition, has been suggested to have contributed to the rise in MV cases, and to partly explain the higher prevalence of NS among the Moru compared with the Dinka peoples in South Sudan^{7,41,63}; this disparity has since been disputed.⁴⁶ Alternatively, it has been hypothesised that different farming practices, the Moru being more reliant on crops and the Dinka on livestock, may have allowed the Dinka to acquire cross-immunity between MV and rinderpest, a related morbillivirus of ruminants.⁴¹ Rinderpest has been absent from Africa since 2001, and it has been suggested that loss of cross-immunity could explain the occurrence of NS among the Dinka after that date.^{41,42}

While the neuropathology of NS remains to be fully elucidated, crystalline inclusions have been observed in histological sections from 6/9 patients.³⁰ Given the absence of MRI evidence for crystalline material, it has been suggested that these may represent post-mortem artefacts.⁶⁴ Characterisation of these postulated inclusion bodies is required, given its reported similarity to NS it is intriguing that the histopathology of SSPE is characterised by the presence of distinct inclusion bodies.⁶⁵

AUTOIMMUNITY

Autoantibodies have been strongly associated with some forms of epilepsy and other neurological disorders.⁶⁶ Like an infectious aetiology, autoimmunity offers a potential explanation for a range of spatially distributed CNS lesions. Although gross CNS pathology has been observed using imaging studies in some NS patients, evidence of neuroinflammation associated with an autoimmune response has to the best of our knowledge not yet been published.^{4,29,38,44} Nevertheless, there have been investigations into the presence of autoantibodies in NS patients. Idro and colleagues identified autoantibodies against the voltage-gated potassium channel (VGKC) in 15/31 NS patients compared to 1/11 controls, but there was no evidence of antibodies against the intracellular glutamic acid decarboxylase, associated with complex epilepsy.³⁰ These data contrasted with that of Dietmann and colleagues who failed to identify VGKC or N-methyl-D-aspartate receptor autoantibodies²⁷; although the sample storage and assays used in this study have been questioned.³⁰ Meanwhile, Soldatos and colleagues examined the CSF of two of three NS patients and found evidence of partially identical oligoclonal immunoglobulin bands.⁴⁸

In 2014 it was suggested that autoantibodies against the autoantigen Ieiodomin-1 (anti-LM-1 immunoglobulin [Ig]) may be associated with NS, with anti-LM-1 Ig present in 11/19 Ugandan cases compared to 5/19 local matched con-

trols.³¹ LM-1 has been reported to be expressed intra- and extra-cellularly in neurons, and is known to be an important component of the actin-myosin complex in myocytes.^{67,68} The expression of LM-1 in the murine CNS closely matches regions observed to be affected in NS and anti-LM-1 Ig has been shown to be neurotoxic to murine CNS tissue.⁸ Moreover, anti-LM-1 Ig exhibits cross-reactivity with OV tropomyosin, with which LM-1 shares 25.5% primary sequence identity (37% similarity) and has localised regions of higher sequence homology, e.g. LKEAExRAE is 66.7% identical to amino acids 362 and 372 of LM-1.⁸ Such cross-reactivity is suggestive of autoimmunity driven by molecular mimicry.

This initial report was followed by a study that investigated the presence of anti-LM-1 Ig in the serum of a further 36 patients from South Sudan. The infection status of the patients was determined by serology (cohort one) or skin snip (cohort two).^{8,31} Together, anti-LM-1 Ig was present in the serum of 29/55 (52.7%) of the pooled population of NS patients compared with 17/55 unaffected pooled controls (30.8%; $P=0.024$; matched OR=2.7 (1.1-6.5)). Notably, 24/44 (54.5%) OV+ NS patients were also positive for anti-LM-1 Ig, while 12/29 (41.3%) OV+ controls were also positive for anti-LM-1 Ig. The difference in the presence of serum anti-LM-1 Ig between the NS and control cohorts (including OV positive (+) and OV negative (-) patients) was reported as significant ($P=0.024$). However, we compared the presence of anti-LM-1 Ig between OV+ patients or OV+ controls and found a 13.2% difference that was not significant ($P=0.273$; 95% CI=-9.81-34.2). CSF samples taken from 16 NS patients were also examined and 50% contained anti-LM-1 Ig, compared to 0/8 North American epilepsy patients.⁸

THERAPEUTIC APPROACHES TO NS

NS shows an almost invariably progressive course, although treatment can improve life expectancy.¹⁵ The condition carries a high burden of social stigma for both patients and their families,^{69,70} including negative stereotypes from healthcare workers.⁷¹ Some NS patients have been isolated by communities afraid of contagion.⁵³ Given the typical age and impaired abilities of NS patients, caregivers are vital in facilitating treatment; they seek help from a variety of sources including health facilities (78%), traditional healers (13%) and self-medication (9%). Half of those who attended health facilities did so a month after the onset of symptoms, indicating that more work is needed to ensure prompt help is sought.⁷² Aside from the work on social stigma there has been little work on the impact of NS on caregivers, although one qualitative study identified a high burden of emotional agony, alongside issues surrounding burnout, safety concerns, stigmatisation and rejection and homicidal ideation.⁷³ Psychological interventions have been shown to mitigate depression in caregivers.⁷⁴

The 2013 guidelines for the management of NS suggest that, depending on severity, care may include anti-epileptics or anti-convulsants, appropriate management of comorbidities, psychiatric support, nutritional assistance and physical, occupational, speech and language therapy.⁵ A cross-sectional cohort study of NS and other convulsive epilepsy (OCE) patients treated according to these guide-

lines showed improvement in both groups of patients, with 25% of NS and 51% of OCE patients being seizure free after 12 months.¹⁵

The 2013 guidelines detail the usage, advantages and disadvantages of anti-epileptics for NS.⁵ However, despite successful reports of the use of anti-epileptics, no clinical trial has been performed. Successful use of sodium valproate has been reported,⁷⁵ and a case-control study showed a 57% reduction in total seizure burden among 22 NS patients treated with sodium valproate for 2–3 weeks.⁵ A 1994 case report demonstrated some initial efficacy for phenobarbitone, but long-term control was not achieved.¹¹ A 2013 case series in which four patients were treated with anti-epileptics provided mixed or no evidence for the efficacy of carbamazepine and phenobarbitone respectively.⁵² In 2014 Winkler and colleagues demonstrated cessation or reduction of head nodding frequency in the majority of patients treated with anti-epileptic drugs.⁷⁶ However, in 2015 de Polo and colleagues treated 21 patients with carbamazepine as a mono- or combination therapy and found that none obtained good control of any form of seizure associated with NS.⁷⁷ Benzodiazepines are indicated for icteric patients,⁵ and given the symptomatic overlap between NS and catatonia, lorazepam has been piloted in NS patients.⁷⁸ Within one hour of lorazepam administration the severity of catatonia symptoms was reduced in 10/16 patients, and by more than 50% in six.⁷⁸

Mental health comorbidities have been observed among NS patients, including post-traumatic stress disorder and depression.⁵² Use of the tricyclic antidepressant imipramine has been recorded for three cases, in which the mood of two improved. However, it was administered as part of a wider treatment programme and the precise contribution of imipramine was unclear.⁵²

Finally, there are treatments aimed at potential aetiologies. Antibiotic elimination of the symbiotic *Wolbachia* bacteria from the OV nematode has been shown to reduce the inflammation caused by, and contribute to premature death of, the nematode.^{79,80} An ongoing clinical trial is investigating doxycycline for the treatment of NS, with the aim of elucidating whether *Onchocerca* or *Wolbachia* may drive the disease.^{80,81} There is also an ongoing clinical trial in the Democratic Republic of Congo examining the effect of ivermectin administration in reducing the frequency of OAE, which may have implications for NS patients.⁸² Three OV-NS patients have been treated with plasmapheresis or intravenous immunoglobulin for presumed autoimmunity, however the results have not been recorded in sufficient detail to appraise treatment efficacy.⁴⁸

DISCUSSION

Although it is 53 years since NS was first described, the underlying aetiology and pathogenesis remain unclear. This systematic review has collated evidence for metabolic, psychogenic, infectious and autoimmune theories, the limitations of which will now be discussed. Whatever the aetiology, it must explain the age range of patients and disparate nature of clinical findings.^{29,38,43,44} Notably, probable cases dating from 1934 would call into question hypotheses based solely on modern phenomena.²

The epidemiological history of NS is intriguing: an endemic pattern of cases in the URT and one large epidemic among a broadly malnourished and traumatised Ugandan and South Sudanese population that appears to have a 5–7 year temporal disparity with conflict, food shortages and/or MV epidemics, and no new epidemic cases since 2013. Familial clustering has also been observed, with one case series reporting that 79.6% of NS patients had a family history positive for NS or epilepsy.^{17,76} Given this apparent familial clustering of NS cases within blackfly exposed locales, genetic and epigenetic genome-wide association studies (GWAS) are warranted and could offer insight into the aetiology of NS and differential susceptibility. The epidemic versus endemic nature of NS is important and calls into question metabolic or psychiatric associations with relief food, IDP camps, conflict and psychological trauma.^{32,83} Alternatively, NS in the URT may represent a distinct condition.⁸⁵ It has been suggested that if NS is driven by a specific pathogen, an epidemic could reflect the movement of a non-immune population into an affected area.⁴⁶ However, if an OV-driven autoimmune aetiology is ultimately described, then regional differences between OV, *Wolbachia* or the blackfly could explain the differential presence or manifestation of NS. Aside from infectious or immunological theories, observed correlations with biomarkers for malnutrition remain unexplained, although these may be incidental.

The epidemiological association between OV and NS has been questioned.⁸⁴ OV occurs in 34 countries in Africa, the Middle East, South and Central America, with an estimated 17.7 million people affected.⁸⁵ In contrast, there have only been several thousand cases of NS in restricted parts of Africa.³ An attempt to resolve this discrepancy has been made by the recent classification of NS under the umbrella term OAE.⁹ There is substantial evidence in favour of OAE,¹⁰ and NS is presumed to represent a point on this proposed clinical spectrum, much of which may remain unappreciated. Meta-analysis of the relationship between OV and epilepsy demonstrated a pooled OR of 2.49 (95% CI=1.61–3.86; $P < 0.001$), or 1.29 (95% CI=0.93–1.79; $P=0.139$) when controlled for age, residence and gender⁸⁶; a significant association was found using studies that reported the presence of OV nodules.⁸⁶ A recent prospective study from an OV focus in Cameroon has demonstrated a relationship between childhood skin microfilarial density and subsequent risk of epilepsy or seizures.¹² Moreover, a fall in the number of cases of NS, as well as cases of epilepsy and Nakalanaga syndrome, appears to correlate with the reestablishment of onchocerciasis control.⁵⁹ Such correlations could be investigated by further prospective studies. Nevertheless, it is unclear, given the large numbers of OV patients, why NS has not been documented in other OV-endemic regions, although this could reflect greater OV elimination efforts or genotypic differences between populations.^{51,87,88} Moreover, the interpretation of case-control studies, including those included in the meta-analysis, may be limited by the availability of data about ivermectin therapy given to individuals in such studies. If NS is indeed associated with OV then administration of ivermectin to NS patients may confound observations of this association. It would be ideal if all case-control studies clearly reported

ivermectin administration data pertaining to periods before and after the onset of NS, however many studies do not.

The clinical similarities between NS and SSPE have been discussed elsewhere,⁴¹ however the association with MV remains unclear. The only significant OR reported had very wide confidence intervals,⁴¹ suggesting the study should be repeated with a larger sample size. There is limited correlative evidence suggesting an association between MV and NS epidemics,⁴¹ the authors are not aware of reports of NS-like disease in other MV endemic areas, and seizures associated with some cases of MV infection may have led to some patients incorrectly being classified as NS cases.⁴⁵ Although MV is immunosuppressive,⁸⁹ it is noted that for immunosuppressed patients to only acquire OV or MP as opportunistic infections is unusual. In contrast, acquired immunodeficiency syndrome patients readily acquire a range of opportunistic infections, including common fungal infections of which there is no recorded association with NS.⁹⁰ Moreover, it has been suggested that the crystalline inclusions thought to mimic those observed in SSPE represent post-mortem artefacts.⁶⁴ Histopathological investigations are ongoing, and recent unpublished investigations suggest that NS may be a unique neurodegenerative disorder comparable to a frontotemporal degenerative tauopathy.⁹¹

An autoimmune reaction driven by molecular mimicry between OV and human LM-1 was recently proposed.⁸ However, while Johnson and colleagues demonstrated an association between the presence of anti-LM-1 Ig (subtypes G and M) and NS, whether anti-LM-1 Ig contributes to, is a consequence of or is coincidental with the pathology of NS remains unclear. The naturally occurring presence of autoreactive B cells is well documented.⁹² While autoantibodies can cause pathology, they can also arise because of cell damage, which may occur secondary to seizures.⁶³ Autoimmune conditions are often associated with inflammatory responses and, at the time of writing, the current lack of evidence for neuroinflammation in NS patients remains intriguing. Moreover, despite expression of LM-1 in myocytes, there are no reports of autoimmune myopathy among NS patients.⁶³ The antibody subtypes identified were IgG and IgM.⁸ The latter could suggest an ongoing immune response, and subtyping of IgG could offer further insights. The response of NS patients to carefully managed corticosteroids could reveal whether sources of inflammation remain to be identified. The outcome of the treatment of three NS patients with IVIG or plasmapheresis has not yet been made available in detail, but will contribute to the debate.⁴⁸ The molecular mimicry theory must also explain the presence of NS in OV- patients, although it's unclear whether or not these were OV naïve patients.⁸ The presence of OV+ NS patients negative for anti-LM-1 Ig could be explained by detection difficulties or the gradual loss of antibodies following an initiating event, however many autoimmune conditions are chronic and progressive.

Limitations of this review include the exclusion of a small number of studies that were not available in full-text form (Appendix S3, Online Supplementary Document). For their studies to have the greatest impact in the field authors should strive to publish in open-access indexed journals. Moreover, publication of the same data multiple times, encountered several times, does not increase its impact.

Assessment of the titles, and where possible abstracts, of these studies suggested that their omission is unlikely to have greatly altered this review. Five potentially relevant studies were not identified by the systematic search strategy. These may have been incorrectly indexed and were included manually to ensure as much relevant data as possible was screened. This approach enhances the transparency and reproducibility of this study, although we cannot exclude the possibility that other non-indexed studies were unknowingly omitted. This study may also be limited by not being pre-registered. Registration of reviews is a non-essential recommendation designed to encourage transparency, improve quality and reduce duplication. Pre-registration of reviews that are never completed is not recommended.⁹³ This study was conceived as a student project, many of which are not published, and the authors therefore decided it was inappropriate to register retrospectively. However, the authors are not aware of any similar studies underway and complied with the PRISMA statement throughout.

A further potential limitation of this study is its focus specifically on NS. While we appreciate that NS may be found to exist as part of a spectrum of OAE, the focus of this study was to review literature pertaining only to NS. A systematic review specifically exploring the link between epilepsy and OV was performed in 2013,⁸⁶ but as there has been much new work in this area an updated review could be considered. Lastly, it must be remembered that systematic reviews are only ever a snapshot of a dynamic literature and at the time of writing the NS field awaits clear and open reporting of important results, including ongoing trials, post-mortem analyses and immunomodulatory treatment efficacy.^{38,61,81,94}

The aetiology of NS remains unclear with each of the proposed theories still having questions to address. Ongoing trials and further correlative work (e.g. GWAS) may help direct the field towards a conclusive mechanism. It is important to understand the aetiology of NS to care for those affected and to better prevent or treat future epidemics. It is intriguing that no new epidemic cases have been reported since 2013, but this will offer little reassurance until the aetiology and therapy of NS is better understood.

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COMPETING INTERESTS

The authors completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf, and declare no conflicts of interest.

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