



Nodding syndrome: 2015 International Conference Report and Gulu Accord



P.S. Spencer^{a,*}, D.L. Kitara^b, S.K. Gazda^c, A.S. Winkler^d

^a Department of Neurology, Oregon Health & Science University, Portland, OR 97201, USA

^b Department of Surgery, Faculty of Medicine, Gulu University, Gulu, Uganda

^c Neurology Institute of San Antonio, San Antonio, TX 78231, USA

^d Department of Neurology, Klinikum rechts der Isar, Technical University of Munich, 81675 Munich, Germany

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ABSTRACT

Nodding syndrome is a pediatric epileptic encephalopathy of apparent environmental origin that was first described in Tanzania, with recent epidemics in South Sudan and Uganda. Following a brief description of the medical geography, setting and case definition of this progressive brain disorder, we report recent advances relating to etiology, diagnosis and treatment described in papers given at the 2nd International Conference on Nodding Syndrome held in July 2015 in Gulu, Uganda. The target audience for this report includes: anthropologists, entomologists, epileptologists, health care workers, helminthologists, medical researchers, neuroepidemiologists, neurologists, neuroscientists, neuropathologists, nurses, nutritional scientists, primary health care physicians, psychiatrists, public health practitioners, toxicologists, and virologists.

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1. Introduction

The objective of this report is to describe advances in understanding the etiology, diagnosis and treatment of Nodding syndrome (NS), as reported in papers given at the 2nd International Conference on Nodding Syndrome, July 26–31, 2015. Hosted in northern Uganda by Gulu University, the 2-day scientific program was bracketed by field visits to a community with high NS prevalence (Tumangu Village, Lamit Parish, Labongo Akwang, Kitgum) and a privately run comprehensive care center for children with NS east of Gulu in Odek Subcounty, the birth village of Joseph Kony, leader of the Lord's Resistance Army (LRA). Between 1986 and 2009, a brutal civil war involving the LRA and the Uganda People's Defence Force resulted in the internal displacement and forced encampment of an estimated 2 million people, many of whom experienced severe food shortages and infectious disease. NS, an epileptic encephalopathy of unknown etiology, affected more than 1600 children in northern Uganda [1]. Cases rapidly increased annually beginning in 2001, with peaks in 2003–2005 and 2008, 5–6 years after peaks in the number of wartime conflicts and deaths. Additionally, the largest number of NS cases followed peak influxes 5–7 years earlier of households into internal displacement camps [2]. While the environmental causes of NS are unknown, factors related to food and nutrition,

vermiform and viral infections, and exposure to toxins and toxicants, have been subjects of exploration or conjecture.

Below, we summarize the medical geography and case definition of NS (Section 2), the national origins of delegates attending the Gulu conference (Section 3); their visits to NS-affected/treated communities (Section 4), and new findings reported in papers delivered orally (Section 5) on disease nosology (Section 5.1), risk factors (Section 5.2), clinical findings and treatment (Section 5.3), seizure types and course (Section 5.4), disease concepts (Section 5.5), future information needs (Section 6.0), and references to cited background papers.

2. Medical geography and case definition

NS clusters are known from East Africa, with initial clinical description in the 1960s by Louise Jilek-Aall among the Wapagoro people of Mahenge, Tanzania [3]. In 2001, epidemic NS was recognized in then-southern Sudan in association with civil warfare, population displacement, food shortages, and disrupted vaccination programs and onchocerciasis control [4]. A similar situation overtook northern Uganda, which reported the peak of their NS epidemic some years later (see [Introduction, vide supra](#) [5]).

NS is a largely age-bound (onset mainly between 5 and 15 years) progressive epileptic disorder with the core clinical feature of repeated head drops of variable duration and frequency in children apparently healthy prior to the onset of the head nodding attacks. Head nodding may be associated, followed or even preceded by other seizure types, mainly generalized seizures, cognitive decline and behavioral problems

* Corresponding author at: Department of Neurology, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, HRC 120 12D651, Portland, OR 97239, USA.
E-mail address: spencer@ohsu.edu (P.S. Spencer).

[3–6]. Head nodding and other seizures are often seen in association with stimuli such as cold and, in particular, food. There are supportive features of NS, including malnutrition, stunted growth, wasting and/or delayed sexual development, among others, but they are not invariably present. There is also clustering in time and/or space, and an epidemiological association with areas endemic for the nematode parasite *Onchocerca volvulus* (OV), which is transmitted to humans by the black fly (*Simulium* sp.) and causes skin disease and river blindness (onchocerciasis) [7].

Without treatment, most children with NS seem to develop a progressive encephalopathy evolving through mainly five stages, including a prodromal period, overt head nodding, additional seizure types, physical decline and severe debilitation [8]. In the past, some of Jilek-Aall's longstanding Tanzanian cases displayed areflexia, hyperreflexia and/or parkinsonian features [10]. Recent data provide strong evidence that symptomatic treatment, including nutrition and seizure control, among other measures, leads to clinical and functional improvement [9].

NS was defined by international consensus at the 1st International Conference on Nodding Syndrome in Kampala in July 2012. Case categories included suspected, probable (further divided in major and minor criteria) and confirmed Nodding syndrome [7]. A proposed modification was suggested during the July 2015 Gulu conference given the availability of more refined epidemiological, clinical, electrophysiological and treatment data. A recognized weakness is the absence of an established biological marker, of particular importance because NS may present with head nodding (for which there is evidence that at least some of the cases correspond to atonic seizures) and evolve with time to generalized seizures or, in some cases, *vice versa*. A revised case definition should recognize this duality by including a category of "Nodding syndrome-related disorder".

3. Conference participants

The scientific program of the Gulu conference attracted approximately 80 participants drawn from across Uganda, three other African countries (Cameroon, South Sudan, Democratic Republic of Congo), from Asia, Europe, and the USA. Distinguished non-scientist participants included representatives of local, regional and national government, and local religious leaders. There was agreement ("*Gulu Accord*") that all should work together – locally, nationally and internationally – to understand the causes, prevention and optimum treatment for those with NS.

4. Field visits

Prior to and following the presentation of new scientific work on NS and epilepsy, a number of delegates visited communities heavily affected by the disease. These field visits provided a graphic understanding of not only the magnitude of the medical disaster represented by NS but also the opportunities for clinical improvement when children are provided with optimal medical, nutritional, educational and social support. This positive experience has demonstrated that NS is a treatable (but not curable) brain disorder of children, adolescents and, with the passage of time, adults, but one that carries a greatly increased risk of disability, injury and premature death. All people with NS should be treated holistically according to individual clinical needs and offered appropriate rehabilitative measures.

5. Conference papers

The following summarizes the oral presentations during the 2-day scientific conference on NS in Gulu.

5.1. Disease nosology

Gina Gora-Stahlberg and colleagues discussed the clinical overlap between NS and Nakalanga syndrome, a seizure-prone disorder with marked physical stunting and wasting, reported from Uganda and several other sub-Saharan African countries as far west as Mali. Although generalized seizures have only been described in a minority, and there is no convincing evidence of head nodding in people with Nakalanga syndrome, a clear distinction between the two syndromes is lacking.

Robert Colebunders and associates considered the possible relationship between NS and cryptogenic epilepsy in Province Orientale, DRC. Findings from an age-matched case-control study linked cases of epilepsy to human activity at rivers known to harbor *Simulium* sp. that carry OV and to an historical lack of OV-sensitive ivermectin treatment.

A strong association between NS and OV infection was reported from case-control studies in South Sudan and Uganda [4,7] but PCR studies of cerebrospinal fluid in patients with NS from South Sudan and Tanzania, and in DRC epilepsy cases (reported at the Conference by Robert Colebunders and colleagues), proved negative for OV DNA [4,7]. Additionally, as discussed by David Lagoro Kitara, OV infection is not uniformly present in Ugandan cases, suggesting that OV is not primarily causal of NS. Adam Hendy and colleagues described planned research to clarify this issue by plotting the blackfly-OV relationship in NS-affected and NS-unaffected regions of northern Uganda.

5.2. Risk factors for Nodding syndrome

Funmilayo Olaoye and colleagues described the results of a NS case-control study of 5–20 year-old subjects ($n = 39$ and 41 , respectively) and an open-ended survey of parental views of disease risks (living in internal displacement camps, river blindness, munitions/war, contaminated food, evil spirits). Low household income and, especially, not purifying drinking water, were reported as risk factors for NS.

Valerie Palmer and Rajarshi Mazumder from the U.S. Oregon-Uganda Nodding Syndrome Academic Research Team reported data from a 2014 age- and gender-matched case-control study of 5–18 year-old NS cases ($n = 50$) and community controls ($n = 50$) carried out in Tumangu, Kitgum. For 2000–13, all-year month of reported onset of NS was non-uniform, with peaks in April and June. Significant NS case associations were found with a history of reported childhood measles (also found before adjustment for age in a 2009 CDC study [see Table 4, [11] but not in a 2002 WHO-led study [4]) and eating moldy maize at the time of onset of NS signs. Qualitative and quantitative examination of year-2014 urine and serum for 87 different fungal toxins is underway.

5.3. Clinical findings and treatment

Nolbert Gumisiriza and colleagues described the results of a cross-sectional survey of the type and prevalence of psychiatric and psychological features of 225 Ugandan (Pader) NS children with a mean age of 13 (range 6–18) years. The majority of cases (51.6% male, 48.4% female) started head nodding while residing in internal displacement camps between 2005 and 2010. Children were found to have emotional problems (>53%), peer problems (49.8%) and conduct problems (38.5%). Psychiatric disorders included: episodic major depression (25.3%), current post-traumatic stress disorder (16.4%), generalized anxiety disorder (30.7%), and pervasive developmental disorder (4%). Children should be tested to determine their degree of intellectual impairment for the design of appropriate education.

Neurologist Suzanne Gazda, who directs the NS-dedicated, U.S.–Uganda NGO *Hope for HumaNS* Comprehensive Care Facility in Odek Subcounty described her experience in treating and following 200 children since 2012. The treatment program consists of correcting malnutrition with a locally prepared nutritious diet; closely monitoring seizure histories and adjusting anti-seizure medication (sodium valproate)

and other medication as needed, providing a special-needs education program, and investing in a high standard of personal attention and care. Traditional Acholi music and dance therapy are also vital components of the treatment protocol. In general, children have shown a dramatic improvement, with marked reduction of seizure frequency (greater among males than females, for unknown reasons), increased body weight, growth and development, and positive attitudinal and emotional change. Cognitive and behavioral problems and social difficulties (both requiring formal evaluation) still confront these children, and deaths occur from drowning and other causes.

David Kitara and Suzanne Gazda also reported a deficiency of biotinidase in urine and blood samples of NS children at the Odek rehabilitation center. More studies are needed to determine if this could be a biomarker of the disease.

5.4. Seizure types and course

Thomas Wagner and colleagues reported data from the Tanzanian NS Study Group relating to electroencephalographic (EEG) studies. During 3 ictal EEGs (recorded during head nodding seizures), electrical patterns of atypical absences, tonic and atonic seizures were seen, the latter reminiscent of the EEG pattern recorded during head nodding seizures in a northern Ugandan child [5]. Also reported were the results of a 10-year clinical longitudinal follow-up study of 38/62 Tanzanian children with NS. Head nodding (daily to once a year) persisted in 14/38 (37%) and had stopped in 24/38 (63%) of the patients, of whom 22 remained on antiepileptic treatment. Twenty-six people reported additional, mainly generalized tonic-clonic seizures that started 0 to 17 years (mean 3 years) after the onset of nodding seizures. Only 13 of 26 patients with additional seizures (50%) experienced seizures within the last 12 months, though nodding seizures persisted in 4 of them.

5.5. Disease concepts

Peter Spencer, who leads the U.S. Oregon–Uganda Nodding Syndrome Academic Research Team, proposed that NS might be a post-measles (family Paramyxoviridae) brain disease akin to subacute sclerosing panencephalitis (SSPE), a progressive and eventually fatal disorder associated with the release of mutant virus from neurons and glial cells 6–8 years after initial measles infection. Evidence offered in support of this hypothesis included: (a) the NS epidemic followed 5–7 years after the measles epidemic in northern Uganda (stopped by measles vaccination in 2003), (b) similar age of onset and aggregate clinical signs/evolution of NS and SSPE, including abnormal behavior, head nodding, seizures, and dementia; (c) epidemiological case association between NS and prior measles in the Uganda focus (*vide supra*), and (d) the possibility that a report of crystalline structures in the pons of three NS brains are SSPE-like intracellular inclusions composed of measles nucleocapsids in paracrystalline arrays. Studies of blood, cerebrospinal fluid (anti-measles antibodies, measles virus by PCR and oligoclonal bands – recently reported in NS by Soldatos et al., *Neurology* 84, Suppl., S37.005, and brain (ultrastructure and immunoreactivity), are needed to test this new hypothesis.

David Lagoro Kitara described 10 northern Uganda (Pader District) NS children referred for seizures, injuries and nutritional rehabilitation. Findings of low serum calcium and bicarbonate levels, coupled with a high anion gap supported his published hypothesis that NS is a mitochondrial disorder associated with metabolic acidosis. Thyroid and vitamin D levels were largely normal. Another child with NS had abdominal wall pyomyositis, a relatively common disease in northern Uganda. (Noteworthy is that inclusion body myositis has been linked with paramyxovirus infection, *vide supra*).

Suzanne Gazda proposed that NS may be related to a form of late-onset autism. Children with this disorder are afflicted with a spectrum of neurodevelopmental problems with no clear-cut etiology. Environmental factors are suggested to play a role in the induction of this

disease leading to alteration of the gut microbiome and the “gut-brain” connection. The latter influences many aspects of growth and development, including development of the nervous system. She postulated that the severe food shortages experienced in internal displacement camps, where the first signs of NS were seen in many cases, might have dramatically altered the microbiome and, hence, gut-brain homeostasis.

Robert Colebunders discussed his hypothesis that (a) NS is part of a spectrum of different types of seizures in OV-endemic areas, and that (b) several of the different types of epilepsy most likely have a related etiology as a direct and/or indirect (potentially immune-mediated) consequence of OV infection.

6. Information needs

The papers presented and the field visits illustrated the broad spectrum of clinical manifestations of NS suggesting the desirability, even necessity, of updating the case definition of this disorder. Adherence to a strict consensus case definition (with periodic revision as knowledge accrues) will enhance research precision and help advance understanding of etiology, pathogenesis and treatment. There is also a need to explore the environmental, medical and nutritional history antecedent to the development of the earliest signs of NS. Discovery of biological markers of beginning brain disease will strengthen this investigation.

While the presently registered NS population in Uganda may benefit from the results and application of a pure randomized therapeutic investigation, advances in understanding etiology and disease evolution are more likely to arise from the study of new cases, both prospectively and with regard to a broad and intensive investigation of subject history from (or before) conception to the onset of neurological/behavioral abnormalities that herald the illness. Age of onset, comorbid symptoms and geographical distribution are key parameters in understanding this disease. Contemporary mobile electronic approaches to area-wide disease surveillance to allow the early detection and location of new cases should be encouraged, as should long-term disease surveillance.

Reliable biological markers of NS are needed, whether in biological fluids or tissues (notably blood, cerebrospinal fluid), including brain function (electrophysiology: intra-, inter- and postictal EEGs) and structure (magnetic resonance imaging and post-mortem histology, ultrastructure, immuno/cytochemistry). Biological markers will be most useful if present throughout the clinical evolution of NS and help classify those individuals as NS cases that are no longer suffering from head nodding seizures.

Neuropathological data are urgently needed to define the brain changes in Nodding syndrome and to advance understanding of disease etiology. The results of the U.S. Center for Disease Control & Prevention pathological study of the brains of three deceased Ugandan children with NS and one brain of a child with epilepsy are anxiously anticipated by the scientific community.

Conflict of interest

The authors declare that there are no conflicts of interest.

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