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Mapping, Associated Factors, and Pathophysiology of Nodding Syndrome in Africa: A Systematic Review

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Keywords
Nodding syndrome · Systematic review · Diagnosis · Associated factors · Treatment

Abstract
Introduction: Nodding syndrome (NS) remains a poorly understood disorder. For a long time, it has been thought to be restricted to East Africa; however, cases in Central Africa have been increasing over time. The objective of this systematic review (SR) was to provide a summary of the state of knowledge on NS to date. ***Methods:*** All original articles published on NS up to November 2021 were searched in four major databases and in the gray literature. Commentaries, editorials, book chapters, books, conference paper, qualitative studies that mentioned NS cases were also included. Data retrieved included study location (with GPS coordinates searched), year of study and publication, population characteristics, definition and diagnosis of NS, associated factors, and treatment if applicable. A meta-analysis of associated factors was performed where possible, and results were presented as odds ratios (ORs) and visualized as forest plots. Geographic information systems were used for cartographic representations. The quality of the articles included was assessed. ***Results:*** Of the 876 articles initially identified, 67 (corresponding to 59 studies) were included in the SR. NS is only present in Central and East Africa. Interestingly, there were reports of NS in Central Africa prior to 2010, earlier than previously thought. The way NS diagnosis was established varies according to studies, and the 2012 WHO classification was used in only 60% of the studies. Approximately 11% of the articles did not meet the quality requirements set for this review. In our meta-analysis, the main factor associated with NS was onchocerciasis (OR = 8.8 [4.8, 15.9]). However, the pathophysiology of the disease remains poorly understood. The lack of common antiepileptic drugs is a significant barrier to the management of head nodding and associated epileptic seizures. ***Discussion/Conclusion:*** The lack of an operational definition of NS is an obstacle to its diagnosis and, thus, to its appropriate treatment. Indeed, diagnostic difficulties might have led to false positives and false negatives which could have altered the picture of NS presented in this article. Treatment should take into account nutritional and psychological factors, as well as associated infections. Some risk factors deserve further investigation; therefore, we suggest a multicentric study with an etiological focus using a more operational definition of NS.

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Introduction

Many studies have been published on numerous cases of nodding syndrome (NS) in East Africa, mainly in Tanzania, Uganda, and South Sudan [1, 2]. The discovery of new cases in Central Africa [3, 4] over the past decade has challenged the belief that NS is contained within East Africa only and may open up new approaches to the etiology, diagnosis, management, and perhaps even prevention of NS. This raises many questions: What is the real burden of NS in East Africa? Which areas exactly have been affected? What is/was the prevalence of NS in these areas? Are new cases still emerging or has the disease disappeared completely? The same questions need to be asked for Central Africa.

Several aspects of NS remain to be explored or better understood. Therefore, it is important to regularly update a topic as important as NS so that researchers in the field can combine their efforts for efficient research.

The current definition of NS varies due to multiple factors, including location and time, making precise diagnosis challenging. In fact, two classifications are commonly used. The first was proposed in 2008 by Winkler et al. [5], "head nodding (HN) only" (exclusively HN) versus "HN plus" (HN associated with other seizure types). The second was proposed in 2012 by the WHO: it defines or classifies cases as suspect, probable, or confirmed [1]. This classification was re-evaluated by a consensus of experts in 2015, with no alternative having been proposed to date [6]. A systematic review (SR) of associated risk and protective factors for NS can guide future etiological research. A case census will allow for more accurate mapping of NS, which is crucial for clinical management. These hypotheses will guide our systematic analysis and help address unresolved questions in the field of NS.

The aim of this SR was to provide an up-to-date overview of NS. More specifically, the aim was to provide an estimate of the total number of cases reported in the literature, map these, provide a list of factors associated with NS which have already been studied and of the pathophysiological mechanisms involved, and finally, take stock of the state of knowledge regarding the diagnosis and management of NS.

Methods

Types of Studies

Our SR includes all original studies published up to November 2021 without language restriction. Commentaries, editorials, book chapters, books, conference paper, qualitative studies that mentioned NS cases were also included.

Information Sources and Design of the Research Strategy

We searched the following medical databases: PubMed, Scopus, Science Direct, and Web of Science because of their relevance to our research question. "Google Scholar" was also used. The African Journals Online (AJOL) database, reports of international scientific meetings, and gray literature were also searched. The relevant references cited in the included articles were also screened, and references were included as appropriate. The following search terms were used in these different databases: "nodding syndrome" OR "nodding disease" OR ("head nodding disease" AND epilepsy) OR ("nodding seizure" AND epilepsy).

Selection Process

We used the Rayyan data processing software (Qatar Computing Research Institute, Data Analytics Medical) [7] which allowed us to (1) collect/save bibliographic records of articles from different databases; (2) eliminate duplicates; (3) assess and select studies for inclusion in our review: studies were assessed and selected by two independent authors. Any disagreements in the selection of studies between the two reviewers were resolved by consensus after discussion and/or by involving a third independent author. The protocol was published in the PROSPERO international prospective register of SRs (CRD42020184438).

Data Extraction

We used a data collection form to collect all the data needed to analyze the studies. These data included first author, objective, type of study, period, year of publication, population description (country, participant age, sex), definition of diagnosis of NS cases, number of participants, main results, associated factors, and, if applicable, treatment provided and tools used in each study. GPS coordinates of study sites were searched in Google Maps.

Quality Assessment of the Included Studies

The methodological quality of the studies included in our review was assessed using the items described in the Newcastle-Ottawa Scale (NOS) tool [8] which has been slightly modified to accommodate all studies (online suppl. Appendix A and online suppl. Table A.1 and A.2; for all online suppl. material, see https://doi.org/10.1159/000536013). In addition to the NOS, we have developed our own scale to assess the quality of studies related to the topic. This scale is called DCP (for definition, clinical, and paraclinical) and takes into account the quality of the procedure used in each study to diagnose NS (online suppl. Appendix A and online suppl. Table A.3). This scale was used for all studies except the ones for which we could only access the abstract.

Data Processing and Statistical Analysis

Quantitative data were summarized as means, while qualitative data were expressed as proportions. A descriptive summary of factors associated with NS was provided. A meta-analysis of association studies was performed where possible. The test for heterogeneity (Q of Cochran) was performed and interpreted. To account for heterogeneity (where present) in the data, random-effect meta-analyses were used. The test for heterogeneity was considered significant for $p \leq 0.05$. Meta-analysis results were expressed as odds ratios (ORs) and visualized as a forest plot. In addition, Geographic Information System (GIS) was used to create a database to produce epidemiological maps.

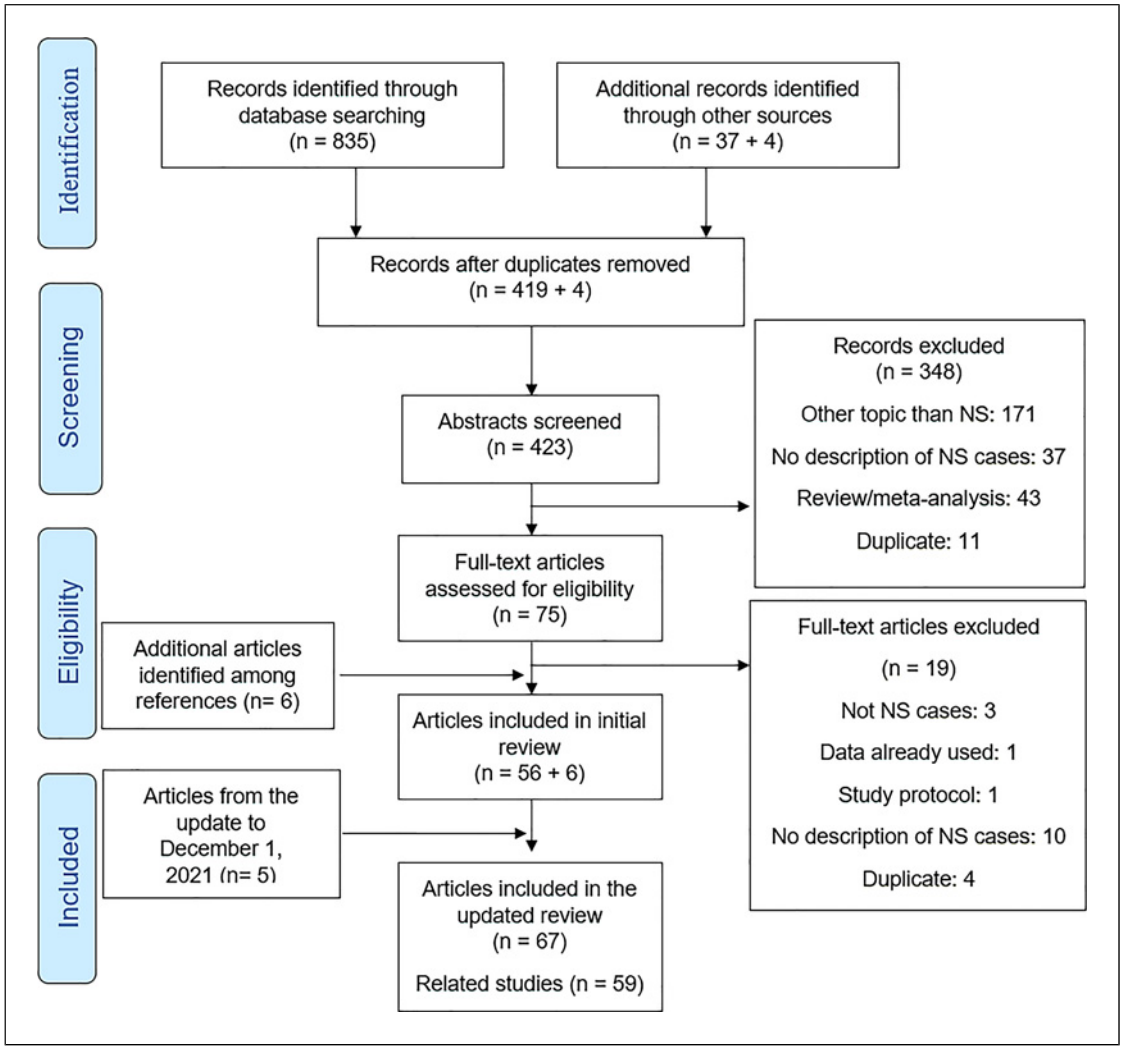

Fig. 1. Flowchart of included articles.

Results

In total, 876 articles were identified in the literature. After the selection process, 67 articles (corresponding to 59 studies) were included in this SR (shown in Fig. 1). Articles reporting the same study and the way they were treated in this review are presented in online supplementary Appendix B.

Epidemiology

Table 1 provides an overview of each article. The 59 studies were conducted in six countries in East and Central Africa, with three studies conducted in more than one country [9–11].

Most of the studies (50.9%) were conducted in the general population, 39.0% in hospital populations, and 5.1% in mixed populations (general and hospital), with three case studies which could not be classified in the previous groups. Participants' average age was 13.8 (±1.6) years (information available in 31 articles). Mean age of onset of symptoms was 8.7 (±1.3) years (information available in 11 articles). The map of Africa in Figure 2 shows the countries with diagnosed cases of NS; the red dots represent the different study sites for each country, with some dots overlapping as a same site might have been surveyed several times. Although countries with NS cases share borders, Burundi and Rwanda (landlocked between Democratic Republic of Congo (DRC), Tanzania, and Uganda) have no known cases of NS. In Figure 3, for each country, each study is represented by a red dot which size is proportional to the number of NS cases identified. The same scale of dots has been used for all countries. The main water areas and lines in each country are also shown. Apart from the DRC, where the proximity of

Table 1. General description of articles included in the SR

No.	Authors	Year of publication	Country	Sites	Study population	Objectives	Number of cases	Age* mean
1	Nyungura et al. [70]	2011	South Sudan	Witto Payam, Jambo	GP and HP	Provide recommendations for the fight against NS	96	MD
2	Tumwine et al. [13] Spencer et al. [19]	2012 2013	South Sudan	Lui, Amadi	GP	Characterizing NS + exploring risk factors	98	12*
3	Centers for Disease Control and Prevention (CDC) [15]	2012	South Sudan	Maridi, Witto	Children between 5 and 18 years	Characterizing NS + exploring risk factors	38	11.1
4	De Polo et al. [72]	2015	South Sudan	Juba	HP	Characterizing NS	21	11.7
5	Colebunders et al. [11]	2016	South Sudan/ Northern Uganda/ Democratic Republic of Congo	Mvolo, Mundri, Lui, Yeri, Kitgum district, Lamwo district, Pader district, Gulu district, Dingila, Titule, Liguga	GP	Compare observations between different countries	MD	MD
6	Colebunders et al. [73]	2018	South Sudan	Maridi	GP	Characterizing NS	335	MD
7	Levite et al. [74]	2020	South Sudan	Mundri	Children known to have NS	Studying pathophysiology	27	14.9
8	Abd-Elfarag et al. [75]	2020	South Sudan	Maridi county	Persons with epilepsy	Investigate the association between the level of OV infection, epilepsy, and related outcomes	158	MD
9	Jada et al. [76]	2020	South Sudan	Amadi	GP	Characterizing NS	36	MD
10	Kitara et al. [77]	2013	Northern Uganda	Gulu Regional Referral Hospital, Uganda	NA	Describing a particular case	1	13
11	Musisi et al. [23]	2013	Northern Uganda	Mulago Hospital/ Kampala	GP and HP	Characterizing NS	6	13.2
12	Foltz et al. [14]	2013	Northern Uganda	Kitgum district	Subjects meeting the surveillance case definition	Exploring risk factors +prevalence	51	11.6
13	Sejvar et al. [31]	2013	Northern Uganda	Kitgum district	GP (5–15 years)	Characterizing NS	35	11.7*
14	Idro et al. [63]	2013	Northern Uganda	Mulago Hospital/ Kampala	HP (5–15 years)	Characterizing NS	22	14.1

Table 1 (continued)

No.	Authors	Year of publication	Country	Sites	Study population	Objectives	Number of cases	Age* mean
15	Kitara et al. [18]	2013	Northern Uganda	Odek sub country in Gulu, Atiak sub country in Amuru	GP	Exploring risk factors	101	11.4
16	Iyengar et al. [78]	2014	Northern Uganda	Kitgum, Lamwo, and Pader districts	GP	Characterizing NS	300	13.9*
17	Idro et al. [38]	2014	Northern Uganda	Atanga, Oyam, Lira, Pader, Kitgum, Pader, Gulu, and Amuru districts	Children with NS in hospital	12-month clinical evaluation of a cohort intervention	484	13.7
18	Kakooza-Mwesige et al. [79]	2015	Northern Uganda	Pader district	GP (10–21 years)	Characterizing NS	33	15
19	Nakigudde et al. [52]	2016	Northern Uganda	Atanga	Children with NS	Explore de perceptions of caregivers	54	14.2
20	Obol et al. [25]	2016	Northern Uganda	Paicho (Gulu district), Atiak (Amuru district)	GP	Exploring risk factors	66	12.5
21	Spencer et al. [22]	2016	Northern Uganda	Tumangu, southwest of Kitgum Town	GP	Exploring risk factors	83	15.6
22	Idro et al. [80]	2018	Northern Uganda	Atanga, Awere	GP	Describe the early features and natural history of NS	210	MD
23	Arony et al. [81] Denis et al. [82]	2018 2018	Northern Uganda	Odek	Subjects meeting the surveillance case definition	Studying pathophysiology	MD	14.1
24	Pollanen et al. [33]	2018	Northern Uganda	Kitgum, Pader, and Gulu districts	Children with NS (deceased)	Studying pathophysiology	5	15.2
25	Ogwang et al. [39]	2018	Northern Uganda	Kitgum, Lamwo, and Pader districts	Children with NS in hospital	Exploring risk factors	240	15.6
26	Gazda et al. [40]	2018	Northern Uganda	Odek	HP	Exploring and presenting the clinical findings and reporting treatment and rehabilitation outcomes of NS children	32	12.7
27	Echodu et al. [27]	2018	Northern Uganda	Kitgum and Lamwo districts	GP	Exploring risk factors	62	MD
28	Hotterbeekx et al. [34]	2019	Northern Uganda	Kitgum and Pader districts	Children with NS (deceased)	Studying pathophysiology	5	17.8

Table 1 (continued)

No.	Authors	Year of publication	Country	Sites	Study population	Objectives	Number of cases	Age* mean
29	Ogwang et al. [16]	2020	Northern Uganda	Kitgum, Lamwo, and Pader districts	Cases in HP (≥8 years) and controls in GP	Exploring risk factors	154	15.5
30	Kaiser et al. [83]	2015	Western Uganda	Kabende parish	NA	Describing a particular case	1	15
31	Kaiser et al. [84]	2018	Western Uganda	Kabende parish	GP	Characterizing NS	15	12.9
32	Gumisiriza et al. [85]	2020	Western Uganda	Kabende Center, Masongora South, Rwesenene	GP	Re-investigated the epilepsy burden after onchocerciasis elimination	1	MD
33	Winkler et al. [5, 86]	2008 2010	Southern Tanzania	Vigoi division, Ulanga district	HP with HN seizures	Characterizing NS	62	14.9
34	König et al. [87]	2010	Southern Tanzania	Mahengue	GP	Study the relationship between epilepsy and O. volvulus	51	MD
35	Spencer et al. [88]	2013	Southern Tanzania	Mahengue	HP	Characterizing NS	33	MD
36	Winkler et al. [21]	2013	Southern Tanzania	Vigoi division, Ulanga district	HP with HN seizures	Document MRI changes in people with different types of epilepsy and investigate whether there is an association with O. volvulus infection	12	14.8
37	Winkler et al. [89]	2014	Southern Tanzania	Vigoi division, Ulanga district	HP with HN seizures	Characterizing NS (follow-up of *n*°34)	53	18*
38	Dietmann et al. [26]	2014	Southern Tanzania	Mahengue	GP	Characterizing NS	22	MD
39	Mmbando et al. [90]	2018	Southern Tanzania	Mahengue area*	GP	Determine the prevalence and incidence of epilepsy following 20 years of onchocerciasis control	13	MD
40	Bwhana et al. [91]	2019	Southern Tanzania	Matumbala, Vigoi, Sali, Mzelezi, Mdindo, Msogezi	GP	Characterizing NS	31	22.5*
41	Prischich et al. [12]	2008	Cameroon	Kelleng	GP	Characterizing NS	4	MD
42	Siewe Fodjo et al. [92]	2018	Cameroon	Bilomo, Kelleng	GP	Characterizing NS	12	MD
43	Boullé et al. [93]	2019	Cameroon	Bayomen, Nyamongon, Ngongol	GP	Assess the impact of repeated CDTI campaigns on the prevalence of epilepsy	23	MD

Table 1 (continued)

No.	Authors	Year of publication	Country	Sites	Study population	Objectives	Number of cases	Age* mean
44	Siewe et al. [4]	2019	Cameroon	Bilomo, Kelleng, Ngongol, Nyamongo, Bayomen, Bilomo, Kelleng	GP	Characterizing NS	34	MD
45	Lenaerts et al. [94]	2018	Democratic Republic of Congo	Logo	GP	Characterizing NS	8	MD
46	Mukendi et al. [95]	2019	Democratic Republic of Congo	Wela, Makoko, Aketi	GP	Investigate the reasons for the high prevalence of epilepsy	9	MD
47	Fodjo et al. [96]	2019	Democratic Republic of Congo	Logo, Aketi	GP	Characterizing NS	33	16*
48	Mandro et al. [42]	2020	Democratic Republic of Congo	Logo	GP	Randomized clinical trial to assess whether ivermectin treatment decreases seizure frequency	7	NA
49	Metanmo et al. [3]	2021	Central African Republic	Landja	GP	Characterizing NS	5	11.6
50	Johnson et al. [9]	2017	South Sudan/ Northern Uganda	MD	HP	Investigate whether autoantibodies could be a contributing factor to the pathogenesis of NS	55	MD
51	Benedek et al. [32]	2020	South Sudan	Mundri	GP	Investigate the role of HLA in NS	48	14.3
52	Benedek et al. [36]	2021	South Sudan	Mundri	GP	Determine whether the MIF polymorphism is associated with susceptibility to NS	48	14.3
53	Duringer et al. [28]	2021	Northern Uganda	MD	GP	Demonstrate that mycotoxin contamination of food is associated to NS	50	MD
54	Gumisiriza et al. [17]	2021	Northern Uganda	Kitgum and Pader districts	GP	Investigate potential risk factors that may lead to NS and other forms of epilepsy	154	15*
55	Hotterbeekx et al. [20]	2020	South Sudan	Maridi county	GP	Detect OV microfilariae or its bacterial endosymbiont, *Wolbachia*, in the CSF of persons with OAE	10	13.4

Table 1 (continued)

No.	Authors	Year of publication	Country	Sites	Study population	Objectives	Number of cases	Age* mean
56	Hotterbeekx et al. [10]	2021	Democratic Republic of Congo/ South Sudan	Ituri province, Maridi county	GP and HP	Identify leiomodin-1 antibodies in the serum and CSF of persons with NS and other forms of OAE from the DRC and South Sudan	16	MD
57	Vieri et al. [35]	2021	Democratic Republic of Congo	Ituri and Kwili province	GP	Investigate whether serotonin may play a pathogenic role in OAE	8	MD
58	Piloya-Were et al. [97]	2014	Northern Uganda	Western Kitgum district	HP	Examine the relationship between serum hormone levels and stature, bone age and sexual development	8	15
59	Kitara et al. [98]	2015	Northern Uganda	Gulu Regional Referral Hospital, Uganda	HP	Case report of nodding episodes and high anion gap	1	13
60	Kitara et al. [29]	2014	Northern Uganda	Pader district	HP	Conduct a hormonal and biochemical studies on 10 patients with diagnosis of probable NS	10	13.5
61	Kitara et al. [53]	2012	Northern Uganda	Odek	HP	Investigate the perceptions of the population in Northern Uganda to NS	19	11.3
62	Gumisiriza et al. [99]	2020	Northern Uganda	Kitgum, Pader, and Moyo districts	GP	Evaluate the effect of community-directed treatment with ivermectin (CDTI) and ground larviciding of rivers initiated after 2009 and 2012, respectively, on the epidemiology of NS and other forms of epilepsy (OFE) in some districts of northern Uganda	MD	MD
63	Soldatos et al. [100]	2015	Northern Uganda	MD	GP	Present phenotyping and immunomodulatory treatment of children with NS	MD	MD

Age = median. GP, general population; MD, missing data; HP, hospital population; NA, not applicable; HN, head nodding; NS, nodding syndrome.

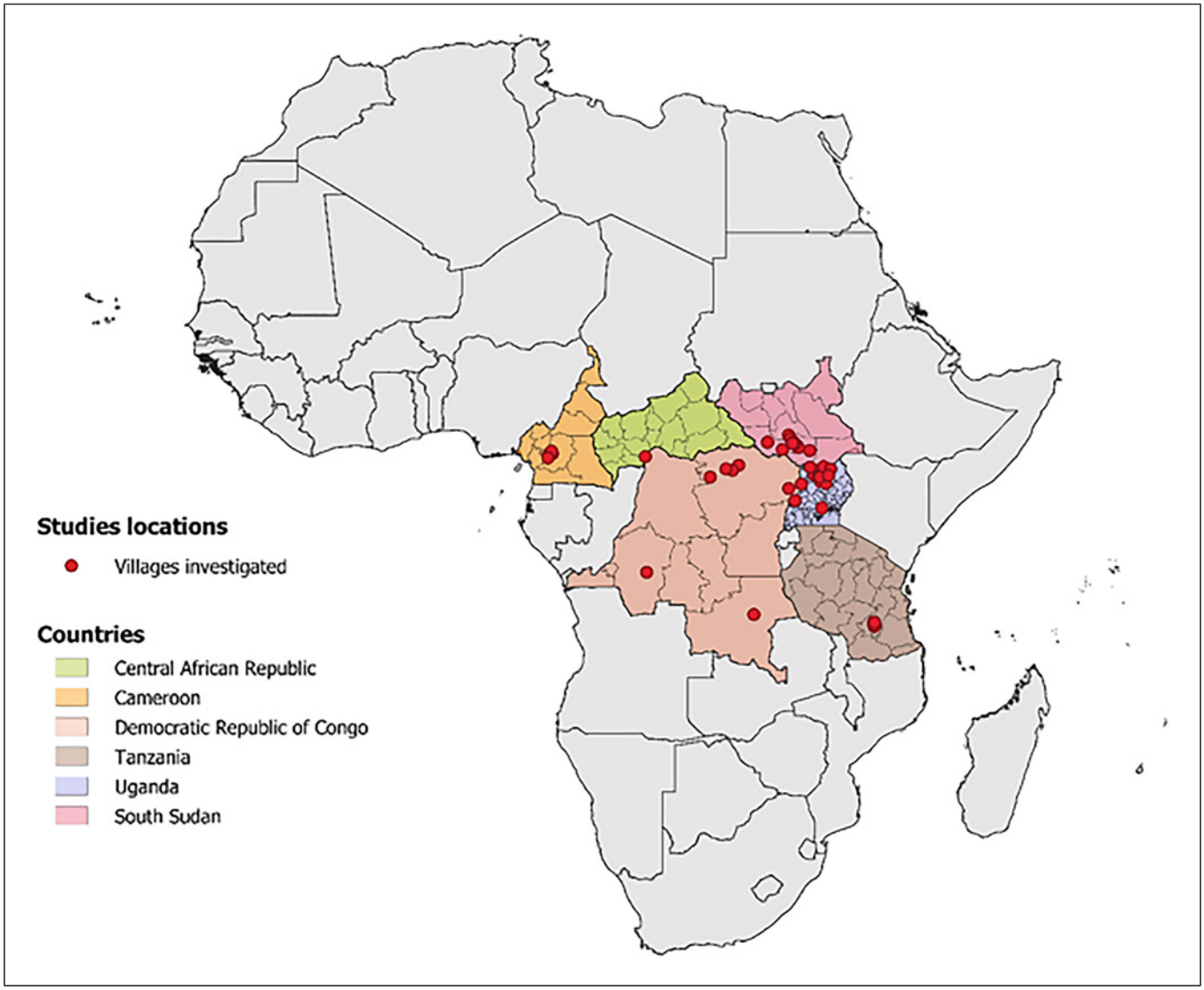

Fig. 2. Countries affected by NS and the location of cases identified.

some study sites to large water areas has been observed, villages where NS cases have been detected in Africa do not appear to be in closer contact with water areas/lines than other villages. Figure 4 shows the evolution of the number of studies and therefore of the number of cases detected from 1994 to the date of this report, with three time periods shown: studies which took place between 1944 and 2005 (red dots), followed by those conducted between 2006 and 2015 (purple dots), and finally those between 2016 and 2021 (green dots). It can be seen that (1) the number of studies and cases has increased considerably over time; (2) cases were described in Cameroon in 2000; (3) there has been a very substantial rise in the number of studies in Uganda and Southern Sudan over the second period; and finally (4) the current incidence is almost nil in Uganda and Southern Sudan, while it is increasing in Central Africa.

Quality Assessment of Articles

Applying the NOS to the articles included in this SR, it was found that of the 49 that were rated, 28 were of good quality, 16 were of fair quality, and 5 were of poor quality. This scale was not applied to some articles (see online suppl. Appendix A). When we applied (to the 62 studies concerned) the DCP scale proposed in this work, 27 were of good quality, 28 were of average quality, and 7 were of poor quality. In online supplementary Appendix B,

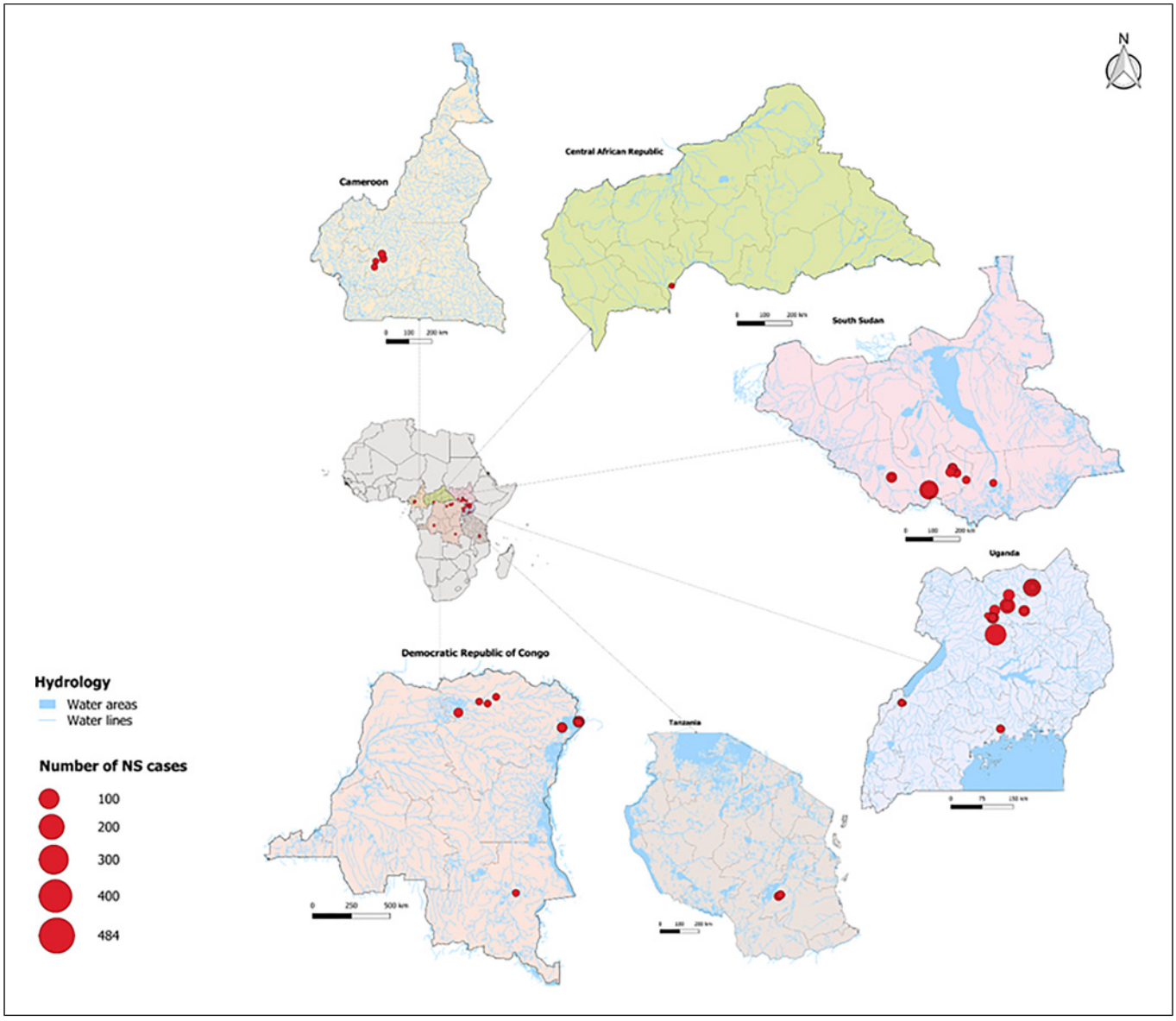

Fig. 3. Number of cases of NS in affected countries.

online supplementary Table B.1 presents a summary of the score of the different scales for each article. online supplementary Figure B1 shows the grouped results of the two scales.

Diagnosis of NS

Different definitions/classifications of NS have been reported in the literature. Thirty-eight studies (60.3%) used the classification proposed by the World Health Organization (WHO) to diagnose cases of NS. In the other studies, 12 (19%) mentioned either "personal" (or non-consensus definition) or "head only" and "head plus" classification, and 13 (20.7%) did not explicitly mention the definition they used. online supplementary Table B.2 shows for each article the diagnostic means used and the number of cases.

In addition to the definition, it is also important to know who makes the clinical diagnosis. Clinical confirmation was made by a neurologist or pediatric neurologist in 28.8% of the studies and by a general practitioner in 22% of the studies. Confirmation of the diagnosis was not performed or reported in 45.5% of

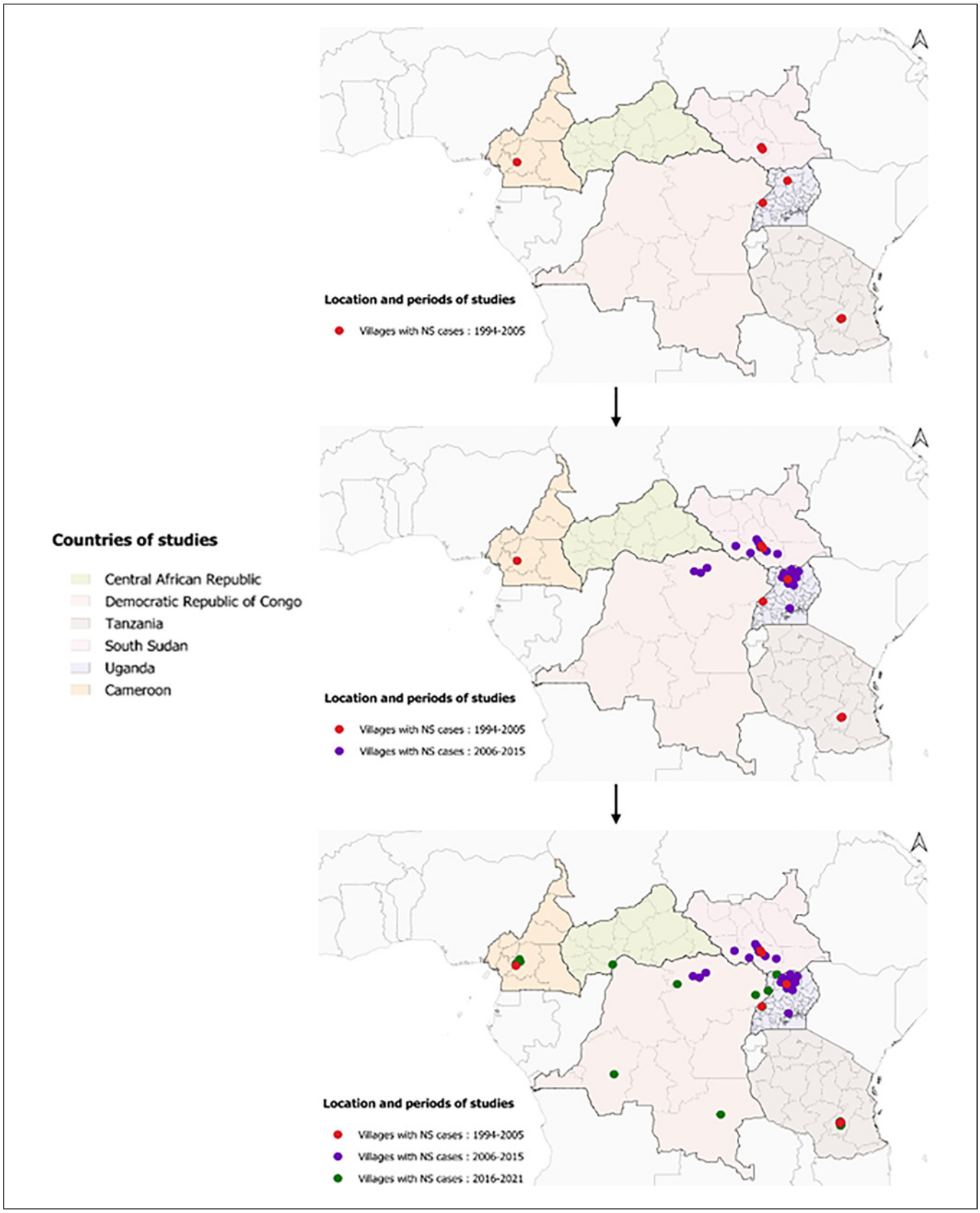

Fig. 4. Temporal evolution of the distribution of NS cases.

Table 2. Infections associated with NS

Pathogen/ pathology	Country [citation] (publication year)	Location (study year)	Assessment of exposure	Cases		Controls		OR (95% CI)
				N	% positive	*N*	% positive	
OV	SS [1] (2012)	Amadi (2001)	Skin snips	30	96.7 (29/30)	34	50 (17/34)	29.0 (3.5–237.7)
		Lui (2001)		39	89.7 (35/39)	31	48.4 (15/31)	9.3 (2.7–32.6)
		Lui (2002)		13	92.3 (12/13)	16	43.8 (7/16)	15.4 (1.6–148.8)
	SS [2] (2012)	Maridi (2011)	Skin snips	25	88.0 (22/25)	25	44.0 (11/25)	9.3 (1.9–52.3)
		Witto (2011)		13	53.8 (7/13)	13	53.8 (7/13)	1.0 (0.2–6.2)
	Uganda [3] (2013)	Kitgum (2009)	Skin snips	45	71.1 (32/45)	39	53.9 (21/39)	1.11 (0.37–3.27)
			Ov16 IgG	39	66.7 (26/39)	44	31.8 (14/44)	3.14 (1.08–9.13)
			OvFAR/MSA	39	94.9 (37/39)	41	48.8 (20/41)	14.40 (2.65–78.31)
	Uganda [4] (2013)	Odek and Atiak sub counties (2012)	Skin snips	101	77.22 (78/101)	101	9.90 (10/101)	7.02 (3.89–12.68)
	Uganda [5] (2021)	Kitgum, Lamwo, and Pader (NA)	Ov16 IgG	154	95.4 (147/154)	154	55.8 (86/154)	17.04 (7.33–45.58)
			Skin snips	154	8.4 (13/154)	154	1.3 (2/154)	7.0 (1.53–64.70)
	Uganda [6] (2021)	Kitgum and Pader (2016)	Ov16 IgG	154	93.5 (144/154)	153	54.9 (84/153)	8.79 (4.15–18.65)
L. loa	SS [1] (2012)	Amadi and Lui (2001)	Blood microscopy	69	0.0 (0/69)	65	0.0 (0/65)	–
M. perstans	SS [1] (2012)	Amadi (2001)	Blood microscopy	30	66.6 (20/30)	17/34	50 (17/34)	3.22
		Lui (2001)	Blood microscopy	39	41.0 (16/39)	31	9.6 (3/31)	
W. bancrofti	SS [1] (2012)	Amadi and Lui (2001)	Immunochromatographic Test (ICT)	26	0.0 (0/18)	24	8.4 (2/24)	–
T. brucei	SS [1] (2012)	Amadi (2001)	Card Agglutination Trypanosomiasis Test (CATT)	30	0.0 (0/30)	34	5.8 (2/34)	0.84
		Lui (2001)	CATT	39	12.8 (5/39)	31	9.6 (3/31)	
	Uganda [3] (2013)	Kitgum (2009)	CATT	36	0.0 (0/36)	40	0.0 (0/40)	–
T. solium	Uganda [3] (2013)	Kitgum (2009)	Antibody	36	0.0 (0/36)	40	0.0 (0/40)	–
Measles virus	SS [1] (2012)	Lui (2002)	Past history	13	15.38 (2/13)	19	58 (11/19)	0.13 (0.02–0.76)
	Uganda [3] (2013)	Kitgum (2009)	Past history		23.5		6.1	3.3 (0.3–3.8)
			PCR	16	0.0 (0/16)	0	–	–
	Uganda [7] (2016)	Tumangu (2014)	Past history	50	–	50	–	6.0 (1.025–113)

Table 2 (continued)

Pathogen/ pathology	Country [citation] (publication year)	Location (study year)	Assessment of exposure	Cases		Controls		OR (95% CI)
				N	% positive	*N*	% positive	
Chicken pox	Uganda [7] (2016)	Tumangu (2014)	Past history	50	–	50	–	0.50 (0.023–5.22)
Hepatitis E virus	Uganda [3] (2013)	Kitgum (2009)	IgM/G	38	47.4 (18/38)	31	41.9 (13/31)	1.03 (0.33–3.21)
Meningitis	SS [1] (2012)	Lui (2002)	Past history	13	0.0 (0/13)	19	5.56 (1/19)	–
Malaria	Uganda [3] (2013)	Kitgum (2009)	Past history	50	43.1	–	59.2	0.7 (0.2–1.9)
	Uganda [4] (2013)	Odek and Atiak sub counties (2012)	Past history	101	15.84 (16/101)	101	1.98 (2/101)	0.107 (0.02–0.48)
	Uganda [7] (2016)	Tumangu (2014)	Past history	50	–	50	–	0.93 (0.431–1.99)
	Uganda [5] (2021)	Kitgum, Lamwo, and Pader (NA)	Blood smear	154	72.7 (112/154)	154	55.5 (84/154)	2.2 (1.34–3.68)
	Uganda [6] (2021)	Kitgum and Pader (2016)	Past history	154	16.9 (26/154)	153	28.1 (43/153)	0.57 (0.30–1.07)

studies, and most of these articles were of average quality according to the DCP scale. In addition, nine studies reported that they performed paraclinical examinations in all or some of their cases. These included electroencephalogram (EEG: eight studies), magnetic resonance imaging (MRI: five studies), and electromyogram (one study). Paradoxically, not all those who carried out a paraclinical examination mentioned a prior clinical confirmation [12, 13].

WHO Classification

The understanding or use of this classification may vary from study to study. Of the 36 articles that used it, only 21 used the terms "suspected, probable, and confirmed cases." These terms are difficult to disentangle in the literature as the terms "suspect" and "probable" in particular have also been used by some authors who have not used the WHO classification. The difference between these articles and those using the WHO definition is that in the former, these terms do not correspond to a well-defined clinical situation. A case is confirmed by either witnessing an attack of HN (defined as repetitive and involuntary dorso-ventral head movements (nodding) on two or more occasions) or evocative elements in paraclinical examinations such as EEG or MRI. However, of the studies that used the WHO classification, only three performed EEGs and one performed MRI. The rest of the studies with complementary examinations (EEG/MRI/electromyogram) therefore did not use the WHO classification.

Associated Factors and Pathophysiology of NS

Parasitic Infections

Onchocerca volvulus. NS has emerged in areas of hyper-endemicity for onchocerciasis (also known as river blindness), hence the interest in *Onchocerca volvulus* (OV). Six case-control studies have been conducted in Southern Sudan and Uganda and report a positive and significant association between onchocerciasis and NS [13–18]. The risk associated with onchocerciasis varies according to study areas and also to the tests used (Table 2). The OR ranged from 3.14 to 29 in those with onchocerciasis compared to those without [13]. The different tests used were skin biopsy and serological tests (detection of Ov16 IgG by enzyme-linked immunosorbent and detection of OvFAR/MSA by the luciferase immunoprecipitation system). It should also be noted that two studies did not find an association between NS and onchocerciasis [14, 15]. The six individual studies mentioned above were of good quality, according to the NOS. On the other hand, according to the DCP scale, two were of good quality

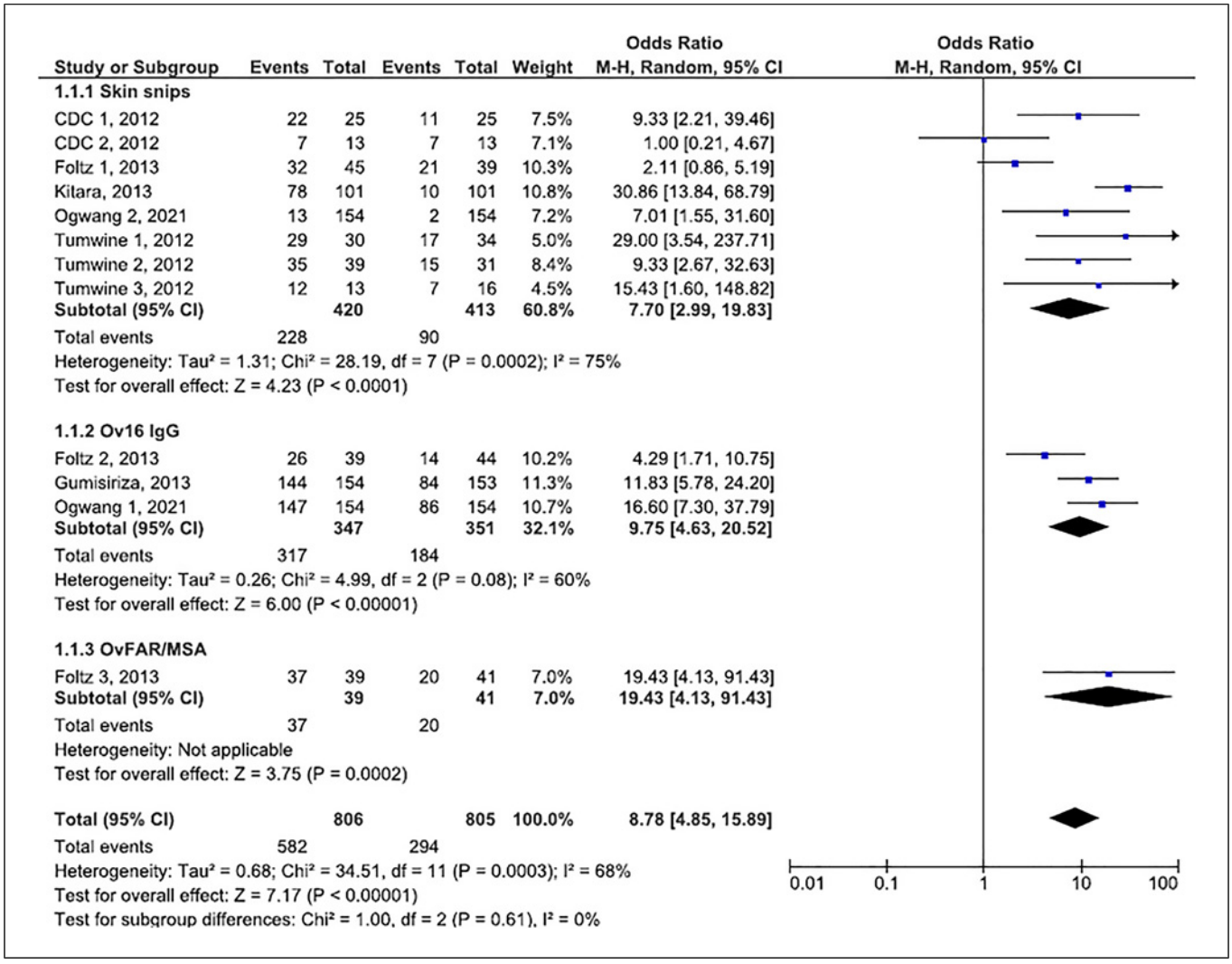

Fig. 5. Forest plot of the association between onchocerciasis and NS.

and the other four were of average quality. Figure 5 shows the forest plot of the meta-analysis of the association between onchocerciasis and NS stratified by the type of test used for onchocerciasis diagnosis. Regardless of the test used for the diagnosis of onchocerciasis, OV remains associated with NS. In addition to case-control studies, a few studies looked for OV in the cerebrospinal fluid (CSF) of people with NS by polymerase chain reaction (PCR), and no OV genetic material was found [5, 19–21]. While the epidemiological association between NS and OV seems clear, there is no evidence to date of direct neuroinvasive activity of the parasite.

Infection with *Mansonella perstans*, another insect-transmitted human filarial nematode, has also been described in one study as a parasitosis associated with NS (Table 2). This study was of good and fair quality according to the NOS and DCP scale, respectively. It was in this same study in Southern Sudan that the association between NOS and other parasites such as *Loa loa, Wuchereria bancrofti, Trypanosoma brucei* was assessed, and none of them were significant [19]. Another study (of good quality by any scale) in Uganda reported that *Taenia solium* (the parasite that causes cysticercosis) and *T. brucei* (the parasite that causes sleeping sickness) diagnosed by serological tests were also not associated with NS [14]. No other studies have been conducted on *L. loa* and *W. bancrofti* to confirm or refute the previous results.

Table 3. Results of meta-analyses of associations between different infections and NS

Infections	Number of surveys	OR [95% CI]	*p* value
Onchocerciasis	12	8.8 [4.85–15.89]	<0.001
Mansonellesis	2	3.2 [1.46–7.07]	0.004
Trypanosomiasis	3	0.8 [0.24–3.03]	0.81
Measles	3	1.2 [0.52–2.83]	0.65
Malaria	5	1.4 [1.02–1.96]	0.04

Viral Infections

The role of measles virus in NS was studied for the first time in 2002 in Southern Sudan, and it was found that a history of measles was a protective factor for NS (Table 2) [13, 19]. In 2009, in Uganda, another study reported that a history of measles was not associated with NS in a multivariate analysis. In addition, no measles virus genetic material was found by PCR in the CSF of either cases or controls [14]. The last study on the subject took place in 2014 and found that a history of measles was ultimately a risk factor for NS [22]. Because of the similarities between NS and subacute sclerosing panencephalitis (SSPE), the authors hypothesized that NS could be a post-measles disorder like SSPE. Other viruses such as hepatitis E [14] and varicella virus [22] have been studied, but none were associated with NS. No studies on bacterial infections have yet been done in the context of the etiology of NS. All results are shown in Table 2. Of the three studies dealing with viral infections [13, 14, 22], two were of good quality according to both the NOS and DCP scales. One article was judged to be of average quality on both scales.

The history of certain diseases such as meningitis (which can be caused by different germs) was also studied, but no significant association was found with NS. A history of malaria was also not associated with NS in several studies in Uganda. In contrast, a positive blood smear for malaria parasites at the time of the survey was associated with NS in one study of good quality according to the NOS and of average quality according to the DCP scale (Table 2).

Table 3 presents an OR (with their 95% CIs) for each infection from a meta-analysis (where appropriate) of the different studies that investigated the association between that infection and NS. It can be seen that, after meta-analysis, only onchocerciasis and mansonellosis remained associated with NS.

Geopolitical Unrest

The link between armed conflict (war) and the occurrence of NS was investigated. One study found that the risk of developing NS was increased in those who reported exposure to munitions (OR = 13.9 [95% CI: 1.4–135.3]). The authors of this study thus hypothesized that exposure to munitions could indicate potential chemical exposure [14]. The association between internal displacement (war-related) and NS was non-significant (OR = 4.29 [95% CI: 0.44–41.95; $p = 0.36$]) [13]. Similarly, a study in northern Uganda found no increased risk of NS in children born after their families had lived in refugee camps compared to those whose families had never lived there. In contrast, children born before their families moved to the refugee camps had an increased risk (OR = 4.28 [95% CI: 1.20–15.15; $p = 0.024$]) compared to those whose families had never lived there [17]. Psychiatric symptoms such as depression regularly found in children with NS were also attributed to the war as part of the post-traumatic syndrome [23]. The three articles included in our review that discussed geopolitical unrest in the context of NS [13, 14, 17] were all of good quality, according to the NOS. According to the DCP scale, two of them were of average quality, and the third were of good quality.

Malnutrition, Nutritional Disorders, and Diet

Subsidiary food insecurity related to wars and frequent household displacements has also led the scientific community toward a possible food etiology [24]. Several nutritional factors have been studied. The first case-control study is probably the one that took place in Mundri County, Southern Sudan, in 2001 [13, 19]. Among the factors that were studied (Table 4), only a specific type of sorghum (Serena) consumed by children was associated with NS (OR = 6.22 (95% CI: 1.2–32.3; $p = 0.049$)). Later in 2013, a study in Uganda also reported that consumption of several foods was not associated with NS [14]. Also in Uganda, emergency food consumption [22, 25] and a history of eating maize or moldy maize [22] were associated with NS. Apart from crushed roots, no other medicinal plants were associated with NS [14]. Of the four articles included in this review that studied food, three were of good quality and one was of fair quality according to the NOS; two were of good quality and two of fair quality according to the DCP scale.

In terms of micronutrients, vitamin B6 (pyridoxine) has been the most studied. In two studies conducted in Uganda in two different areas and over two different time periods, one found no association [14],

Table 4. Nutritional factors associated with NS

Factor	Country [citation] (publication year)	Location (study year)	Assessment of exposure	Cases	% positive	Controls	% positive	OR (95% CI)
				N		*N*		
Malnutrition	Uganda [3] (2013)	Kitgum (2009)	Past history	–	3.9	–	4.1	1.0 (0.2–4.8)
	Uganda [4] (2013)	Odek and Atiak sub counties (2012)	Laboratory investigations	101	47.52 (48/101)	101	35.64 (36/101)	1.63 (0.93–2.87)
Micronutrients								
Vitamin B6 (pyridoxal-5′-phosphate)	Uganda [3] (2013)	Kitgum (2009)	HPLC fluorometric detection	41	73.2 (30/41)	42	64.3 (27/42)	1.22 (0.41–3.59 s)
	Uganda [8] (2016)	Paicho and Atiak sub counties (2013)	ELISA assay	66	88.0 (58/66)	73	42.0 (31/73)	7.22 (2.24–23.26)
	Tanzania [9] (2014)	Mahengue (2005)	HPLC fluorometric detection	10	2.11 µg/L (range 1.0–4.86)	10	2.76 µg/L (range 1.07–6.33)	No difference
Vitamin B12 (cobalamin)	Uganda [3] (2013)	Kitgum (2009)	Immunoassay	25	8.0 (2/25)	12	8.3 (1/12)	1.46 (0.09–22.82)
Vitamin A (retinol)	Uganda [3] (2013)	Kitgum (2009)	HPLC-UV/VIS	25	40.0 (10/25)	12	33.3 (4/12)	2.15 (0.41–11.12)
Vitamin B9 (folate)	Uganda [3] (2013)	Kitgum (2009)	Microbiological assay	11	9.1 (1/11)	9	0.0 (0/9)	–
Zinc	Uganda [3] (2013)	Kitgum (2009)	–	17	47.1 (8/17)	12	66.7 (8/12)	0.72 (0.13–3.94)
Selenium	Uganda [3] (2013)	Kitgum (2009)	–	17	100 (17/17)	12	100.0 (12/12)	–
Copper	Uganda [3] (2013)	Kitgum (2009)	–	17	0 (0/17)	12	0.0 (0/12)	–
Foods								
Serena (sorghum type)	SS [1] (2012)	Lui (2002)	Past history	–	53.85	–	15.79	6.22 (1.20–32.3)
Baboon meat	SS [1] (2012)	Lui (2002)	Past history	–	69.23	–	33.33	4.50 (0.97–20.83)
Baboon brain	SS [1] (2012)	Lui (2002)	Past history	–	46.15	–	22.22	3.00 (0.63–14.23)
Colored seeds	SS [1] (2012)	Lui (2002)	Past history	–	83.33	–	50.00	5.00 (0.82–30.46)
Unripe sorghum	SS [1] (2012)	Lui (2002)	Past history	–	92.3	–	83.33	2.40 (0.22–26.12)
Red sorghum	Uganda [3] (2013)	Kitgum (2009)	Past history	–	98.0	–	100	1.3 (0.0–125.9)
Relief foods	Uganda [8] (2016)	Paicho and Atiak sub counties (2013)	Past history	66	64.0 (40/66)	73	27.0 (18/73)	4.05 (1.23–13.28)
	Uganda [7] (2016)	Tumangu (2014)	Past history	50	–	50	–	4.0 (1.27–17.6)
Spoiled relief foods	Uganda [3] (2013)	Kitgum (2009)	Past history	–	43.1	–	46.9	0.3 (0.1–1.3)
			Past history	–	21.6	–	12.2	1.5 (0.0–5.5)

Table 4 (continued)

Factor	Country [citation] (publication year)	Location (study year)	Assessment of exposure	Cases	% positive	Controls	% positive	OR (95% CI)
				N		*N*		
Supplementary foods	Uganda [3] (2013)	Kitgum (2009)						
Seeds meant for planting	Uganda [3] (2013)	Kitgum (2009)	Past history	–	60.8	–	65.3	0.6 (0.1–2.3)
River fish	Uganda [3] (2013)	Kitgum (2009)	Past history	–	96.1	–	100	0.3 (0.0–125.9)
Insects	Uganda [3] (2013)	Kitgum (2009)	Past history	–	41.2	–	32.7	0.8 (0.2–2.9)
Rodent brain	Uganda [3] (2013)	Kitgum (2009)	Past history	–	54.9	–	51.0	1.8 (0.3–12.3)
Guinea fowl brain	Uganda [3] (2013)	Kitgum (2009)	Past history	–	7.8	–	4.1	2.4 (0.4–14.8)
Bush meat	Uganda [3] (2013)	Kitgum (2009)	Past history	–	100	–	100	–
Cassava	SS [1] (2012)	Lui (2002)	Past history	–	84.62	–	94.44	0.32 (0.03–4.01)
	Uganda [3] (2013)	Kitgum (2009)	Past history	–	100	–	100	–
Maize	Uganda [7] (2016)	Tumangu (2014)	Past history	50	–	50	–	4.0 (1.002–26.5)
Moldy maize	Uganda [7] (2016)	Tumangu (2014)	Past history	50	–	50	–	4.33 (1.39–18.9)
Use of traditional or herbal medicines								
Crushed roots	Uganda [3] (2013)	Kitgum (2009)	Past history	–	39.2	–	16.3	5.4 (1.3–22.1)
Crushed leaves	Uganda [3] (2013)	Kitgum (2009)	Past history	–	7.8	–	2.0	3.4 (0.2–45.8)
Crushed flowers	Uganda [3] (2013)	Kitgum (2009)	Past history	–	0.0	–	2.0	0.9 (0.1–5.6)
Inhaled medicine	Uganda [3] (2013)	Kitgum (2009)	Past history	–	2.0	–	0.0	0.2 (0.0–1.5)

HPLC, high-performance liquid chromatography; HPLC-UV/VIS, HPLC method with ultraviolet-visible spectrophotometry detection; ELISA, enzyme-linked immunosorbent; SS, South Sudan; NU, Northern Uganda.

while the other found a strong association [25] (Table 4). An earlier study in Tanzania found no difference between the mean pyridoxine measured in 10 cases and their 10 controls [26]. Vitamins A (retinol) and B12 (cobalamin), zinc, copper, and selenium were not associated with NS [14] (Table 4). Among these three studies providing information on micronutrients, the first was of good quality according to both scales [14], the second was of good quality according to the NOS and of average quality according to the DCP scale [25], and the third was of average quality according to the NOS and good quality according to the DCP scale [26].

Apart from certain infections and vitamin B6 (meta-analysis: OR = 4.3 (95% CI: 2.34–7.83; $p < 0.001$)), no other factors were studied repeatedly in the NS. It can be seen that vitamin B6 remains a factor positively associated with NS.

Malnutrition itself was not associated with NS [14]. Elsewhere, there was no association between the nutritional status of NS cases and controls in bivariate analysis (Table 4), but in multivariate logistic regression, a positive correlation and significant difference were observed ($t = 0.142$; $p = 0.044$) [18]. Both studies were of good quality, according to both scales.

Pathophysiology

The pathophysiology of NS is often confused with the study of risk factors in the literature. Indeed, certain factors are often studied in an attempt to understand their role in the pathogenesis of NS. In this section, we will present these risk factors along with their possible role in the pathogenesis of NS.

Toxins

It has been suggested that the positive association found between ammunition and NS in Uganda was related to the chemical toxins released by the ammunition [14]. This association was not found in Sudan [15, 19]. Similarly, the mechanism proposed to explain the association between NS and foods or herbs previously mentioned is the contamination of these by toxins. In a study conducted in Uganda (and judged to be of good quality according to the DCP scale), similarly high levels of total aflatoxin and ochratoxin, mainly in millet, sorghum, maize, and groundnuts, were found in homes with and without children with NS. Furthermore, they did not find a significant association between NS and levels of total aflatoxin, ochratoxin, and doxynivalenol, thus concluding that there was no evidence of an association between NS and consumption of mycotoxins in contaminated food [27]. Another study (this time on individuals) measured the amount of α-zearalenol, T-2 toxin, and aflatoxin M1 in the urine of 50 children with NS and 50 controls. There was no difference between NS cases and controls [28]. It should be noted that this study was rated as poor quality according to both our scales.

Autoimmunity/Immunity

Since evidence of direct neurotoxicity of OV could not be demonstrated despite epidemiological evidence of its association with NS, it was hypothesized that an immune-mediated mechanism might be involved [9]. When comparing serum levels of leiomodin-1 antibodies between cases (52.7%) and controls (30.9%), the difference was significant (p = 0.024), and these antibodies were associated with NS (OR = 2.7 [1.1–6.5]). It was then confirmed that leiomodin (an intracellular protein) is not only expressed in smooth muscle tissue and the thyroid but also in the central nervous system and neurons. Finally, leiomodin-1 antibodies, purified from NS patients, were cross-reactive with OV. The authors concluded that NS could be an autoimmune seizure disorder caused by molecular mimicry with OV antigens [9]. This study was judged to be of fair quality according to both scales.

In another case-control study aimed at confirming this association, the detection of anti-leiomodin-1 antibodies was done by a cell-based test, and Western blot, in the sera and CSF of the participants; no association was found between the presence of anti-leiomodin-1 antibodies and onchocerciasis-associated epilepsy (OAE), including NS. Moreover, these antibodies were not found in the CSF of people with OAE or in that of their controls (persons with acute-onset neurological conditions). Finally, the leiomodin-1 protein was found in the capillaries of post-mortem brain tissue and not in the brain cells. The authors concluded that NS was not caused by anti-leiomodin-1 [10]. In the same study, onchocerciasis-positive individuals did not have more leiomodin-1 antibodies than onchocerciasis-negative individuals. However, this study was judged to be of fair quality according to the NOS and of poor quality according to the DCP scale.

Other autoantibodies have been studied in the pathogenesis of NS in Tanzania. These are anti-NMDA (N-Methyl-D-Aspartate) and anti-voltage-gated potassium channel, but none of these antibodies were found in the serum of patients with NS alone (n = 6) or NS with other types of epilepsy (n = 16). Voltage-gated potassium channel antibodies were found in 1 of 7 controls [26]. This was a medium-quality study according to the NOS and good quality according to the DCP scale.

Metabolic Disorders

The plasma concentration of the neurotoxic substance 3-hydroxykynurenine (3-HK) was higher in children with NS than in their controls (OR = 4.5 [95% CI: 1.37–14.77; p = 0.013]). It has been hypothesized that the decrease in plasma vitamin B6 concentration is linked to an increase in 3-HK concentration, which would explain why these two biological parameters are inversely associated in individuals with NS [25]. These results come from a study of good quality according to the NOS and of fair quality according to the DCP scale.

Other metabolic disturbances have been observed including low serum calcium and bicarbonate levels and an elevated anion gap (difference between the sum of cations and anions in blood plasma) in 10 children with NS [29]. A case-control study (judged to be of good quality by both scales) of 101 NS cases and their 101 controls in Uganda found that high anion gap was associated with NS [18].

Also at the metabolic level, biotinidase and acetylcarnitine deficiency (involved in mitochondrial cell metabolism) were associated with NS in Uganda [30].

However, this was a poor-quality study according to the NOS and of average quality according to the DCP scale.

Genetics

Due to the occurrence of several cases in the same family and the absence of NS in some neighboring families in the same environment [3, 13, 14, 31], the role of genetics in the pathophysiology of NS has also been studied. In 48 NS cases and their 48 controls, NS was significantly associated with both the protective HLA haplotype: HLA-B*42:01, C*17:01, DRB1*03:02, DQB1*04:02, and DQA1*04:01, and the susceptible motif: Ala24, Glu63, and Phe67 in the peptide-binding groove of HLA-B. These results suggest that immunogenetic fingerprints in HLA peptide-binding grooves are tentatively associated with protection or susceptibility to NS. Therefore, different HLA molecules may explain why, under similar environmental factors, only some children within the same families, tribes, and districts develop NS, while others do not [32]. This study was judged to be of fair quality according to the two scales.

Other Elements of the Pathophysiology

After observing a small difference in monkey meat consumption between cases and their controls in 2013 (OR = 4.5 (95% CI: 0.97–20.83; $p = 0.07$)) [19], the first post-mortem study of 5 cases of NS in 2018 concluded that NS is a tauopathy and could be a neurodegenerative disease [33]. A second post-mortem study refuted this hypothesis 1 year later in favor of a neuroinflammation process involved in NS [34]. These two post-mortem studies were not assessed by the NOS and were of fair quality according to the DCP scale. In addition, results from a study of good NOS quality and fair DCP quality suggest a possible role for central nervous system complement activation in the pathogenesis of chronic NS [16].

In the context of the role of OV in the pathogenesis of NS, it was found that epilepsy was associated with low serotonin levels ($\beta = -2.967$; $p = 0.017$). High levels of serotonin (a neuromodulator) therefore do not seem to be involved in the pathogenesis of OAE (including NS) [35]. This study was of average and poor quality according to the NOS and DCP scales, respectively.

Other results suggested that macrophage migration inhibitory factor (MIF) may play a dual role in NS. Highly expressed MIF genotype seems to be associated with disease protection. However, high plasma MIF levels may contribute to autoimmunity, neuroinflammation, and epilepsy [36]. These results are from a study of fair quality according to the NOS and good quality according to the DCP scale.

Management and Treatment of NS

Although much remains to be discovered about NS, in particular regarding its pathophysiology and etiology, numerous studies have made it possible to make considerable progress in the management of the disease. In the case of symptomatic treatment of NS, guidelines for the management of NS have been proposed [37] under the leadership of the Ugandan Ministry of Health. A study was then conducted to observe the response to this management (including sodium valproate for seizures, management of behavior and emotional difficulties, nutritional therapy, and physical rehabilitation) [38]. The primary outcome was seizure freedom (over a period ≥1 month), and 25% (121/484) of NS patients achieved this goal. The results of the secondary endpoints were also satisfactory: >70% reduction in seizure frequency; behavior and emotional difficulties resolved in 194/327 (59%) patients; 193/484 (40%) patients had enrolled in school including 17.7% who had earlier withdrawn due to severe seizures; and over 80% had achieved independence in basic self-care. This study was of good quality according to both scales.

Another study, conducted by the same team in Uganda, assessed the relationship between *Plasmodium falciparum* and seizure control in children with NS [39]. The authors concluded that in patients with NS, both asymptomatic and symptomatic malaria were associated with an increased risk of seizures and poorer seizure control. This study was also of good quality according to both scales.

A descriptive, retrospective study aimed to describe the presentations and rehabilitation outcomes of a series of 32 cases of children with NS [40]. After 13 months of regular nutritional and multivitamin supplementation and anticonvulsant treatment, severe wasting was reduced from 9.7% to 2.6% and moderate wasting from 19.7% to 2.6%, respectively, while severe and moderate stunting were reduced from a combined prevalence of 54.8–12.8% and 7.7%, respectively. According to the authors, a regular, high-quality local diet, multivitamin supplementation, anticonvulsants, and regular monitoring can help reduce or even completely stop epileptic seizures in children. This study was of fair quality according to the DCP scale. Another longitudinal study (of average quality according to the NOS and good quality according to the DCP scale) also reported that after treatment (local food supplements, sodium valproate (200 mg BD) with or without carbamazepine (200 mg BD), multivitamins, and psychosocial support), NS was associated with better nutritional status [41].

A randomized clinical trial was conducted to assess whether ivermectin could reduce the frequency of seizure in OAE [42]. It found a borderline association between ivermectin treatment and seizure freedom at the fourth month of follow-up (OR = 1.652, 95% CI: 0.975–2.799; $p = 0.062$). However, ivermectin treatment did not significantly increase the probability of being seizure free at individual follow-up visits. This study was of fair quality according to both scales.

Discussion

The aim of our work was to map out the exact number of cases of NS, to provide a list of factors associated with NS that have already been studied and the pathophysiological mechanisms involved, and finally to take stock of the state of knowledge regarding the diagnosis and management of NS. In the discussion, the level of evidence will be taken into consideration.

All the articles included in our work have contributed significantly in one way or another to one or more of the objectives of this study. Thus, studies that specified the definition of NS they used combined with those that deal with pathophysiology, contributed to enriching the debate around the definition; those that reported clinical and/or paraclinical confirmation of NS in their method also enriched the discussion on the definition (with a view to its refinement) but also provided a synthesis for caregivers in daily clinical practice. Similarly, the articles describing the treatment of NS cases in their study helped review the different options for managing the disease and thus enrich the clinical data. All the articles were used to produce maps of the spatio-temporal evolution of NS, and those that specified the number of cases enabled us to observe the extent of the disease on these maps. As a reminder, online supplementary Table B.2 in the appendices identifies the effective contribution of each article.

What We Know about NS

Spatial and Temporal Distribution of NS

The results of our SR suggest that NS is only present in sub-Saharan Africa (SSA), specifically in Central and East Africa. Liberia (West Africa) was not included in this review, although it is sometimes reported in reviews [43]. Indeed, a study in Liberia [44] is often cited in the literature as presenting cases of epilepsy with HN that would have occurred even before those in Tanzania described by Aall-Jilek [45] and therefore considered the very first cases of NS. However, this article was excluded due to lack of case description and unclear symptomatology. Whereas cases from Tanzania previously described by Aall-Jilek were reviewed more than once by other researchers, once the disease was better defined, and the diagnosis was "confirmed," this was not the case in Liberia. Another reason for not including this article is that no other cases were reported later elsewhere in Liberia. However, the possibility that other cases of NS have occurred elsewhere and perhaps even earlier than in East Africa cannot be ruled out.

Another paper from a completely different part of the world was also removed from this SR for similar reasons. This is an article describing a case of NS in India [46].

This review also reveals that NS may have existed in Central Africa for longer than previously thought. This suggests that there are probably some small errors in the timing of NS. The number of cases has been increasing over time (shown in Fig. 4). In particular, the substantial rise during the second period coincides with the wars in Uganda and South Sudan. This increase in cases could also be linked to the WHO conference which helped researchers better understand the disease. The third period is essentially about the increased interest in Central Africa.

Our study reveals that cases of NS were already present in Cameroon in the 2000s and possibly earlier. This finding could be relevant for other countries in Central Africa. It is possible that the public health actions of the ministries in these countries were focused on other issues of interest, which explains why cases were not discovered earlier. Indeed, the studies conducted in Central Africa so far have been by teams and researchers with an interest in NS. There is therefore no national funding for NS research. In contrast, in Eastern countries, it is the involvement of the government that has enabled progress in research on the subject and collaboration with organizations such as the WHO or the CDC. The discovery of cases in war refugee camps has been a major factor in the involvement of governments; however, East Africa remains an example in the fight against NS. It is therefore important for Central Africa that NS becomes a political cause so that actions are not isolated to one group of researchers but coordinated by states.

It would also be important for local research teams to take more interest in NS and then train health workers. Indeed, teams involved in Central Africa remain mainly external teams, and the lack of disease knowledge remains an obstacle to the establishment of an adequate management system.

Just as the temporality of the onset of NS cases may have been distorted, it is possible that their spatiality was also distorted or at least incomplete. We are indeed particularly intrigued by Burundi and Rwanda, which have no recorded cases. However, no study has been conducted there, which may explain this phenomenon. In addition, knowledge of the disease is limited, and therefore, few doctors/health workers outside those working on the topic or present in high-prevalence areas know about it.

Quality of the Articles and Operational Definition of NS

The quality assessment of the articles included in this review was not intended to exclude "poor quality" articles from the final analyses but rather to highlight the methodological difficulties of the studies that had been conducted on the topic in order to draw the attention of researchers to future studies.

Although the majority of the studies in this review were assessed as being of good quality according to the NOS, 11% were of poor quality and 31% were of fair quality. These figures reflect the methodological and logistical difficulties associated with NS studies, which may also be expressed through the difference in results often observed from one study to another, particularly in studies regarding associated factors.

In addition to the methodological challenge, there is the challenge of diagnosing the cases. Even if a study is methodologically well designed, its results will be of little value if it did not confirm the diagnosis of NS. The DCP scale we proposed revealed that less than half of the studies were of good quality, and the percentage of poor-quality studies was similar (10%) to that observed with the NOS. This result shows once again that several studies in the literature need to be interpreted with caution, but above all, it shows the need to propose a clear, evidence-based definition of NS that would be simple, operational, and easy to set up in an epidemiological survey.

Onchocerciasis and NS

Case-control studies regarding the association between NS and OV were not "real" case-control studies since the exposure was measured at the same time as the disease. It is therefore impossible to say with certainty that onchocerciasis preceded NS in children with NS. ORs from these studies should therefore be interpreted with caution.

The meta-analysis carried out in this work shows that overall, onchocerciasis is well associated with NS (OR = 8.78 [95% CI: 4.85–15.89; $p < 0.001$]). Similarly, a 2019 SR of the prevalence, etiology, and treatment of NS found a significant difference ($p < 0.0001$) of 21.4% between the pooled prevalence of OV in NS cases and controls [2]. However, the interpretation of the association (in our meta-analysis) must take into account the large heterogeneity between the different studies. In our opinion, this heterogeneity is probably related to the various diagnosis approaches used, which varied greatly from one study to another, despite the tests being all standardized and validated. In addition, it would be interesting to look for NS-associated factors outside of Sudan and Uganda; this may or may not corroborate the association between OV and NS. Indeed, despite the epidemiological association found, so far, no biological substrate supports the role of OV in the pathogenesis of NS. While awaiting its identification, we believe that we should remain cautious in interpreting this association (which remains epidemiological) and the emphasis that some authors put on OV, which could imply a "causal role" of the latter with regard to NS.

In the context of the discussion around the association of OV and NS, the work of some researchers has led them to create a new concept: "onchocerciasis-associated epilepsy (OAE)" [47]. The following criteria define OAE: person with epilepsy living in an onchocerciasis-endemic region; onset of epilepsy between the ages of 3 and 18 years, geographical clustering of persons with epilepsy in the village; no obvious cause for the epilepsy; normal neurological development before the onset of epilepsy [48]. The problem with this term is that over time, it has become accepted that all so-called epilepsies are in fact due to OV, which is incorrect and leads to much confusion. The definition of OAE not only ignores the fact that in OV-endemic areas the causes of epilepsy are diverse and co-infection with OV can be purely coincidental, but it also leads researchers to believe that OAE and NS are one and the same entity, which is not the case. For example, the authors of a recent review [43] reported that no association was found between viruses and NS in the paper by Roach et al. [49]. However, in this article, OAEs were included, among which there were no cases of NS (which is why this article is not included in our SR). The risk of grouping certain forms of epilepsy together in this way is that one may draw the wrong conclusions. Further studies on NS should only consider proven cases of NS to draw conclusions.

In a recent paper, it was reported that onchocerciasis as a risk factor for epilepsy met some of Bradford Hill's criteria for causality (strength of association, consistency, temporality, and biological gradient) and not others (specificity, plausibility, consistency, experimentation,

and analogy) [50]. These results both reinforce that there is indeed a link between some epilepsies and onchocerciasis, but also reinforce the idea that this relationship should be taken with great caution because of the many misunderstandings that remain, such as the pathophysiological mechanism. To date, there is no study that suggests that onchocerciasis is the "cause" of NS.

Management of NS

From the results of this SR, we can say that symptomatic management of NS cases is effective in reducing their symptoms. This management must start early and be adapted to the clinical situation of each individual. Management must be multifactorial and multidisciplinary, based on two main axes: the pathophysiological (or somatic) axis and the psychological axis. The treatment is symptomatic and not curative. It is mainly a question of drug (anticonvulsant) and nutritional management. The current spatio-temporal distribution (East vs. Central Africa) of NS may also reflect the availability of the usual anti-epileptic drugs (phenytoin, phenobarbitone, and carbamazepine). The lack of availability of these common anti-epileptic drugs in areas with a high prevalence of epilepsy is therefore a real obstacle to the adequate management of children with NS. Some work suggests that metabolic acidosis should also be monitored and eliminated [18, 29]. Good control of malaria would also help with better seizure control [39]. From a psychological perspective, one study reported: "socially, daily seizures and physical characteristics such as salivation and mood changes make it difficult to interact with children with NS. In addition, sick children are often separated from their siblings for fear of transmission of the disease through saliva" [51]. They therefore have psychosocial difficulties which deserve specialized follow-up. The psychological component will also help with social reintegration. This psychological aspect also concerns, if not more so, the parents (or guardians) of these children [23, 51, 52], who often have to make many sacrifices in order to follow their children.

Wars

Most of the countries in East Africa where NS has been prevalent have been subject to numerous wars, internal displacements, food insecurity, and malnutrition [1]. The majority of the population believes that the war played a role in the occurrence of NS in children [53, 54]. Although self-reported exposure to ammunition was found to be associated with NS in one study [14], we believe that geopolitical unrest can be eliminated as a factor in the occurrence of NS. Rather, they may play an intermediary role in the link between malnutrition and NS. The first epidemiological argument against war in NS is that not all areas where NS cases occurred were conflict zones (e.g. Cameroon or Tanzania) or where conflicts were not on the same scale or rather did not lead to the same dire situations as in Uganda (e.g. CAR). The second epidemiological argument is the lack of association found between internal travel and NS [13].

What Should Be Clarified

Clearer Definition and Diagnosis

The definition or diagnosis of NS is not unanimously accepted by the research community. We found a significant proportion of studies (20.7%) that referred to NS without giving a definition. This raises the problem of diagnostic certainty. Although HN would be the "pathognomonic" feature of NS, this symptom can occur in contexts other than NS, such as myoclonic epilepsy [55–58] or complex partial seizures of temporal lobe origin [59, 60]. These facts highlight the complexity of this syndrome and, consequently, the difficulty of making a definite diagnosis. As the disease is not well known, it is important that experts in the field can give their opinion and verify the diagnosis of NS whenever possible. Case confirmation was performed in 70.5% of the articles in this review. The large number of articles that failed to confirm or report on who confirmed the cases raises a methodological problem as a simple report of HN may not be sufficient to make a diagnosis of NS in a patient.

The articles including paraclinical examinations have added value in terms of diagnostic certainty. The most frequently performed test was EEG. However, it was only reported in nine articles, and there are two reasons for this: first, it is often difficult to carry out certain tests in population-based studies because of the large number of people. Second, the areas where NS cases occur are often precarious areas lacking adequate technical facilities. Other investigations such as MRI could contribute to the elucidation of pathophysiological mechanism of NS but are even less accessible than EEG [5].

All the above points, i.e., the use of a precise definition of NS, the confirmation by neurologists and/or general practitioners trained in the diagnosis of NS, the use of paraclinical examinations, in particular EEG, would certainly contribute to improving both the diagnosis of NS and the quality of the studies. This also raises questions about the validity and reliability of the

cases reported in the literature and therefore about the real prevalence of NS, which may have been overestimated in the areas where the disorder has been studied.

Special Case of the WHO Classification

The WHO expert consensus classification is currently the most structured procedure for diagnosing NS [61]. However, it has limitations. The main limitation is in the confirmation of cases. A case is said to be "confirmed" if the HN seizures have been observed by a healthcare professional, if there is a video recording of these seizures, or if there are evocative signs on EEG or MRI [61].

The first two methods (having observed a seizure or being in possession of a recording) are not objective, and furthermore, the presence of HN does not necessarily equal NS. In this case, even a trained healthcare worker could make a mistake. Ideally, one would need a biological substrate to confirm the diagnosis, which so far has not been determined, or a consensus of several experts rather than relying on a single person who may not be that experienced. In many studies, the description of the patient's parents or guardian was sufficient to make the diagnosis if the preconditions were met (i.e., suspect case and probable case). Probable cases were immediately treated as NS. Indeed, of the 36 papers that used the WHO classification, only five (13.9%) were able to confirm cases according to the WHO criteria.

The third method of confirmation (paraclinical examinations) is also a limitation of this classification. This is a logistical and financial limitation both in epidemiological studies and in routine clinical practice due to the resource limitations of the areas in which NS cases occur. Furthermore, there is no radiological image or EEG pattern that is "pathognomonic" of NS. The similarities between the findings of a number of studies (such as generalized electrodecrement and paraspinal electromyography dropout consistent during EEG [31, 62] and cerebral/cerebellar atrophy [31, 63, 64] or intraparenchymal pathologies (changes in the hippocampus, gliotic lesions, and subcortical signal abnormalities) [21] visible on MRI in some patients) are the only clue to date. In other words, a normal image is not synonymous with the absence of NS, and the paraclinical features (whether electrophysiological or radiological) could equally well be a function of the stage of the disease. The WHO classification therefore refers to EEG patterns which are "suggestive" of NS and not EEG patterns which diagnose NS.

Ultimately, not seeing HN during a consultation is not synonymous with the absence of NS. Similarly, a normal EEG or MRI is not synonymous with the absence of NS, and conversely, an abnormal image is not synonymous with NS. The history of the disease and the clinical signs/symptoms should allow us to get as close as possible to the diagnosis. What seems to be most relevant is confirmation by a neurologist, a pediatrician, or a general practitioner trained in the detection of epilepsy and NS. Complementary examinations, when available, support the diagnosis, but in no case should their absence delay the management of a case. Another expert conference held in Gulu in 2015 [6] already raised the idea of modifying this WHO definition, but no proposal has yet been made in this sense.

Factors Associated with NS

As mentioned above, the only factor that is known to be associated with NS is OV. The other factors that have been studied have only been studied to a limited extent and deserve to be further explored.

Mansonellosis

Apart from OV, *M. perstans* is another parasite found associated with NS. Although the study that provided this result was judged to be of good and fair quality according to the NOS and DCP scales, respectively, the association of *M. perstans* with NS should be investigated further, as should parasites found not to be associated with NS.

Measles

Challenges for the study of infectious agents are not the same. While for onchocerciasis, several examinations can either demonstrate an ongoing infection or a past exposure, it is more complex to confirm a past medical history of measles during an epidemiological investigation. This explains why in the three studies addressing the relationship between measles and NS, two [13, 22] of them relied only on patient history (self-report) and only one [14] performed CSF PCR of cases only. The value of self-reporting, especially for this type of infection, is limited (due to its rather particular clinical picture); however, there are differential diagnoses such as Kawasaki syndrome [65, 66] which limit the reliability of this self-reporting. The inconsistency of results in the measles-NS association may be related to the specificities of each geographical area, but it could also be related to biases created by self-reporting. It is therefore complicated to determine what role measles might play in the pathogenesis of NS, even if some authors equate it with SSPE [22] with arguments mentioned earlier. Many of these arguments have recently been refuted [43]. An argument against the association between measles and NS is certainly

the negative CSF PCR of the 16 patients [14]. Measles should also be the subject of future multicentric epidemiological studies.

Nutritional Factors

We have made a clear distinction between the food consumed (the type of nutrition) and the abnormalities of certain micronutrients in the serum which, together with certain clinical features (such as stunting, etc.), indicate malnutrition. The consumption of food aid received in the refugee camps was associated with NS. This result is quite surprising, especially since all families ate this emergency food, including families in which no case of NS was diagnosed. The low-quality food to which the refugees were exposed may have led to poor nutritional status, particularly in growing children. This hypothesis is one of the arguments that led to the idea that malnutrition could be a risk factor for NS.

The role of toxins in food (regardless of their origin) cannot yet be completely ruled out, although the only case-control study that examined mycotoxins in children's urine found no association with NS [28]; the latter was judged to be of poor quality by both our scales. It would be necessary to re-evaluate these toxins in future case-control studies, especially as another study of good quality according to the DCP scale found toxins (total aflatoxin, ochratoxin, and doxynivalenol) in some foods consumed in a Kitgum district (Ugandan) [27]. A recently published review (April 2022) looks at the key role that food sources may have in the development of NS [67]. In this paper, the authors investigated the sources of nutrition (other than emergency food aid) in food-insecure populations at risk of NS. A wild mushroom (*A. bingensis* Heinem; species known only in SSA) is reported to harbor a hydrazine compound (phenylhydrazine agaritine) with the potential to lower vitamin B6 levels, generate DNA-damaging free radicals, and modulate neuronal expression of tau. B6 hypovitaminosis was shown to be present in individuals with NS, but further studies should confirm this association, especially as this hypovitaminosis was accompanied by an increase in the average plasma level of 3-HK, a potentially neurotoxic molecule [25].

In any case, good nutrition is a fundamental part of the management of NS and has proved its worth as we have discussed above. This may support the hypothesis that malnutrition is more a consequence of NS than a risk factor.

Pathophysiology of NS

It is also difficult to say whether the metabolic disorders (acidosis, high anion gap) found in NS are causes or consequences of the disease. Also, the number of studies conducted on the subject is limited, and more studies should be performed (if possible, at an earlier stage of the disease) in different places. It has been previously suggested that the metabolic acidosis found in NS may be the result of mitochondrial dysfunction [18]. Although this hypothesis has not yet been tested, researchers note that the clinical presentation of NS cases is similar to that of individuals with mitochondrial diseases. These same authors raise the possibility that these mitochondrial dysfunctions may be linked to specific family exposure, as in the case of environmental contamination or specific contaminated food rations in refugee camps [18]. NS could be caused by these mitochondrial abnormalities and thus be part of the so-called mitochondrial epilepsies [68, 69]. This avenue should also be explored in the pathophysiology of NS.

Post-mortem examination of brains has suggested a neuroinflammatory process [34]. The question now is what causes this neuroinflammation? This inflammation could itself be triggered by the factor involved in NS. Improving our knowledge of the origin of NS will certainly help elucidate the pathophysiological mechanism behind this neuroinflammation.

Some Recommendations

In relation to the above, we make the following recommendations: as discussed previously, the geographical distribution of NS might not be accurate. To improve the detection of NS cases, healthcare teams in SSA should be made aware of the existence of NS and trained to detect it. Therefore, there is a need to further raise awareness and improve knowledge of NS by including it, for example, into the neurology curricula of medical schools in SSA and by implementing more epidemiological studies on NS, to get a better picture of its prevalence.

We also mentioned the need to have a more operational definition of NS to improve the quality of studies on NS while harmonizing them. We believe that NS is indeed an epileptic encephalopathy with atonic seizures. Based on the WHO classification, we propose the following definition for NS in epidemiological surveys: "non-isolated occurrence (at least two people in a small geographical area such as a village) of HN between 3 and 18 years of age in a previously normal person. The frequency of HN can be variable from 1 to 20 HN/min but has a better diagnostic value if it is above 5 HN/min (HN frequencies are lower in Central Africa, particularly in CAR [3]). HN may or may not be accompanied by other neurological, psychiatric, or physical disorders. Prodromal signs/symptoms (especially diminished intellectual capacity) can be a major criterion in the diagnosis. The diagnosis should be made by a neurologist or a trained physician. In the clinical evaluation of a patient

(outside of an epidemiological investigation), the diagnosis may be enhanced by EEG or MRI abnormalities. However, the absence of these examinations should in no way prevent diagnosis and management of the patient." Until the mystery of the etiology of NS is solved, the scientific community, with the help of public authorities, should work to provide effective care for children suffering from NS.

Limitations of the Study

The main limitation of this SR is the aggregation of data. Indeed, data such as age and especially the number of cases are certainly biased due to the fact that several studies took place in the same places and on the same participants in some cases. However, the aim was to give an order of magnitude of what was done without seeking perfect accuracy of the figures. Furthermore, when aggregating the data, our rationale was based on studies and not articles, which allowed us to limit duplication. The choice not to include articles from qualitative studies could be seen as a limitation but remains a methodological choice, and our results are related to this choice. Finally, the DCP score proposed in this work is not yet validated.

The risk of bias within studies was considered through the assessment of article quality by two scores. Even if there was a publication bias, we think it was very limited. Indeed, we did not place any restrictions on the language or type of journal for the publications included in this SR. Furthermore, in addition to gray literature, we considered all other forms of scientific publication. We also found and included certain articles through the references of previous articles. The existence of articles describing a single case suggests a willingness to publish in this field (given the limited knowledge and interest in the subject).

Conclusion

NS does exist in Central Africa, notably in Cameroon, DRC, and CAR, and is therefore no longer restricted to East Africa, where the incidence now seems to be zero. Numerous studies have shown that early symptomatic management of patients with NS is effective and can be carried out (depending on the case) even at the community level. In addition, the psychosocial impact of NS is significant, and it is therefore up to public authorities to design care programs for these children (depending on the scale of the problem in each geographical area).

The main challenge for the scientific community remains the identification of NS etiology, which would not only improve patient management but would also help prevent the disorder. Although no single factor has been identified as the cause of NS so far, some deserve special attention. As most of the etiological studies have been done in East Africa, we believe that a multicentric and inter/transdisciplinary etiological study which would take into account several potential factors in different environmental and social contexts should be envisaged.

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Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no competing interests to declare.

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Author Contributions

The authors' contributions according to the ICMJE recommendations are as follows: substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: S.M., D.D., D.N.A., and F.B; drafting the work or reviewing it critically for important intellectual content: S.M., A.S.W., and F.B; final approval of the version to be published: S.M., A.S.W., and F.B; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: S.M., D.D., D.N.A., A.S.W., and F.B.

Data Availability Statement

Data supporting the findings of this study are available from the corresponding author upon request.

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