

## Nodding Syndrome – An Investment Case for Global Health?

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### Abstract

Nodding syndrome (NS) represents a complex encephalopathy in previously healthy children and adolescents that occurs in hot spots of South Sudan, northern Uganda and southern Tanzania. The core feature of this neurological disorder is a repetitive forward bobbing of the head towards the chin for variable lengths of time. Associated features include: generalized epileptic seizures, psychiatric symptoms/signs, stunted growth, wasting and delayed sexual development, among others. The etiology of this neuropediatric disorder so far has remained obscure, but there seems to be some evidence in support of a latent neurotropic viral disorder as well as an involvement of the parasite *Onchocerca volvulus*, which can cause skin and eye disease (River Blindness). While discussing the potential etiology and pathogenesis of NS, we also explore reasons why funding NS research has been so scarce and compare it to other similarly neglected diseases. Furthermore, we discuss the inclusion of Nodding syndrome in the WHO list of neglected tropical diseases with the aim of creating a disease-specific lobby, thereby supporting financing and collaboration on NS-related research and development. In the last paragraph we examine a global health approach to Nodding syndrome via the Sustainable Development Goals and conclude that by investing in some of the goals concerning health, poverty alleviation and quality education, among others, individuals suffering from Nodding syndrome and their families may derive clear benefits which eventually can lead to an overall reduction in morbidity and mortality. However, other diseases will also benefit from employment of the Sustainable Development Goals and therefore awareness of Nodding syndrome needs to be raised, so that it will not be forgotten.

### Nodding Syndrome– Setting the Scene

Nodding syndrome (NS) has been defined as an age-bound epileptic encephalopathy in previously healthy children and adolescents. Confirmed cases have been reported in southern Tanzania [1,2], northern Uganda [3] and South Sudan [4] but the cause remains unknown. Described in the 1960s in southern Tanzania by Jilek-Aall [5], more advanced clinical work-up, including investigation of the cerebrospinal fluid and neuroimaging, led to the first classification of NS in 2008. In northern Uganda, the incidence of NS increased rapidly after 2001 until 2013 when a total number of 1687 children with NS in three districts was reported [6]. Reported cases thereafter seem to have declined precipitously suggesting termination of the epidemic in Uganda. Official numbers from South Sudan and Southern Tanzania are lacking to date.

Children with NS have been categorized as suspect, probable and definite cases according to a classification based on international consensus during the first International Conference on Nodding Syndrome in Kampala in July 2012 [7]. Five to six years later, it now seems necessary to adjust that classification based on new scientific evidence, a thought that was already put forward during the 2015 Nodding Syndrome Conference in Gulu [8].

The core feature of NS is a repetitive forward dropping of the head towards the chest (i.e. head nodding) in an approximate frequency of 5-20/min [7]. In most NS cases, head nodding is associated with other

types of epilepsy [1-3]. In addition to these and other subtler neurological signs, affected children are often stunted, malnourished, wasted and cognitively impaired [8]. Delayed sexual development is also a common feature [7]. Treatment is mainly symptomatic with anti-epileptic drugs (preferably sodium valproate, if available), management of psychiatric co-morbidity, correction of malnutrition, and physiotherapy as well as family support, among others [9,10]. Previously, NS was thought to be a progressive encephalopathy leading invariably to death within a rather short period of time; however, over time it became evident that with good symptomatic treatment such as that previously provided by the financially-strapped and therefore recently-shuttered U.S.-Uganda NGO *Hope for Humans* NS Comprehensive Care Facility in Odek Subcounty, Uganda, children can improve dramatically with reduction in frequency of epileptic seizures, increased body weight, growth and development, among others [8]. However, stringent criteria for treatment success have yet to be developed and adverse effects from prolonged valproate therapy, such as low serum biotinidase activity and/or biotin levels, seem likely [11].

### Etiology and Pathogenesis of Nodding Syndrome

While the etiology and pathogenesis of NS are still unknown, the disease was first described in Tanzania in 1960 [1] and may have been present decades earlier [5]. Circumscribed epidemics of NS in recent years have occurred in South Sudan and northern Uganda. NS has surfaced in times of privation associated with seasonal food shortages,

civil conflict and population displacement [12]. A case-control study in northern Uganda identified food dependence on moldy corn, which typically harbors the immunomodulatory mycotoxins, immediately prior to onset of head nodding [13]. Poor nourishment resulting in protein-energy malnutrition can also alter the immune response and increase susceptibility to infections that can further compromise host immunocompetency. Prior undernutrition probably accounts for the short stature, low body weight and delayed development of secondary sexual characteristics of many NS children [4,13].

The first formal investigation of NS was carried out in 2002 in southern Sudan by a multidisciplinary WHO team, which ruled out neurotoxic factors without excluding mycotoxins [4,14]. A rapidly performed case-control study by the WHO team found a case association with *Onchocerca volvulus* (OV) and *Mansonella perstans* infection [4]. Subsequent studies in South Sudan and Uganda confirmed by skin snip or serologic analysis a case association with these nematode infections [7,15]. However, all tests for OV antibodies in cerebrospinal fluid proved negative for OV. Thus, an autoimmune-mediated disease has been proposed based on the detection in sera and cerebrospinal fluid of autoantibodies to the actin-binding protein leimodin-1 (LMOD-1), which cross-reacts with OV antigen [16]. While LMOD-1 antibodies were present to a greater extent in NS cases than healthy controls, they were not specific for NS and immunotherapy has failed to benefit NS-affected children [17]. Thus, instead of causing NS, the presence of nematode microfilaria may represent opportunistic infections of immunocompromised hosts [18].

Two case-control studies of the same NS-affected Ugandan population found an association with prior measles infection, but significance was lost in the 2013 U.S. Centers for Disease Control and Prevention (CDC)-led study when the unmatched population samples were adjusted for age and sex [13,15]. However, a previous rapidly performed WHO outbreak investigation was negative for self-reported prior measles infection [4,14]. When measles infection occurs in the opening years of life, the virus can migrate to the brain and reside intracellularly in an apparently dormant mutated state. However, several years later, the cerebral measles infection can reappear in the form of a progressive brain disorder (subacute sclerosing panencephalitis (SSPE)) in which head nodding and other NS-like clinical features are reported [13]. The presence of an SSPE-like illness can be rapidly determined by immunocytochemical confirmation of neurocellular viral particles, which form intranuclear or cytoplasmic paracrystalline inclusions (Cowdry body types A and B). Intracellular crystalline structures (fixation artifacts?) and neurofibrillary changes have been found in the brains (pons) of Ugandan children with NS but formal neuropathological findings are unavailable [13, 18, CDC, personal communication to P.S.]. Of related interest is experimental evidence that mice injected intracerebrally with Measles Virus develop increased concentrations of glia-derived glutamate excitotoxins (3-hydroxykynurenine and quinolinic acid) in the hippocampus prior to onset of glial activation, electroencephalographic evidence of seizure activity, behavioral seizures, and histological evidence of hippocampal neurodegeneration [19]. Increased plasma concentration of 3-hydroxykynurenine neurotoxin, resulting from low plasma vitamin B6 levels, has been reported as a major risk factor for NS [20]. Although an increased accumulation of 3-hydroxykynurenine neurotoxin based on different mechanisms (persisting Measles Virus and/or low vitamin B6 levels) represents an interesting hypothesis for the pathogenesis of NS, another study found that vitamin B6 levels were not decreased in children with NS [21, see also *Note Added in Proof*].

## Financing and Collaboration on Research and Development for Nodding Syndrome

Research funding is scarce for NS, a disorder that affects only a handful of children when compared to malaria and other childhood diseases of sub-Saharan Africa. NS has the unfortunate distinction of being doubly neglected– it not only affects few, but they also live in some of the poorest countries of the world. Both the paucity and poverty detract funders of disease research and development (R&D). For the private sector, there is no market and for the public sector, investing in more prevalent diseases will have a greater impact on saving lives.

This distinction is clearly evidenced through the financing of neglected diseases R&D where HIV/AIDS, tuberculosis and malaria routinely receive the vast majority of funding. In 2014 (the last year data are available), these three diseases received 68% (or USD 2.3 billion) of the total neglected disease R&D financing [22]. This financing is well justified as HIV/AIDS killed one million people in 2016, tuberculosis 1.8 million in 2015, and malaria 429000 in 2015 [23-25].

G-FINDER, the survey that gathers financing data on neglected disease R&D, does not track funding for NS, but does have financing figures for other neglected tropical diseases (NTDs) with similar burdens of disease [22]. Like NS, Buruli ulcer affects mostly children and 2037 new cases were reported from 13 countries in 2015 [26]. Human African trypanosomiasis (HAT) occurs in 36 sub-Saharan countries and significant efforts have reduced the number to 2804 new cases in 2015 [27]. In 2014, Buruli ulcer received USD 1.4 million to fund basic research but also received USD 2.7 million in development funding (for medicines, vaccines, and diagnostics) [22,28]. In the same year, HAT received USD 20.7 million for basic research and USD 26 million for development [22,28].

Whereas Buruli ulcer and HAT may have similar case numbers to NS, a key difference from NS is that their causative agents are well understood, facilitating the development of diagnostics, medicines, and/or vaccines. NS requires significant basic research funding before any development activity – be it diagnostic, therapeutic or preventive – can start. A separate study found that NS researchers have been allocated a total of €5 million from 2013 to 2019 in grant research funding, which is a significant increase from previous years but still insufficient to accelerate research [29].

The greater understanding of the causative agents for Buruli ulcer and HAT also means that concrete and achievable plans can be made and tracked. This has been done through the World Health Organization's (WHO) Roadmap on neglected tropical diseases which has gained significant political and funding support via the London declaration on neglected tropical diseases [30-32]. The Declaration is a coalition of pharmaceutical companies, donors, endemic countries, and non-governmental organizations that have committed to control, eliminate, or eradicate specified diseases by 2020. However, NS is not included in the WHO list of NTDs.

There is no clear reason for the exclusion of NS from that list. The WHO definition of a NTD seems rather imprecise, representing “a diverse group of communicable diseases that prevail in tropical and subtropical conditions in 149 countries” [33], whereas others, like the journal *PLoS Neglected Tropical Diseases* have promoted more precise definitions such as “a group of poverty-promoting chronic infectious diseases, which primarily occur in rural areas and poor urban areas of

low-income and middle-income countries” [34]. This imprecision has led to lobbying for disease-specific inclusion. For example, in 2016, the World Health Assembly adopted a resolution for mycetoma to be included in the list [33]. Steps were also taken to give more precision to the list and the resolution includes a task for WHO “to define a systematic, technically-driven process for evaluation and potential inclusion of additional diseases among the ‘neglected tropical diseases’” [33]. This could be an opportunity for Nodding syndrome to gain much needed attention, especially by using the information needs agreed upon at the 2015 International Conference and Gulu Accord as actionable goals with associated budgets [8]. Another opportunity for NS to gain more attention may be through the Sustainable Development Goals.

### Nodding Syndrome in the Context of Global Health

In September 2015, the United Nations agreed on 17 Sustainable Development Goals (SDGs) including 169 targets, representing a roadmap for the next 15 years throughout all disciplines and sectors of society, including governments, business and civil societies around the world [35]. The 2030 agenda has been adopted by almost all United Nations Member States requiring major rethinking about national and international financing principles. The vision is to create better lives globally, whereby the well-being of people is inextricably linked to that of their environment. Within the SDG, Goal 3 deals with health that has been redefined in a much broader sense and so far, neglected disease entities, such as non-communicable diseases and mental health, have come on board. Not only has the disease spectrum been diversified compared to the SDG predecessor, the Millennium Development Goals, but aspects pertaining to health system strengthening, such as access to essential medicines and universal health coverage, that has been defined as “all people receiving the quality health services they need, without being exposed to financial hardship”, have been added [36].

#### Reducing morbidity and mortality of NS fits well into the context of Goal 3 with the following targets

- “end preventable deaths of newborns and children under 5 years of age” (3.2),
- “end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases” (3.3),
- “reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being” (3.4),
- “achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all” (3.8).

Achievements in other SDGs may also reduce the burden of NS. For example, investing in ending poverty (Goal 1) and hunger (Goal 2) could have a large impact as NS is a disease of conflict and poverty, and malnutrition represents an important morbidity [12-14]. Inclusive and equitable quality education (Goal 4) may lead the way out of poverty and, thereby, indirectly alleviate poverty-associated diseases. The areas affected by NS are former and present war zones stricken by poverty and belonging to the most underprivileged regions within the respective countries. If sustainable economic growth of affected areas could be achieved (Goal 8), it would reduce inequality within countries (Goal 10) and promote peaceful and inclusive societies (Goal 16). Achievement of these goals would lay the foundation for elimination of

diseases of poverty. Global partnership for sustainable development (Goal 17) calls on rich and poor nations to take joint responsibility and actions towards the successful establishment of lasting global health. Nodding syndrome is not unique in that it would benefit from progress on achieving the SDGs. The SDGs are broad in scope, and there is a great risk that NS will continue to be forgotten, unless greater awareness of Nodding syndrome is achieved. A suitable tool to raise more awareness may be the WHO’s list of NTDs which, however, needs a transparent and inclusive definition for its listed diseases [33]. Funders need to be made aware that relatively small investments (under USD 5 million) in NS research could reap a very large reward in accelerating the scientific understanding with ensuing possibilities for potential treatments for Nodding syndrome.

*Note Added in Proof:* In October 2015, WHO Uganda reported that ‘some of the reported measles outbreaks have turned out to be rubella’ [36-38]. Congenital or early post-natal infection with Rubella Virus is very rarely associated with the delayed onset of Post-Rubella Panencephalitis (PSP), an SSPE-like but more benign, later-onset, slow virus brain disorder, in which Cowdry bodies are absent.

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