

# BMJ Open Nodding syndrome: bridging the gap – a scoping review protocol

Ana Cristina De Castro , Ivan Ortega-Deballon

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## ABSTRACT

**Introduction** Nodding syndrome (*NS*) is an encephalopathy of unknown origin that affects children aged between 3 and 15 years old. Cases have been reported since the 1950 in Tanzania and South Sudan, the most heavily affected population is the Acholi community in Uganda. In response to the high incidence of the disease, the Ugandan Government has developed a management algorithm, but access to such measures in affected communities is limited. There is little funding for research on the disease, consequently, few studies have been conducted to date. Nevertheless, the number of scientific publications on *NS* has increased since 2013, reporting several aetiological hypotheses, management algorithms and cases of stigmatisation; however, none has obtained conclusive results.

This document describes a protocol for a scoping review of *NS* to date aimed at obtaining a broad overview of the disease. The results will identify gaps in knowledge in order to better guide future research, intervention strategies, health policies in areas at risk and cooperation and development programmes.

**Methods and analysis** To identify the relevant data, we will conduct a literature search using the electronic databases PubMed/Medline, Embase, Social Science Citation Index Scopus, Scientific Electronic Library Online (SciELO), Literatura Latinoamericana y del Caribe en Ciencias de la Salud (LILACS), Social Science Citation Index Expanded and The Cochrane Library. We will also include grey literature. The search strategy will be designed by a librarian.

Two members of the team will work independently to identify studies for inclusion and perform data extraction. The search results will be assessed by two independent reviewers and data from the included studies will be charted and summarised in duplicate. The data will be summarised in tables and figures to present the research landscape and describe and map gaps.

**Ethics and dissemination** Ethical approval is not required. The scoping review will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses-ScR guidelines. The results will be disseminated at scientific congresses and meetings.

## INTRODUCTION

### Background

Nodding syndrome (*NS*) is an encephalopathy of unknown origin that affects children aged between 3 and 15 years old.<sup>1–3</sup> The first cases of *NS* date back to the 1950s, when Louise Jilek-Aall, a Norwegian psychiatrist

## Strengths and limitations of this study

- This scoping review is aimed to provide new perspectives after approaching broadly nodding syndrome.
- We will conduct a systematic and exhaustive search of the literature that addresses the proposed study parameters.
- To avoid bias, two expert reviewers will work independently to identify studies for inclusion and perform data extraction.
- We acknowledge two main limitations: the possibility of misidentifying relevant articles in the grey literature, mitigated by consulting international experts, and an input bias secondary to an objective overrepresentation of *Onchocerca volvulus* aetiology in the literature.
- The scoping review will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses scoping review guidelines.

working in southern Tanzania, reported an unusual form of epilepsy that began with head nodding and progressed to various deficits in cognitive function.<sup>4–6</sup> In 1990, health programme workers in South Sudan reported a steady increase in the incidence of *NS* in children.<sup>7–9</sup> Warren Cooper (1997) reported to the WHO on this unknown disease, and in 2001, the Sudanese health authorities acknowledged the existence of an emerging epidemic of *NS*.<sup>6 10 11</sup>

The first cases in Uganda appeared in 1997, where districts of Kitgum, Pader and Lamwo, in the north of the country, were specially affected.<sup>5 6 9 10</sup> However, it was not until 2003 that *NS* was first reported in the biomedical literature<sup>12 13</sup> In 2009, the Ugandan Ministry of Health began investigating the possible aetiology of the disease, identifying up to 2000 affected children in the north of the country.<sup>5</sup> In 2011, the scientific community began to take an interest in the disease,<sup>14 15</sup> which presented the characteristics of an epidemic and was associated with significant morbidity and mortality.<sup>16–18</sup> The term *NS* was not coined until 2012, on the



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Facultad de Medicina y Ciencias de la Salud. Departamento de Enfermería, Universidad de Alcalá, Alcalá de Henares, Madrid, Spain

### Correspondence to

Dr Ivan Ortega-Deballon; [ivortega@gmail.com](mailto:ivortega@gmail.com)



occasion of the first International Scientific Meeting on Nodding Syndrome convened by the WHO and held in Kampala (Uganda). At the subsequent NS Workshop in Nagasaki, observations made on the ground in northern Uganda were reported and it was concluded that due to the high prevalence of the disease, a research strategy was to elucidate the epidemiology, pathophysiology, diagnosis and management of NS in the region.<sup>5,6</sup> Since then, NS has aroused increasing research interest among the scientific community specialising in tropical diseases.<sup>19–21</sup> Nevertheless, few studies have attempted to clarify the aetiology of NS.<sup>6</sup> Consequently, its aetiology remains unknown and treatment is symptomatic.<sup>19</sup>

Current research has proposed various aetiological hypotheses,<sup>10</sup> autoimmune<sup>22</sup> disease following infection by the nematode *Onchocerca volvulus* (OV)<sup>23–25</sup> and a possible viral origin related to measles. In collaboration with the Government of South Sudan, the Atlanta Centers for Disease Control and Prevention (CDC)<sup>26</sup> and UNICEF, the WHO has funded research on NS in the South Sudan counties of Witto and Maridi aimed at describing NS, confirming the risk factors, establishing possible connections with the OV parasite and determining the possible role of malnutrition and its effects on this disease. Although it may take years to discover the cause and cure for NS, the CDC has pledged to collaborate for as long as necessary.<sup>27,28</sup>

On October 2017, during the first international workshop on onchocerciasis-associated epilepsy was accepted that OV is an important contributor to epilepsy in endemic areas, and is associated with a spectrum of epileptic seizures, mainly generalised tonic-clonic seizures but also atonic neck seizures (Nodding), and stunted growth.<sup>22</sup> Accordingly to this hypothetical relationship between NS and onchocerciasis, ongoing studies do exist in endemic areas of OV (eg, Democratic Republic of Congo and Cameroon).<sup>29,30</sup>

Clinical stages of NS include inattention and blank stares, aggressive behaviour, dizziness, lethargy, vertical head nodding, convulsive seizures, cognitive and psychiatric dysfunction, catatonia, physical deformities and severe cognitive and motor system disability.<sup>31,32</sup>

The Ugandan Government developed a NS management algorithm<sup>33</sup> to assess and classify the severity of the disease and identify the consequent health interventions and treatment to apply. Nevertheless, these measures fail to reach all affected families because most of them live in remote and impoverished areas, hindering their access to the resources available. Furthermore, considerable stigma<sup>34,35</sup> is associated with NS in these communities, as demonstrated by several qualitative studies in which semistructured interviews with family members, teachers and religious leaders in the villages revealed substantial social stigma and isolation in the affected children's environment. Authors propose strategies to combat epilepsy stigma and the associated psychosocial consequences.<sup>36</sup>

A recent publication has described how and why NS has become politicised in Uganda, the effect of

this politicisation on health interventions—including research and dissemination—and the possible implications for disease prevention and treatment.<sup>37</sup>

## Rationale

Scientific publications on NS have proposed several aetiological hypotheses, management algorithms and have described the associated social stigma, but none has obtained conclusive or effective results.

## Objectives

Consequently, it is necessary to systematically review NS literature. Following objectives have been identified for this scoping review<sup>38,39</sup>: (1) to identify gaps in knowledge which impede research progress, providing directions for future research; (2) to systematise present knowledge by generating an evidence map and disseminating it in high impact publications; and (3) derived from the above, to propose a comprehensive approach to NS, helping to improve prevention policies, treatment protocols and health strategies for affected children in their social and geographic context.

The above objectives will be achieved on the basis of the following questions:

Principal question: Which hypothesis proposed in the research conducted to date provides evidence-based criteria to clarify the etiopathogenesis of NS and thus identify a treatment and design prevention and support programmes for affected children and their families?

Secondary questions:

1. What are the different aetiological hypotheses?
2. From an epidemiological perspective, what regions are affected by NS?
3. How can we improve current NS prevention and treatment programmes for those affected, in their social and geographical context?
4. Do affected children and their families receive comprehensive care that helps reduce the stigma they are subject to in their communities?

## METHOD, DESIGN AND ANALYSIS

Scoping reviews offer a robust method to map areas of research and present results in an accessible format for scientists. They thus represent a rigorous and systematic approach to synthesising knowledge.

We will adhere to the methods described by Arksey and O'Malley and the initiative of Evidence Synthesis International in partnership with Cochrane for scoping reviews.

## Eligibility criteria

We will include theoretical and empirical studies published between January 1999 and September 2019, with no language limitation. The following types of documents listed in the selected databases will be included: original articles reporting quantitative studies (eg, randomised controlled trials, case-control studies, clinical cases, prospective or retrospective cohort studies and quasi-experimental studies) and qualitative research,

**Table 1** Search items

N	Search item
1.	Nodding Syndrome (NS)
2.	Aetiology
3.	Onchocerca Volvulus (OV)
4.	Epilepsy
5.	OAE
6.	Epidemiology
7.	Treatment
8.	Stigma
9.	Care* (caregiver/health care)
10.	Prevention

project reports, literature reviews, comprehensive and systematic reviews with or without meta-analysis, scoping reviews, guidelines, leaflets, protocols, theses and dissertations. In addition, reference lists in the included publications will be reviewed for any other relevant studies on NS.

Any search limitations, date of publication or study design filters, will be documented clearly and accompanied by a rationale.

### Information sources

A search for articles listed in online databases will enable us to identify relevant studies. The following databases will be consulted: PubMed/Medline, Embase, Social Science Citation Index, Social Science Citation Index Expanded, Scopus, SciELO, LILACS and The Cochrane Library. We will include grey literature through Opengrey as also the following clinical trials registries: ClinicalTrials.gov, WHO, International Clinical Trials Registry Platform and EU Clinical Trials Register. Finally, we will contact individuals or organisations adding handsearching, conference and workshop proceedings.

### Search strategy

Our search terms will be combined (table 1). The search strategies will be adapted to each database. We will develop the final search strategy in collaboration with an expert medical sciences librarian.

The strategy will be defined so as to facilitate replication and retrieval of the information by others and will be described in its entirety in the text, a table or an appendix. Additional information will include the person who performed the literature search (eg, an experienced librarian or information specialist) and whether it was reviewed by another librarian using the *peer review of electronic search strategies* checklist, intended for use by librarians and other information specialists to assess electronic search strategies.

A complete search strategy will be provided for one electronic database PubMed/Medline. Other search strategies can be found in online supplemental file 1. In

the case of grey literature, a detailed description will be given of the method employed.

### Study selection

The research team will compile the results obtained from the database searches, eliminating any studies retrieved from more than one database in order to exclude duplicates. Subsequently, one member of the team will screen the article titles and abstracts to exclude those that do not meet the eligibility criteria. For those that do meet the criteria, the complete article will be retrieved. Another member of the team will then screen a sample of the retrieved articles to ensure consistent application of the eligibility criteria and correct inclusion in the review. In the event that the first reviewer is unable to determine eligibility for inclusion, the article titles and abstracts concerned will be reviewed a second time. Disagreements about eligibility will be discussed between the two reviewers until reaching consensus or, if necessary, will be decided by a third reviewer.

### Data presentation

The literature search results will be presented in a chart showing the number of references screened, the duplicates eliminated and the included documents. In accordance with the original Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, a flow chart will be included detailing the grounds for exclusion.

The results obtained will be presented in tables and graphs according to the review questions and objectives.

### Data synthesis

We expect research on NS to present very heterogeneous characteristics, ranging from the population of children affected, epidemiology, aetiological hypotheses and access to prevention and the prevention procedures and treatment implemented by governments in affected countries. Therefore, we will summarise the data obtained using tables and figures (bubble chart) to present the research landscape and describe possible gaps.

The results will be presented in tables and figures according to their relationship with the review questions and objectives.

### Patient and public involvement

No patient involved.

### PERSPECTIVE

This scoping review will provide us with sufficient study data to create an evidence map informing new lines of research for a broad approach to NS. To our knowledge, this is the first scoping review on NS and underpinned on a comprehensive approach. Not only because of a complete search strategy, but also because explores and compiles the existing literature related to the different aetiological hypothesis, system to detection, intervention strategies, health policies in areas at risk and cooperation and development programmes.

Other approaches tend to be narrow in scope and there has also been a tendency for research on NS to be siloed within limited academic communities and research groups, hindering knowledge translation.

This protocol will undertake a comprehensive scoping review, to systematically capture the broad corpus of health-related research, without disregarding the important social stigma that NS implies.

## ETHICS AND DISSEMINATION

This study will only use previously published data and therefore does not require ethical approval. We intend to publish the review in scientific journals on tropical medicine, neurological diseases and parasitology, and in high impact general interest journals.

In addition, the project, the protocol and the results will be presented at scientific conferences and congresses.

**Twitter** Ana Cristina De Castro @lunapersa6

**Contributors** ACDC is the guarantor, Tropical Medicine and International Health expert, and drafted most of the protocol. IO-D gave information and support for a good practice in systematic reviewing and drafting process. Both authors read and provided feedback on the final version of the protocol.

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## ORCID iD

Ana Cristina De Castro <http://orcid.org/0000-0002-5924-0100>

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