Technische Universität München, Fakultät für Medizin

Comprehensive analysis of current knowledge of Nodding Syndrome

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Vollständiger Abdruck der von der
Fakultät für Medizin
der Technischen Universität München zur Erlangung des akademischen Grades eines Doktors der Medizin (Dr. med) genehmigten Dissertation.

Vorsitzender: Prof. Dr. Ernst Rummeny

Prüfer der Dissertation:

1. Prof. Dr. Bernhard Hemmer
2. Priv.-Doz. Dr. Jan St. Kirschke

Die Dissertation wurde am 25.01.2018 bei der Technischen Universität München eingereicht und durch die Fakultät für Medizin am 20.02.2019 angenommen.

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Directory of abbreviations

- AED = antiepileptic drugs
- BMI = body mass index
- CDC = Centers for Disease Control and Prevention
- CNS = central nervous system
- CSF = cerebro-spinal fluid
- CT = computed tomography
- DJ-1 = protein deglycase DJ-1
- EEG = electroencephalography
- EMG = electromyography
- GH = growth hormone
- IDP = internally displaced people
- Ig = immunoglobulin
- IGF = insulin-like growth factor
- LRA = Lord's Resistance Army
- Max. = maximum
- mf = microfilariae
- Min. = minimum
- MRI = magnetic resonance imaging
- n = number
- NCHS = National Center for Health Statistics
- NGO = non-governmental organization
- NIH = National Institutes of Health
- NMDAR = N-methyl-D-aspartate receptor
- NS = Nodding syndrome
- NTV Uganda = National Television of Uganda
- *O. volvulus* = *Onchocerca volvulus*
- PCR = polymerase chain reaction
- pH = potential of hydrogen
- PNES = psychogenic non-epileptic seizures
- PTSD = post-traumatic stress disorder
- SPLA = Sudan People's Liberation Army
- SSPE = subacute sclerosing panencephalitis
- *T. solium* = *Taenia solium*
- T4 = thyroxine
- TSH = thyroid-stimulating hormone
- UN = United Nations
- VGKC = voltage gated potassium channel
- WHO = World Health Organization

Acknowledgements

I wish to thank Prof. Dr. Dr. Andrea Sylvia Winkler for her mentoring, continuous support and guidance. I am also grateful to Prof. Dr. Bernhard Hemmer for accepting me as a student.

Furthermore, special thanks go to Dr. Christoph Kaiser for his dedication and precision in the publishing process. I wish to express many thanks to Prof. Dr. Guido Kluxen, Prof. Dr. Seggane Musisi and Prof. Dr. Robert Colebunders for kindly providing further references. Many thanks go to Dr. Raffaele Pezzani and Prof. Dr. Clarissa Prazeres Da Costa for their valuable scientific input. I also want to thank Prof. Dr. Louise Jilek-Aall and express my deepest respect for her accomplishments. Many thanks also to Dr. James Sejvar, Prof. Dr. Emilio Ovuga, Prof. Dr. Erich Schmutzhard and Dr. Gina Gora-Stahlberg for their assistance in the process of publication.

Finally, I wish to thank my friends and family for their support and motivation.

1. Abstract

Background: Nodding syndrome (NS) represents an epilepsy disorder in children born healthy which so far has only been described in Uganda, Tanzania and South Sudan, mainly in areas of conflict and war. It is characterized by spells of head nodding, which in the majority of children is accompanied by other types of epileptic seizures, and can lead to progressive cognitive deterioration as well as stunting and wasting, amongst other physical symptoms/signs. To date the pathogenesis of this disorder is inconclusive. Antiepileptic medication may be effective as symptomatic treatment together with other measures such as correction of malnutrition, psychological stimulation and physical activity.

Nakalanga syndrome, which has also been described in Uganda and other African countries, resembles NS and so far has not been described well. Alongside impaired growth, physical deformities, endocrine and sexual dysfunction and cognitive impairment, epileptic seizures, which are not well characterized, may be present, but are not mandatory.

Aims: By means of a thorough literature research (landscape analysis), this work aims to analyze possible causes of NS and also provide an overview over clinical features, epidemiological details, diagnostic findings and possible treatment options of NS. Furthermore, it tends to examine possible causes and clinical features of Nakalanga syndrome and develop criteria for the definition of this hitherto little-known disease. Finally, a comparison between both disorders shall be achieved.

Findings: As yet, the cause of NS remains obscure. Among the examined infectious diseases, a consistent association of NS with onchocerciasis is striking. An association with prior measles infection has also been demonstrated, suggesting that NS may be comparable to subacute sclerosing panencephalitis. As NS is common among the victims of civil war, malnutrition and psychiatric disorders (amongst others, post-traumatic stress disorder) have been held responsible for the epidemic emergence of the syndrome in Uganda and South Sudan. Mycotoxins, vitamin B6 deficiency, metabolic causes and mitochondriopathies have also been evoked as possible factors contributing to its pathogenesis. Furthermore, recent findings strongly point toward autoimmunity as an integral element of NS.

Our literature research on Nakalanga syndrome found different fundamental criteria on which our proposed definition of the syndrome relies. These include stunting, wasting, impaired sexual development, cognitive impairment, facial dysmorphia, kyphoscoliosis and epileptic seizures other than head nodding. Our findings do not point towards pituitary or adrenal dysfunction as the origin of disease, which was suspected earlier. Nakalanga syndrome appears to present with largely normal cortisol and growth hormone levels and normal thyroid function. No connection with various infectious causes could be established, with the exception of a persistently documented association with onchocerciasis.

A comparison between Nakalanga syndrome and NS yields striking resemblances: Both disorders widely affect the same age group and seem to develop in children that have been healthy previously. Western Uganda represents a focus which both syndromes share. Both frequently show growth retardation and wasting as well as mental impairment and epileptic seizures other than head nodding. Furthermore, onchocerciasis is a consistent finding in both conditions (although this does not necessarily imply a causative role of *O. volvulus* in the pathogenesis of disease).

2. Introduction

Nodding syndrome is a little-known epilepsy disorder of childhood which has so far been described in Uganda, Tanzania and South Sudan. Its cause is as yet obscure.
The aim of this work is primarily to conduct a thorough literature research on NS and analyze possible causes for the disorder.
Secondly, it comprises a comparison of NS and Nakalanga syndrome. The latter has also been described mainly in Uganda. It includes various features (stunting, wasting, physical deformities, psychiatric disorders etc.) in addition to neurological signs and symptoms in part resembling NS.
The goal of our literature research on both disorders is to determine whether the conditions differ from one another or whether both terms actually designate the same disease.

3. Methods

This work aims

- to analyze available information on NS and its possible etiological factors by means of a landscape analysis
- to analyze available information on Nakalanga syndrome by means of a landscape analysis
- to compare NS and Nakalanga syndrome.

3.1 Search results for Nodding syndrome

We performed a landscape analysis and evaluated all results delivered for the search term „nodding syndrome“ by means of the search engine PubMed (Table 1). The goal of this search was to gather information on different aspects of NS in a widespread and comprehensive way. This was achieved based on the PRISMA flowchart, designed to assist authors in structuring systematic reviews. Our literature research began in 2014, the latest search was conducted on July 05 2017. This search revealed 99 articles. Articles were screened for relevance, which resulted in the exclusion of 34 articles describing conditions unrelated to NS. The remaining 65 articles were considered for further investigation.

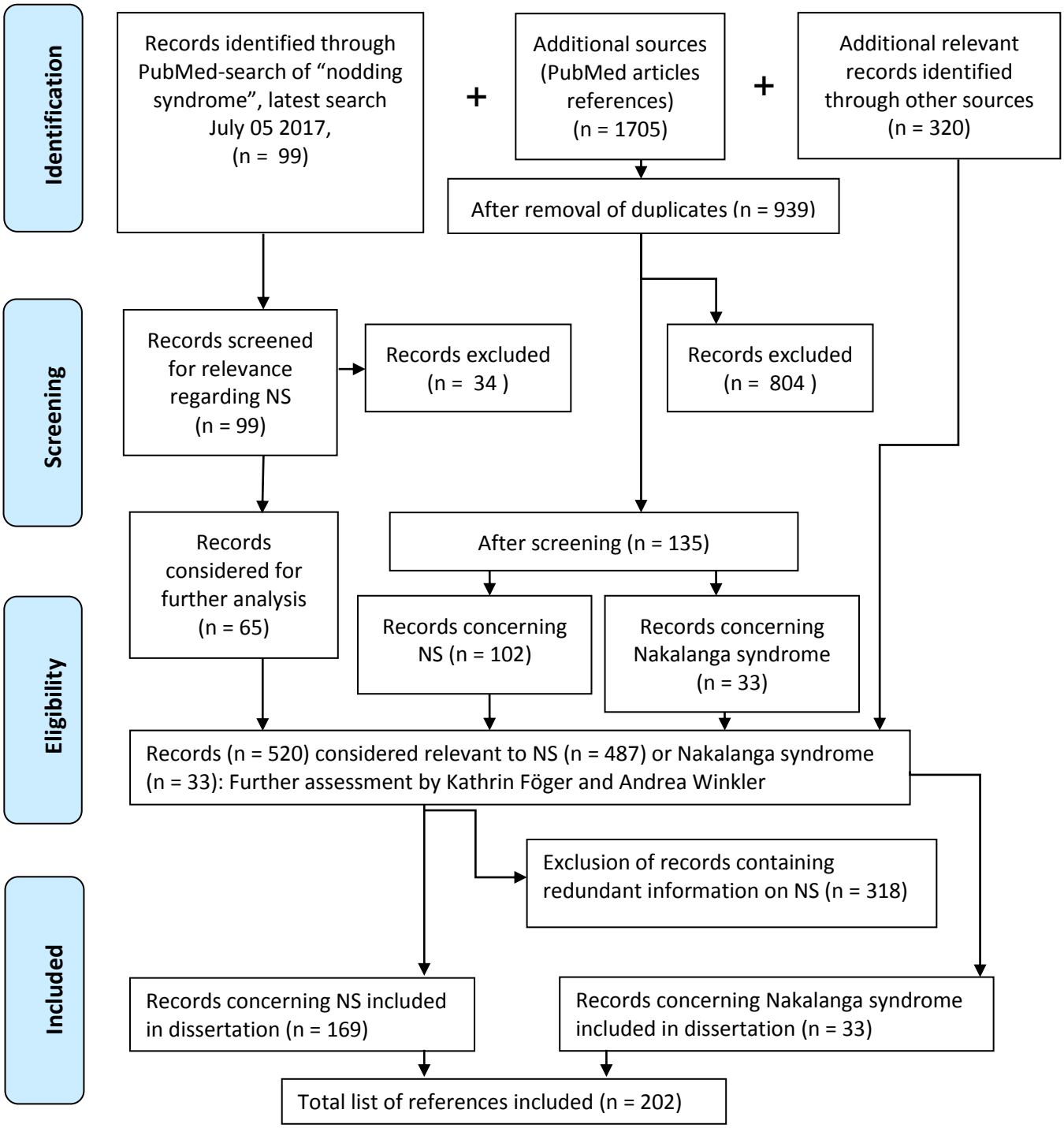
As a next step, all reference lists of these 65 PubMed articles were assessed for their relevance to NS. These reference lists added up to 1705 references. Among these, there were also records describing Nakalanga syndrome, for which a second literature search was subsequently conducted (chapter 3.2). After removal of duplicates, a total of 939 references remained, which were procured from the Bayerische Staatsbibliothek or by personal communication with the authors. All of these were screened, which resulted in the exclusion of 804 articles which contained no relevant information on NS or Nakalanga syndrome. The remaining 135 articles were considered for further investigation. Out of these articles, 33 concerned Nakalanga syndrome and 102 concerned NS.

Additional articles which had been referred to in the reference lists, including grey literature on NS, were procured from various sources including the Bayerische Staatsbibliothek or by personal communication with the authors. This approach yielded 320 more articles.

Altogether, 520 articles were considered for further investigation and were assessed in full length by Kathrin Föger and Andrea Winkler. Out of these, 33 records concerned Nakalanga syndrome, and 487 records concerned NS. All of these comprised valuable information on NS, however, information was in many cases redundant. This resulted in an exclusion of another 318 articles, leaving a total of 202 articles to be included in our qualitative synthesis. Among these, 33 articles concern Nakalanga syndrome and 169 articles concern NS.

Table 1: Literature research on NS and Nakalanga syndrome

Literature search for Nodding syndrome and Nakalanga syndrome by Kathrin Föger based on the PRISMA Flow Diagram[1]



[1] Derived from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

3.2 Search results for Nakalanga syndrome

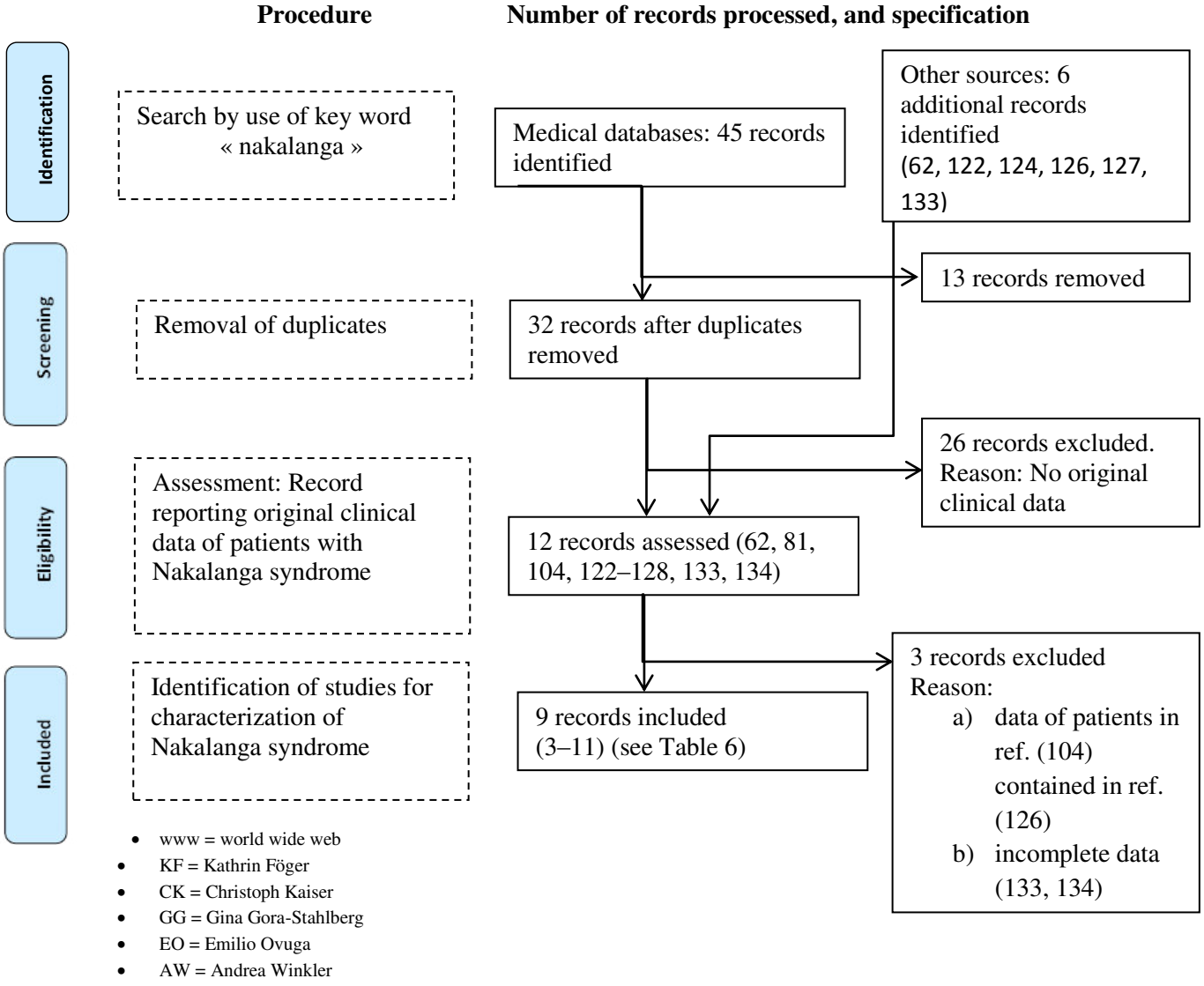
During research on NS, its resemblances to Nakalanga syndrome became apparent. To investigate the overlap between the two conditions further and to complete the information on Nakalanga syndrome, an explicit search for the search term "nakalanga syndrome" was conducted. As there appeared to be only rare, isolated accounts of Nakalanga syndrome, we aimed to screen as many publications as possible, and thus searched a variety of medical databases in addition to PubMed.
We combined this with a second search for publications presenting original clinical information on NS. The goal of this search was to enable a comparison between the clinical features of NS and Nakalanga syndrome. It was thus less extensive than our broad landscape analysis on NS outlined above (chapter 3.1), with a rigid exclusion of articles not presenting original clinical data. The results of this search, which was last updated on May 23 2016, were published in a separate disclosure (Föger et al. 2017). The following passage is taken verbatim from this publication:

"We searched several medical databases (Medline, ScienceDirect, African Neurology Database of the Institute of Neuroepidemiology of the University of Limoges) using the search term „nakalanga". Other sources, such as commercial search engines or unpublished congress proceedings, were searched without specific limits, and reference lists of retrieved articles and reviews were screened for further records of relevance (latest search: May 23, 2016). The database search identified 45 records, and 6 additional records were found from other sources. After removal of duplicate entries and assessment of relevance, 12 articles were found to present original clinical data (Raper and Ladkin 1950; Jelliffe et al. 1962; Bagenda et al. 1964; Ovuga et al. 1992; Kipp et al. 1996; Höfer 1999; Kaiser et al. 2007; Newell et al. 1997; Oomen 1967; Marshall and Cherry 1961; Stanfield 1963; Leonard and Stanfield 1965). Three of these were excluded because they contained redundant or insufficient information (Leonard and Stanfield 1965; Stanfield 1963; Kaiser et al. 2007). The remaining nine records (Raper and Ladkin 1950; Jelliffe et al. 1962; Bagenda et al. 1964; Ovuga et al. 1992; Kipp et al. 1996; Höfer 1999; Newell et al. 1997; Oomen 1967; Marshall and Cherry 1961) represent the evidence base for a systematic characterization of Nakalanga syndrome (Table 8). A flow diagram describing the search procedure is available as supporting information (Table 2)" (Föger et al. 2017).

"A second literature search for records presenting original clinical information on patients with NS retrieved 20 publications (Winkler et al. 2008; Lacey 2003; Tumwine et al. 2012; Spencer et al. 2013b; Sejvar et al. 2013; Idro et al. 2013b; Foltz et al. 2013; Spencer et al. 2013a; Kaiser et al. 2015; Winkler et al. 2010; Nyungura 2011; Reik et al. 2012; Musisi et al. 2013; Winkler et al. 2013; Kitara et al. 2013; Piloya-Were et al. 2014; Idro et al. 2014; Winkler et al. 2014; Polo et al. 2015; Kakooza-Mwesige et al. 2015). Nine of these were excluded from the analysis (Winkler et al. 2008; Spencer et al. 2013b; Idro et al. 2013b; Foltz et al. 2013; Reik et al. 2012; Musisi et al. 2013; Winkler et al. 2013; Idro et al. 2014; Winkler et al. 2014) because they presented incomplete data or redundant information which was found in more detail in another article. The remaining 11 articles were systematically screened for symptoms and signs, which beforehand had been identified as characteristic for Nakalanga syndrome (Table 9). Details of the search procedure and a flow diagram is available as supporting information (Table 3)" (Föger et al. 2017).

Table 2: Literature search for Nakalanga syndrome

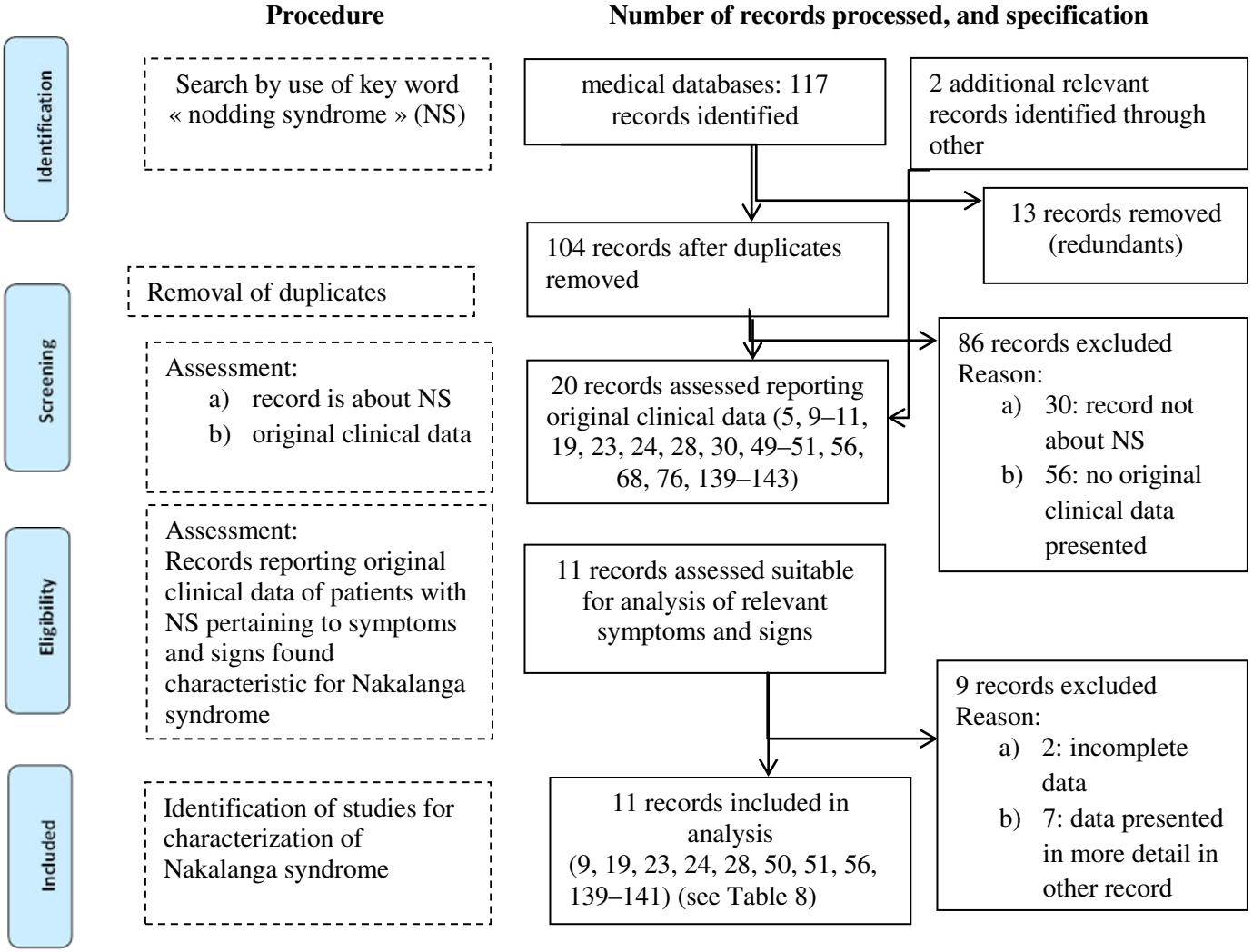
Objective: To identify publications (case reports and case series) reporting original clincal information of patients affected by Nakalanga syndrome.
Sources: Medical Databases (Medline; Science Direct; African Neurology Database; Institute of Tropical Neurology, Limoges). Other sources: www-search with no defined limits, reference list of published articles.
Procedure: Search period: All years until present date, latest search May 23, 2016. Database search and screening for redundant entries performed by KF and CK. Search of other sources by KF, GG, EO, CK and AW. Verification of retrieved records for eligibility by KF and CK. (Criterion: original clinical data on clinical symptoms and signs of Nakalanga patients).
Result: 9 publications identified.



(Adapted from Föger et al. 2017)

Table 3: Literature search for NS

Objective: To identify publications (case reports and case series) reporting original clinical information of patients affected by NS, suitable for analysis on the presence of symptoms and signs characteristic for Nakalanga syndrome in NS patients.
Sources: Medical Databases (Medline PubMed; Science Direct; African Neurology Database; Institute of Tropical Neurology, Limoges). Other sources: www-search with no defined limits, reference list of published articles.
Procedure: Search period: All years until present date, latest search May 23, 2016. Database search and screening for redundant entries performed by KF and CK. Search of other sources by KF, GG, EO, CK and AW. Verification of retrieved records for eligibility by KF and CK.
Result: 11 publications identified.



- www = world wide web
- KF = Kathrin Föger
- CK = Christoph Kaiser
- GG = Gina Gora-Stahlberg
- EO = Emilio Ovuga
- AW = Andrea Winkler

(Adapted from Föger et al. 2017)

Part I: Landscape review on Nodding syndrome

4 Nodding syndrome: Results

4.1 Demographic and geographical features

4.1.1 Affected age group

NS commonly has its onset at the age of five to 15 years (WHO 2012; Spencer et al. 2016a), though there are reports of elder patients from Uganda (Anena 2012; Grosse 2012). The International Scientific Meeting on NS has included the 3-18-year age group in the case definition of "NS" (WHO 2012; Winkler et al. 2008). Reports from Liberia (Gerrits 1983) suggest an onset in early puberty for males and in late puberty for females.

4.1.2 Distribution across the sexes

NS occurs equally in both sexes (WHO 2012).

4.1.3 Tribal distribution

Prevalence of NS does not seem to be identical in different tribes: In Tanzania, it has only been described in the Wapogoro tribe in Mahenge area (Jilek-Aall et al. 1979; Jilek-Aall 1976; Winkler et al. 2010; Winkler et al. 2008; Winkler et al. 2014). In Sudan (Lui and Amadi), investigations by Spencer et al. demonstrate the appearance of NS only in the sessile Moru tribe, not in the Dinka tribe, who are itinerant cattle-herders (Spencer et al. 2013b).

4.1.4 Familial clustering

NS often affects several children within the same family (Winkler et al. 2008; Kitara D. et al. 2013; Spencer et al. 2016b). Family members of NS patients frequently also seem to suffer from other forms of epilepsy (Colebunders et al. 2016a) in addition to "nodding episodes" (chapter 4.2.1). In a study on 101 NS cases in Uganda (Kitara D. et al. 2013), 34% of cases had at least one sibling also affected by NS, compared to 18% of controls. Controls had lived in the same circumstances (identical Internally Displaced People's (IDP) camps), thus this statistically significant finding is unlikely to result solely from environmental factors. In a Tanzanian study from 2008, 52/62 (84%) of patients with head nodding had at least one relative affected by epilepsy or head nodding (Winkler et al. 2008).

4.1.5 Geographical distribution

The affected areas (mostly southern Tanzania, northern Uganda and South Sudan) are geographically isolated from one another (Smith 2012a; Dowell et al. 2013), though refugee movements across the Sudanese-Ugandan border were documented in 1994 (Spencer et al. 2013b).

4.1.5.1 Tanzania

The first cases of NS in Tanzania were reportedly described by Jilek-Aall in 1934 (Spencer et al. 2013b) and documented in detail in the 1960s (Jilek-Aall 1964). Mothers were aware that nodding commonly preceded the development of grand-mal seizures (Jilek-Aall et al. 1979; Smith 2012b; Spencer et al. 2013a) and cases were present in this region for at least 80 years (Spencer et al. 2013a). The incidence of NS does not seem to have increased much in this area over the past few years, researchers have therefore described it as "endemic" (Grosse 2012).

4.1.5.2 Isolated accounts from Great Britain, South America and various African countries

Apart from isolated accounts from Great Britain in 1909 (Gibson 1909), the first episodes reminiscent of NS were described in Mexico in the 1930s (Casis-Sacre 1938). In the literature, findings similar to NS, which may constitute the same entity, have also been described in Cameroon in 2008 (Prischich et al. 2008). Their clinical presentation is described as one of "seizures characterized by one or several repeated head movements named "head nodding" which were usually accompanied by an episode of impaired responsiveness lasting from a few seconds up to several minutes" (Prischich et al. 2008, 204). These patients showed focal epileptiform activity and non-specific focal slow wave activity (Prischich et al. 2008). In Liberia in 1983, Gerrits described two different forms of epilepsy, namely the "big jerking" and "to drop the head in the pan". Epilepsy was first reported in this region (Grand Bassa County) in 1939, there was a gradual increase in cases since that time (Gerrits 1983). Van der Waals et al. (van der Waals, F. W. et al. 1983) mention further manifestations of epilepsy which seem to resemble NS. Accounts from the Republic of the Congo also point towards the possible existence of Nodding syndrome (Colebunders et al. 2016a). Apart from these rather isolated cases, a recent epidemic spreading has been observed in South Sudan and northern Uganda.

4.1.5.3 South Sudan

NS presumably appeared in South Sudan in 1991 in Mundri County (Spencer et al. 2013b). Mundri County lies in the state of Western Equatoria in South Sudan, it does not border Uganda. Locals remember NS occurring in the Jambo area (Witto Payam) in Mundri County in 1992 (Lacey 2003) "even before displacement took place" (Nyungura 2011). In 1995, the first cases appeared in Lui, a town in Mundri County which, as the epicenter of NS in South Sudan, was studied in detail by Spencer et al. (Spencer et al. 2013b).

The first cases of NS occurred in a time of political turmoil marked by displacement of major parts of the population. This was provoked by ongoing fighting between the rebel group Sudan People's Liberation Army (SPLA) and the Sudanese army.

From 1987 on, the mining of roads had cut people in Lui and Amadi off from food supplies.

From 1988 on, airlifting of food was installed for the areas which were thus isolated in Equatoria. The "Operation Lifeline Sudan", composed of United Nations (UN) agencies and non-governmental organizations (NGOs), provided humanitarian help (Spencer et al. 2013b).

Food insecurity in Mundri County, a prosperous region and former breadbasket of Sudan, set in during the year of 1990. Large-scale displacement in Mundri County began in 1991 when Mundri and Maridi were captured by the SPLA. United Nations (UN) field staff reports the finding of deserted villages during that time. Reports from 1993 to 1994 also describe refugee movements across the border to Uganda (Gulu district) (Spencer et al. 2013b).

From 1997 on, the Kenyan government, as well as "Operation Lifeline Sudan", were able to offer relief to the population, including the distribution of seeds and tools for planting. But Mundri and Maridi were not among the areas benefiting from relief flights. Immunization campaigns were conducted by the United Nations Children's Fund (UNICEF) (Spencer et al. 2013b). The semi-autonomous Government of South Sudan was created in 2005 following a Comprehensive Peace Agreement (Carter Centers).

4.1.5.3.1 Association of Nodding syndrome with internal displacement

85% of Lui's population have a history of displacement. Such experiences were more common in families of NS cases than controls, but the association was not significant (Spencer et al. 2013b).

4.1.5.3.2 Attention of the scientific community towards Nodding syndrome

NS was first reported to the World Health Organization (WHO) in 1997, six years after its appearance in Sudan, by Warren Buffet from the NGO Samaritan's purse (Richer et al. 2008). For three years, incidence kept rising, then the situation stabilized (but new cases were still appearing). The WHO conducted an investigation in 2001, 2002 and 2006. 300 cases were described from Mundri County

until 2003 (WHO 2012; Korevaar and Visser 2013). The term "Nodding disease" was first used in 2003 (Korevaar and Visser 2013).

4.1.5.3.3 Geographical distribution in South Sudan

The epicenter of NS prevalence is Mundri County in Western Equatoria State with the villages Lui and Amadi near Yei river (prevalence 2.3% in Lui and 6.7% in Amadi 2001/2 (Tumwine et al. 2012)). The higher prevalence rates in Amadi have been attributed to its closer proximity to the Yei river (Spencer et al. 2013b), the breeding ground for simulium flies which act as vectors to *Onchocerca volvulus* (*O. volvulus)*. Prevalence is also high in another village in Western Equatoria State: Witto Payam, a former IDP camp (Nyungura 2011).

Of the ten subcounties of Western Equatoria (Yambio, Nzara, Ibba, Ezo, Tambora, Najero, Mvolo, Maridi, Mundri, Mundri West), several others have also reported cases of NS, including Yambio (Yambio), Mvolo (Bogori, Yeri, Mvolo), Maridi (Kozi) and West Mundri (Kotobi). In Central Equatoria (consisting of Juba, Lainya, Morobo, Yei, Terekeka and Kajo Keji Counties), Juba (Katigiri, Rokon), Yei and Morobo, as well as the Lakes State Rumbek (Billing, Wulu, Kulu) have reported cases (Richer et al. 2008).

4.1.5.3.4 Prevalence

According to Dowell et al. (Dowell et al. 2013), 260 cases were reported in Western Equatoria State until 2013 by investigations applying a stringent case definition. Media reports suggest there are thousands of cases in South Sudan (Dowell et al. 2013). The South Sudan Ministry of Health estimate 2012 mentioned 6000-7000 cases (WHO 2012). Dr. Abubakar (WHO) estimates the burden of NS in South Sudan at 8000 cases, however, he does not speak of an epidemic development, noting that many of these cases may have had onset years ago. Improving quality of roads allows for migration into cities/towns and thus increased reporting of cases (Smith 2012a).
A peak in NS incidence seems to have occurred in South Sudan between 1998 and 2001 (Spencer et al. 2016b), but new cases continue to be reported (Colebunders et al. 2016a).

4.1.5.4 Uganda

In Uganda, cases were apparently noticed several years before 2008/9, when they were first officially reported to the Ugandan Ministry of Health by the Kitgum District Health Officer (Makumbi and Mugagga). The first cases seem to have appeared before 2004 in Kitgum and Pader (Makumbi and Mugagga). Some sources even find first descriptions of NS starting from 1997 (Foltz et al. 2013; Musisi et al. 2011; Iyengar et al. 2014; Colebunders et al. 2016a) and alleged first reports by NGOs to the Ministry of Health in 2000 (Hochstrasser 2013). The number of individuals affected by NS in Uganda is difficult to quantify, some sources report over 2000 cases of NS to have occurred in northern Uganda by 2009 (Wadman 2011), others speak of over 3000 cases and 170 deaths by 2012 (WHO Regional Office for Africa 2012). Of these, 1,488 cases and 66 deaths are reported to have occurred in Pader, 1,278 cases and 98 deaths in Kitgum, 328 cases and 6 deaths in Lamwo (Ministry of Health Uganda 2012). However, cases were not defined according to the present case definition as issued by the International Scientific Meeting on NS (WHO 2012).
In a survey conducted by the Ugandan Ministry of Health and the Centers for Disease Control and Prevention (CDC), the prevalence of NS in 2012/2013 in the three northern Ugandan districts of Pader, Kitgum and Lamwo was 6,8/1000 inhabitants, with a total of at least 1834 children affected by 2013 (Iyengar et al. 2014).
NS incidence reached a peak in 2004/5, and another peak in 2008 (Landis et al. 2014). There were no cases of NS reported in 2013 (Colebunders et al. 2016a), and only two more until 2015 (Wamala et al. 2015).
Of note, according to local perception, NS is definitely attributable to the raging civil war between the Lord's Resistance Army (LRA) and the Ugandan government (Buchmann 2014). Yet, apparently, NS has not been observed in children abducted by the LRA, but only among those who had spent some time living in IDP camps (Landis et al. 2014).

4.1.5.4.1 Geographical distribution in Uganda

Kitgum, Lamwo and Pader districts in northern Uganda were affected first, cases have also appeared in Gulu district (also northern Uganda) (Curtis 2011; Makumbi 2012), and by the end of 2011 in the adjoining districts of Agago and Amuru, lying south of Lamwo (Wasswa 2012), Oyam and Lira districts (van Bemmel et al. 2014) and Yumbe in north-western Uganda (Curtis 2011). In Gulu and Amuru districts, over 300 NS cases have been reported and over 20 deaths have occurred; civil war has been ongoing in the area for 20 years (Kitara D. et al. 2013).

Of note, the most affected sub-counties are traversed by the (for Uganda unusually) fast-flowing rivers Pager and Aswa (Ministry of Health Uganda 2012). Health ministry teams found the disease to occur more commonly close to streams – there are five streams cutting across the affected villages (Pager, Lakankodi, Adinga, Lanyalyang, and Anyuka) (Integrated Regional Information Networks (IRIN) humanitarian news and analysis 2009).

4.1.6 Interpreting figures on Nodding syndrome prevalence

The true prevalence of NS might be underestimated (due to stigma or the inaccessibility of information / transport to treatment centers). It might, however, also be overestimated, because of willful feigning of symptoms in order to profit from free treatment (including food supplies), or due to a broad case definition encompassing many similar conditions, e.g. of psychiatric nature (van Bemmel et al. 2014). The Ugandan and South Sudanese governments are possibly no reliable source of figures, as they, too, profit from the international attention and aid that NS delivers (Grosse 2012). The Ministry of Health allegedly reported 500 cases from Usratuna hospital in Juba, while Usratuna physician Dr. Anna Mary Otim speaks of 24 cases at most (Schenck 2012).

4.2 Clinical presentation

4.2.1 Nodding episodes

The defining feature of NS is head nodding. In order to outline the characteristics of this disorder, the International Scientific Meeting on NS has suggested certain criteria for the diagnosis of NS:

4.2.1.1 Definition of nodding episodes (WHO 2012)

Suspected case	Description of head nodding in a previously normal person
Probable case	= suspected case with: Age 3-18 years Frequency of nodding: 5-20/min plus one of the following: • Other neurological impairments (cognitive decline, school dropout due to cognitive/behavioral problems, other seizure types, other neurological abnormalities) • Clustering in space or time with similar cases • Triggered by cold/food • Stunting/wasting • Delayed sexual/physical development • Psychiatric symptoms
Confirmed case	= probable case plus one of the following:

- Head nodding seen by a trained health care worker
- Head nodding videotaped
- Electroencephalography (EEG)/ Electromyography (EMG) records

The attacks may be triggered by food or cold weather (WHO 2012; Dowell et al. 2013). A case report from Tumwine et al. describes nodding seizures to be repeatedly elicited by eating the local food ugali, while not occurring when the patient was offered western candy bars (Tumwine et al. 2012). There are reports that only the sight of food may trigger the attacks, which allegedly stop when patients avert their eyes (APA 2012). Of note, these triggers are only present in approximately 20% of Tanzanian cases (Grosse 2012; Winkler et al. 2008). However, the association may also result from higher attention at meal times, where social gathering takes place, while actually also occurring in other situations (Gerrits 1983).
Other, less common triggers include early arousal (Richer et al. 2008) and exercise (Kitara D. et al. 2013). Flashbacks of traumatic war experiences are also hypothesized to trigger nodding episodes (Musisi et al. 2013), though it is unclear whether such psychiatric diseases actually constitute NS.

Nodding episodes occur between one and several times per day (Sejvar et al. 2013; Winkler et al. 2008; Idro et al. 2013b; Dowell et al. 2013; Gerrits 1983). The duration of attacks typically ranges between two and five minutes (Tumwine et al. 2012). The attacks have been described to appear "as though someone is forcing his chin down onto his chest" (Harding 2003). During these attacks, consciousness may be impaired (Kaiser et al. 2000; Winkler et al. 2008), but some cases also continue to follow commands (Sejvar et al. 2013). Nodding may be accompanied by staring, drooling, eye deviation or rhythmic jerking (WHO 2012), there can be tongue-biting (Fallon 2012) and upper arm movements (Sejvar et al. 2013). The episodes are reminiscent of generalized epileptic seizures and often result in patients falling into wells, fireplaces, etc. Such accidents, in combination with behavioral problems such as "wandering off", account for the alleged high mortality (Tumwine et al. 2012; Santosh 2004). Another frequent cause of death is status epilepticus (Jilek-Aall et al. 1979)) .
Over time, additional forms of epileptic seizures may develop in patients with NS (Spencer et al. 2016a).

4.2.2 Cognitive impairment

If untreated, some NS patients eventually develop cognitive decline (Polo et al. 2015) with loss of memory and reduced attention span (Sejvar et al. 2013) as well as impaired speech (Idro et al. 2013b), though these findings could not be verified in all patients (Winkler et al. 2010). Jilek-Aall and colleagues (Jilek-Aall et al. 1979) report a monotonous voice from the onset of disease, and an apparently progressive process of mental deterioration in her patients. A subsequent study confirmed the presence of cognitive impairment in 40% (25/62) of Tanzanian patients with NS, which was significantly associated with additional seizures (Winkler et al. 2010).

The International Scientific Meeting on NS declared cognitive decline to be the result of an "epidemic epileptic encephalopathy", although other authors suggest a common cause might lead to both cognitive decline and seizures (Cross 2013), or even that parental neglect and isolation may cause mental retardation (Schenck 2012).

In Liberia, Gerrits et al. describe 39 of their 114 patients with epilepsy, of which some presented with nodding symptoms/signs, as mentally "disturbed" i.e. not able to participate in farming, household and social activities, with this decline invariably beginning after the onset of seizures (Gerrits 1983). Physical and social development in childhood was impaired after the onset of nodding episodes in 101 cases from Uganda, and cases dropped out of school significantly more often than controls (Kitara D. et al. 2013).

4.2.3 Psychiatric signs/symptoms

There are also behavioral (aggression, shouting, running in circles, withdrawal, lethargy, mutism, wandering off, sleeping difficulties) and psychiatric signs/symptoms (fear, hallucinations) commonly associated with NS (Idro et al. 2013b; Tumwine et al. 2012). Many parents resort to tying their children up in order to prevent them from running away (Abbasi 2013). Jilek-Aall also describes acute psychotic reactions, fugue and hallucinations (Jilek-Aall 1964; Jilek-Aall et al. 1979; Jilek-Aall 1976). Some authors suggest psychiatric disturbances to be the root of the problem, not only one of its symptoms (Musisi et al. 2013).
The amount of comorbidity of psychiatric disorders in NS cases is very high and includes episodic major depression (25.3%), PTSD (post-traumatic stress disorder, 16.4%), generalized anxiety disorder (30.7%) and pervasive developmental disorder (4% (Spencer et al. 2016a)).

4.2.4 Malnutrition, stunting and wasting

Malnutrition is a prominent feature in NS. It may result in wasting (as an acute effect) and stunting (as a chronic effect, though this may not be solely explained by malnutrition, suggesting additional endocrine dysfunction). Idro et al. observed stunting which was disproportionate to the degree of malnutrition in many of their patients (Idro et al. 2013b).
Malnutrition was significantly associated with NS case status in some studies (Kitara D. et al. 2013; Sejvar et al. 2013), but not in others (Foltz et al. 2013; Tumwine et al. 2012). Winkler et al. did not observe physical decline in the majority of their patients (Winkler et al. 2014).
In 101 probable NS cases compared to 101 controls, impaired nutritional status was more frequent in cases and a head circumference lower by 20-30% compared to controls was present in 80% of cases (Kitara D. et al. 2013).
Idro et al. (Idro et al. 2013b) found 16/22 patients to be wasted and 9/22 stunted and the severity of wasting was correlated with duration of symptoms. In severe cases, patients might exhibit multiple complications of malnutrition, including anemia, heart failure and others (Idro et al. 2013a).
A significant association of NS with lower body weight, the consumption of relief food in IDP camps and the consumption of moldy maize could be demonstrated in a recent case-control study examining 50 Ugandan NS patients (Spencer et al. 2016b).

Malnutrition has been reported to have its onset after the beginning of head-nodding episodes (Korevaar and Visser 2013). In a South Sudanese study (Mindra 2012), 38 NS case-control pairs were examined. The question was raised whether poor nutritional status was a consequence of NS or whether malnutrition might be a factor contributing to NS. An association of low height-for-age (stunting) and low weight-for-age (wasting) with duration of illness was found. The mean onset of NS was at eight years and there was also a significant positive correlation between age of onset and severity of stunting (Mindra 2012). This would suggest malnutrition is a consequence of NS, not its cause.

There are different reasons which might lead to poorer feeding in NS patients than in controls (fear of triggering seizures, neglect, etc.). However, when asked for a history of going hungry, there was no statistically significant difference between cases and controls in this study (Mindra 2012), which suggests other factors might also be involved – e.g. hormonal changes or metabolic disorders. Cognitive impairment might also lead to malnutrition.

In Tanzania, severe malnutrition, coupled with increased susceptibility to infection, anemia and muscular atrophy were described by Jilek-Aall in the setting of a resource-poor population of subsistence farmers who regularly suffer from famine (Jilek-Aall 1964). As patients with epilepsy suffer considerable social stigma in the Wapogoro tribe (Jilek-Aall et al. 1979), this may be a consequence of neglect, not a causal factor contributing to the disease. However, Jilek-Aall also mentions children with epilepsy failing to grow no matter how much food they are given (Jilek-Aall 1964).

4.2.5 Stunting, wasting and impaired sexual development

Other prominent features of NS are muscle wasting and delayed sexual development (Dowell et al. 2013; WHO 2012). In Uganda, wrist x-rays of 22 NS patients suggest a delay in bone age of two years (Idro et al. 2013b). A combination of stunting, impaired sexual development and epilepsy has also been described and termed the "Nakalanga syndrome". It has been suggested that the two diseases may present different phenotypes within a continuum of one and the same disease (Föger et al. 2017).

4.2.6 Other signs/symptoms

There may be additional neurological deficits in NS, which especially include motor deficits, e.g. inability to stand or walk, and upper motor neuron abnormalities (Sejvar et al. 2013; Dowell et al. 2013). Jilek-Aall describes distinct signs reminiscent of Morbus Parkinson in her patients with epilepsy (of whom a significant percentage may be classified as NS patients) (Jilek-Aall et al. 1979). These include a mask-like face, drooling, monotonous voice, shuffling, clumsy movements, stooping gait etc. Other neurological abnormalities mentioned in this report included pathological reflexes and muscular atrophy. Autonomous symptoms comprising drooling and urinary incontinence were also reported (Dowell et al. 2013; Jilek-Aall 1964).
Less frequently reported symptoms associated with NS include trembling of the hands (Wasswa 2012), facial edema (Jilek-Aall et al. 1979), skeletal deformities, dental caries (Otim and Odong 2013) and golden hair (Ovuga et al. 1992), which may be a sign of malnutrition, as well as thick lips, especially the lower lip (Höflinger 2012; Idro et al. 2013b). Lip changes might result from repeated biting during nodding episodes, as may be observed in tic patients (Lin et al. 2006). A high temperature gradient between cold extremities and the trunk has been reported (Idro et al. 2013b), which has given rise to speculations that vasoconstrictive mycotoxins might be involved in the pathogenesis (Spencer 2013). Reports of dry, scaly skin (Otim and Odong 2013) and pachydermia (thickened skin) (Jilek-Aall et al. 1979) may point towards possible onchocerciasis-related dermatitis.

4.2.7 Prognosis

Case fatality rates were assessed in Tanzania, revealing that 19 of 33 NS patients survived the period between first diagnosis (1962 at the latest) and follow-up (1971) (Spencer et al. 2013a). In another study, the death of 2/62 patients after four years could be ascertained, seven were lost to follow-up, corresponding to a case fatality rate of 9-36 per 1000 patient years (Winkler et al. 2014). However, case fatality rates are reported to be much higher in Uganda and South Sudan, and the manifestations of disease more severe (Idro et al. 2013b), raising the question whether NS in Tanzania and NS in Uganda and South Sudan might be of different origin (Grosse 2012; Williams 2012). In Liberia, Gerrits et al. (Gerrits 1983) report that patients with epilepsy anecdotally do not reach the age of 30 years.

Over time, NS patients tend to develop additional other types of seizures including absence, generalized tonic-clonic (grand-mal) and partial complex seizures (WHO 2012).

This disease progression towards severe malnutrition, cognitive decline, psychiatric and behavioral deterioration and development of additional seizure types has been classified by Idro et al. into five stages as follows (Idro et al. 2013b): They consider NS to begin with apathy (1) followed by head nodding (2) after which other seizure types develop (3). Further complications arise in form of psychiatric and cognitive problems, physical deformities and wasting (4), which eventually lead to severe disability (5). The NS cases evaluated in this study had often received only intermittent treatment or treatment at subtherapeutic doses (Idro et al. 2013b), which may have contributed to the severe progression of the disease.

4.3 Diagnostic findings

4.3.1 Cerebro-spinal fluid

Cerebrospinal fluid (CSF) was repeatedly analyzed in NS patients and did not reveal any specific pathology (Table 4). (Some of the CSF samples were included in more than one of the below-mentioned publications in the following cases: The samples examined by Foltz et al. (Foltz et al. 2013) correspond to those examined by Sejvar et al. (Sejvar et al. 2013). The samples examined by König et al. (König et al. 2010) correspond to those examined by Winkler et al. (Winkler et al. 2008; Winkler et al. 2013)).

Table 4: Cerebro-spinal fluid findings in patients with NS

Country	References	Number of samples	Pathological findings
Uganda:	(Sejvar et al. 2013)	16	None (normal cell count, glucose and protein concentrations)
	(Foltz et al. 2013)	14	Abnormal glucose levels in 1/14, multiplex polymerase chain reaction (PCR) for 19 virus families and measles PCR negative
	(Idro et al. 2013b)	22	None (normal cell count, glucose and protein concentrations, bacteriological cultures without growth)
Tanzania	(Winkler et al. 2008)	48	Mildly elevated cell count in 3/48, Glucose ratio, protein content and albumin ratio normal, CSF/serum IgG-index elevated in 3/48, CSF/serum antibody-index for *O. volvulus*-specific antibodies: borderline elevation in one case, PCR negative for *O. volvulus* in all cases
	(Winkler et al. 2013; König et al. 2010)	51	CSF/serum *O. volvulus*-specific antibody index raised in two, PCR negative for *O. volvulus* in all cases
South Sudan	(Spencer et al. 2013b)	Max. 26	None (*O. volvulus* PCR negative)
	(Tumwine et al. 2012)	Max. 69, min. 16	None (*O. volvulus* PCR negative)

(In several publications, authors do not specify the exact number of CSF samples obtained. In these cases, the entire number of NS patients analyzed is considered as the maximum number of possibly obtained CSF samples, while all CSF results mentioned explicitly constitute the minimum number of obtained samples).

4.3.1.1 Routine parameters

CSF analysis by Sejvar et al. (Sejvar et al. 2013) revealed normal protein and glucose levels in 16/16 and a normal cell count in 4/4. Foltz et al. (Foltz et al. 2013) detected normal levels of protein in 14/14 patients and abnormal glucose levels in 1/14 patients. Idro et al. (Idro et al. 2013b) reported normal

protein, glucose levels and cell counts in 22/22 patients. Winkler et al. also (Winkler et al. 2008; Chevallier et al. 2014; König et al. 2010) found a normal blood-CSF glucose ratio, a normal protein content and albumin ratio. They measured a (mildly) elevated cell count of cells/µl in 3/48, which mainly consisted of lymphocytes and monocytes, and of which one was contaminated with blood.

4.3.1.2 Infectious agents

The CSF-PCR for *O. volvulus* microfilariae (mf) was negative in all 48 patients examined by Winkler et al. (Winkler et al. 2008; König et al. 2010). In onchocerciasis-positive patients in South Sudan, CSF-PCR also failed to detect mf presence in two studies (Tumwine et al. 2012; Spencer et al. 2013b). König et al. analyzed 197 CSF samples from 300 Tanzanian individuals, of which 51 had head nodding. There were no mf detectable in the CSF by PCR (König et al. 2010).
The presence of other mf species in CSF has not been evaluated in NS patients. CSF-PCR for measles was negative in 14/14 cases, as was multiplex PCR covering 19 virus families (Foltz et al. 2013). Bacteriological cultures of CSF in 22/22 patients in Uganda revealed no growth (Idro et al. 2013b).

4.3.1.3 Antibodies

CSF was also analyzed for antibodies in light of a possible auto-immune mechanism (König et al. 2010; Soldatos et al. 2015; Johnson et al. 2017b).

4.3.1.4 Interpretation

Repeated CSF analysis failed to demonstrate central nervous system (CNS) invasion by *O. volvulus* mf (Winkler et al. 2008; Spencer et al. 2013b, 2013b; Tumwine et al. 2012).
However, it has been suggested that mf invasion of CSF may have been present in Winkler et al.'s patients before ivermectin treatment (Kaiser et al. 2009), leaving small scars acting as seizure foci. Routine parameters in CSF of NS patients are normal (Sejvar et al. 2013; Foltz et al. 2013; Winkler et al. 2008; Idro et al. 2013b), yet this cannot exclude helminthic infection. Normal routine CSF parameters may routinely be observed in mf invasion (e.g. in cases of *Loa loa* (van Bogaert et al. 1955) or neurocysticercosis (Machado et al. 2013)).

4.3.2 Infections

4.3.2.1 *O. volvulus*

An overview of diagnostic findings linking onchocerciasis and NS is provided below (Table 5).

4.3.2.1.1 Skin snips

A common method of diagnosing infection with *O. volvulus* is microscopy of a skin snip. The sensitivity of this method must, however, be questioned: In 9/10 patients with negative skin snip, PCR was able to detect mf (Freedman et al. 1994).
Onchocerciasis is a consistent finding in NS. Analysis of skin snips demonstrated an association of both conditions in three studies in South Sudan and two studies in Uganda (Table 5).

- South Sudan: An association between NS case status and positive skin snips for onchocerciasis was significant in a study examining 38 case-control pairs. The association was highly significant for pairs in Maridi but not significant in Witto (Reik et al. 2012). In Lui/Amadi, Spencer et al. also found this association to be significant in 69 cases and 65 controls (Spencer et al. 2013b), and three case-control studies with a total of 82 cases/81 controls were all highly significant as well (Tumwine et al. 2012).
- Uganda: A significant association was found in 101 case-control pairs in one Ugandan study (Kitara D. et al. 2013). In another Ugandan study, there was a trend towards association demonstrated in 49 case-control pairs, but it was not significant (Foltz et al. 2013).

These observations are backed by other studies of different design, which also commented on the prevalence of onchocercal infection among children with NS. In Tanzania, positive skin snips were found in 43/51 (84%) of patients (Winkler et al. 2008), an association between positive skin snip PCR for onchocerciasis and magnetic resonance imaging (MRI) pathologies (gliosis and hippocampus pathologies) was significant in a sample of 12 patients (Winkler et al. 2008). In Uganda, 3/10 (30%) of Ugandan children had positive skin snips (Idro et al. 2013b). Another Ugandan study found no evidence of onchocerciasis among their eight patients (Musisi et al. 2011).
Evidently, past onchocercal infections may have left their mark on the organism even though the infection might no longer be detectable by skin snip. In order to rule out a source of bias, the use of ivermectin, which is distributed regularly in areas where *O. volvulus* is endemic, was assessed by several of these case-control studies. In three of the five studies, cases had experienced ivermectin treatment more often, but not significantly so (Spencer et al. 2013b; Tumwine et al. 2012; Foltz et al. 2013). One study even found a significant association of case status with absence of ivermectin use (29% of cases, 46% of controls) (Kitara D. et al. 2013), the remaining case-control study (Reik et al. 2012) and the studies without case-control design (Idro et al. 2013b; Winkler et al. 2008) do not comment on ivermectin use in their patients.

4.3.2.1.2 Microfilarial load

Skin snips can also be used to quantify the burden of onchocerciasis which a person is subjected to. A study evaluating mf density as measured by skin snip showed no significant association of higher mf density with MRI pathologies (gliotic lesions and hippocampus pathologies) in 12 patients (Winkler et al. 2008).

Table 5: Association between onchocerciasis and Nodding syndrome

Country	References	Study population	Association of positive skin snip and NS case status	Association of positive skin snip and MRI pathologies	Association of positive serology and NS case status
South Sudan	(Reik et al. 2012)	n=38 cases	Highly significant association in Maridi, not significant in Witto		
	(Spencer et al. 2013b)	n=69 cases	Significant		
	(Tumwine et al. 2012)	n=82 cases	Highly significant		
Uganda	(Kitara D. et al. 2013)	n=101 cases	Significant		
	(Foltz et al. 2013)	n=49 cases	Association not significant		Significant association of *O. volvulus*-specific IgG antibodies
	(Johnson et al. 2017b)	n=55 cases (19 Ugandan, 36 South Sudanese)	Positive *O. volvulus* status in 44/54 NS cases and 29/54 controls		Anti-leiomodin-1-antibodies in 29/55 NS cases and 17/55 controls
	(Soldatos et al. 2015)	n=3 cases	Skin snips negative in 3/3		
Tanzania	(Winkler et	n=12 cases		Significant	

	al. 2008)			association	
	(Winkler et al. 2008)	n=51 cases			In 44/51 NS cases *O. volvulus* specific antibodies, controls not assessed

4.3.2.1.3 Antibodies in Nodding syndrome

In some forms of epilepsy, the occurrence of anti-voltage-gated potassium channel (VGKC) antibodies (Bien and Scheffer 2011) and anti-N-methyl D-aspartate receptor (NMDAR) antibodies is a well-known phenomenon (Bien and Scheffer 2011). A study on six Tanzanian patients could not demonstrate either of these antibodies in patients' sera (Dietmann et al. 2014). However, Idro et al. found anti-VGKC antibodies in the sera of 15/31 NS patients and one out of 11 controls, though this data was not explicitly published (Idro et al. 2016). The authors mention the hypothesis of NS being a neuroinflammatory disorder caused by antibodies directed against *O. volvulus* or Wolbachia.
In light of a possible auto-immune mechanism involved in the generation of NS, the presence of antibodies (Table 6) directed against *O. volvulus* is of pathogenetic relevance. Such antibodies could be demonstrated repeatedly in the sera of NS patients (Foltz et al. 2013; Winkler et al. 2008; Johnson et al. 2017b). Winkler et al. also analyzed antibodies detected in the CSF, the CSF-serum IgG-index was raised in 3/48 (Winkler et al. 2008). In 19 patients, *O. volvulus* specific antibody index was calculated from the amount of *O. volvulus*-specific antibodies in serum versus in CSF, but there was only one patient with a borderline increase in this parameter (König et al. 2010; Winkler et al. 2008).
Pezzani analyzed 11 serum samples of NS patients. Immunohistochemistry showed intense staining of rat cerebellum brain tissue after incubation with the patients' sera. The reactivity of NS patients' sera was markedly increased compared to his neurological patients used as controls (personal communication with the author). As these results may suggest the presence of antibodies, Western blot was performed on the patients' sera and one serum sample was analyzed via IgG affinity column, showing an elevation of immunoglobulin G (IgG) compared to a negative control and two controls with anti-neuronal antibodies of different origin (Anti-Yo and Anti-Hu, personal communication with the author). All this provides some suggestion of an autoimmune mechanism, but Western blot could not identify a common band suggestive of one concordant antibody elevated in all the patients' sera (Pezzani 2006).
Screening the CSF of Ugandan NS patients for known anti-neuronal antibodies apparently delivered negative results (the details of which remain unpublished) in 15 CSF samples of NS patients, of which 12 were analyzed at the Mayo Clinic, and 3 at Emory University (Dowell et al. 2013).
A study at the National Institutes of Health (NIH) that so far has been published only as an abstract found oligoclonal bands in CSF suggestive of an auto-immune disorder with possible prior onchocerciasis (Soldatos et al. 2015).
In a highly interesting study designed to further clarify auto-immune processes in NS, serum auto-antibodies were significantly elevated in patients with NS, showing a marked increase of especially two antibodies (anti-protein deglycase-DJ-1(DJ-1)-antibodies and anti-leiomodin-1-antibodies). The presence of anti-leiomodin-1-antibodies could also be shown in the CSF in 8/16 NS cases (Johnson et al. 2017b). The authors were able to reveal the expression of leiomodin-1 in cerebral cortex, cerebellum and hippocampus, regions which, in previous MRI findings, show atrophy and gliosis in NS patients (Winkler et al. 2013). Neurotoxicity of leiomodin-1-antibodies in vitro and cross-reaction of the antibodies with *O. volvulus*-antigens (amongst others, tropomyosin) could also be demonstrated (Johnson et al. 2017b).

The pathophysiological significance of raised antibodies in NS still remains to be clarified. As leiomodin-1 is (in contrast to other targeted structures in autoimmune epilepsies) commonly known as an intracellular antigen, Johnson et al. suggest that a possible immunopathology in NS could in fact be mediated by T-cell-activation with accompanying antibody production against multiple *O. volvulus* antigens as a bystander-effect of this immune response. Alternatively, the authors discuss possible pathogenic mechanisms of antibodies directed against intracellular antigens, including cell-penetrating antibodies, altered antigen localization due to apoptosis or changes in antigen expression due to tissue

repair following injury (Johnson et al. 2017b). Furthermore, Johnson et al. mention as yet unpublished results which seem to indicate an expression of leiomodin-1 on the cell surface of neurons, in contrast to other cell populations, where its presence is considered purely intracellular (Johnson et al. 2017a).

Table 6: Antibodies in Nodding syndrome

Area of investigation	Authors	Study population	Antibodies in patient serum	Antibodies in CSF
Uganda	(Foltz et al. 2013)	n=49 cases	Significant association of *O. volvulus*-specific IgG antibodies	
	(Idro et al. 2016)	n = 31 cases	Significant association of anti-VGKC antibodies	
	(Soldatos et al. 2015)	n = 3 cases	Oligoclonal bands partially identical to oligoclonal bands in CSF in 1/3	Oligoclonal bands in CSF in 2/3, partially identical to oligoclonal bands in serum in 1/3
	(Dowell et al. 2013)	n = 15 cases		Negative results for known anti-neuronal antibodies at Mayo Clinic and Emory University
	(Pezzani 2006)	n = 11 cases	Intense reactivity to rat cerebellum in immunohistochemistry attributable to IgG, however, no single common IgG band detectable in Western blot	
Uganda and South Sudan	(Johnson et al. 2017b)	n = 55 cases (19 Ugandan, 36 South Sudanese)	Raised auto-antibodies in NS cases versus Ugandan / South Sudanese controls, including anti-leiomodin-1 antibodies (increased 33.000 fold) and anti-DJ-1-antibodies (increased 750-fold)	Anti-leiomodin-1 antibodies present in 8/16 NS cases, 0/8 in controls (US patients with epilepsy)
Tanzania	(Winkler et al. 2008)	n = 51 cases	44/51 NS cases: *O. volvulus* specific antibodies, controls not assessed	Raised CSF-serum IgG-index in 3/48; borderline increase of *O. volvulus* specific CSF-serum antibody index in 1/19
	(Dietmann et al. 2014)	n = 6 cases	No anti-VGKC or anti-NMDAR-antibodies	

4.3.2.2 Measles

A recent case-control study in northern Uganda analyzing 50 cases and controls was able to demonstrate a significant association of NS case status with prior measles infection (Spencer et al. 2016b). Two case-control-studies had evaluated a history of measles in NS patients before. One of these found no significant association between the two conditions (Tumwine et al. 2012). The other had shown an association between NS case status and a history of measles infection, which was,

however, no longer significant after age-matching of cases and controls (Foltz et al. 2013). Similar to *O. volvulus* mf, the measles virus was not detectable in the CSF of NS patients (Foltz et al. 2013). The hypothesis has been brought forward that NS may result from a progressive inflammatory brain disease, comparable to SSPE (Spencer et al. 2016b).

4.3.2.3 Mansonella

In South Sudan, a significant association of NS with *Mansonella perstans*, a filarial worm, was found in 69 cases and 65 controls (Spencer et al. 2013b; Tumwine et al. 2012).

4.3.2.4 Neurocysticercosis

No antibodies against *Taenia solium* were detectable among 36 NS cases and 40 controls in Uganda (Foltz et al. 2013). In another study, 12 / 110 patients with epilepsy had a positive cysticercosis serology (Newell et al. 1997). Among the nine out of these 110 patients who also presented with growth retardation (possible cases of Nakalanga syndrome), only one had detectable antibodies against cysticerci.

4.3.2.5 *Loa loa*

In a study on NS from South Sudan, evidence of infection with *Loa loa* was not found in any of the 69 cases and 65 controls (Tumwine et al. 2012).

4.3.2.6 Malaria

Malaria in thin and thick smears among 22 Ugandan cases was less common in cases than in controls (2.3% vs 4.7%; (Foltz et al. 2013)). A childhood history of severe malaria or other severe illnesses was significantly more prevalent among 101 Ugandan NS cases than controls (16% vs 2%; (Kitara D. et al. 2013)).

4.3.2.7 Trypanosomiasis

There were no antibodies against *Trypanosoma brucei gambiense* detectable among 36 NS cases and 40 controls in Uganda (Foltz et al. 2013). In a study from South Sudan, there was no evidence for an association with trypanosomiasis (positive testing in 5/69 cases compared to 5/65 controls (Tumwine et al. 2012)).

4.3.2.8 Others

No association of NS could be shown with either meningitis, prion diseases, hepatitis E (Dowell et al. 2013) or African Swine fever (WHO 2012). Also, MRI results in 12 Tanzanian and five Ugandan patients were not indicative of acute disseminated encephalomyelitis, which can be observed after infection with various bacteria/viruses or immunization (Sejvar et al. 2013; Winkler et al. 2008).

4.3.3 Electroencephalography

EEGs (Table 7) were recorded in Uganda (22+3+12 EEGs (Idro et al. 2013b; Sejvar et al. 2013; Musisi et al. 2013), Tanzania (10+25 EEGs; (Winkler et al. 2008; Winkler et al. 2014) and South Sudan (32 EEGs (Tumwine et al. 2012)). There were also four cases in Cameroon which might represent NS cases (Prischich et al. 2008).

4.3.3.1 Interictal findings

Interictal abnormalities were common in NS patients from Tanzania, Uganda and South Sudan alike (Idro et al. 2013b; Sejvar et al. 2013; Winkler et al. 2010; Winkler et al. 2014; Tumwine et al. 2012; Prischich et al. 2008; Winkler et al. 2008; Polo et al. 2015). The most common interictal finding was diffuse background slowing (Sejvar et al. 2013; Idro et al. 2013b; Winkler et al. 2008; Winkler et al. 2014; Polo et al. 2015). There were also generalized spike-and-wave-complexes of 2.5-3 Hz (Sejvar et al. 2013) or < 2.5 Hz (Winkler et al. 2014). Bilateral epileptiform activity in the form of spike-and-wave discharges from 2-3.5 Hz and sharp waves was demonstrated in NS patients from South Sudan (Polo et al. 2015). Furthermore, epileptiform discharges in form of generalized sharp waves in Tanzania and Uganda (Winkler et al. 2008; Idro et al. 2013b) and "universal" recurrent paroxysmal pathological discharges in South Sudan were observed (Tumwine et al. 2012). Focal temporal epileptiform discharges in two out of 22 patients, suggestive of a focal brain lesion, and pronounced

frontotemporal epileptiform discharges have been described in Uganda (Idro et al. 2013b). Focal sharp waves were also seen in five patients from South Sudan (Polo et al. 2015). A study from Cameroon also describes 4/19 epilepsy patients within a village presenting with apparent head nodding. These patients showed focal epileptiform activity and non-specific focal slow wave activity (Prischich et al. 2008).

4.3.3.2 Ictal findings

Ictal EEG (during head nodding episodes) was obtained in two Ugandan patients (Sejvar et al. 2013). They presented with generalized electrodecrement, accompanied by a loss of activity in cervical paraspinal EMG. The attacks were followed by generalized slowing (theta activity). Ictal EEG during seizure activity other than head nodding suggested focal epileptiform activity in this study.
Three ictal EEGs were also recorded during nodding episodes in South Sudan (Tumwine et al. 2012). Nodding manifested in EEG as "an isolated, diffuse delta theta slow wave complex increasingly polymorphous as the disease progressed, followed by a brief and small fast discharge" (Tumwine et al. 2012, 245). Another study from South Sudan demonstrated high-amplitude, bi- or triphasic slow waves with an inverse phase reversal over the vertex region during nodding attacks. The slow wave lasted 0.5-1.4 seconds and was sometimes followed by an electrodecremental pattern for 1-4 s. The entire pattern was repeated every few seconds in periodic sequences for an entire duration of several minutes (Polo et al. 2015).
In Tanzania, two ictal EEGs showed generalized 2.5 Hz spike-and-wave activity (Winkler et al. 2014). As reported at the 2015 Gulu Conference on NS, Wagner presented his observation of atypical absences, tonic and atonic seizures in three ictal EEGs in patients from Tanzania (Spencer et al. 2016a).
In Uganda, three EEGs were performed on presumable NS patients referred to Mulago National Hospital by Musisi et al. (Musisi et al. 2013) of which two were normal and one showed a "nonspecific epileptic pattern". EEG in one other case report was normal (Musisi 2011). Among eight further cases of suspected NS referred to Mulago National Hospital, some cases were diagnosed with Lennox-Gastaut-Syndrome and grand-mal seizures based on EEG, however the EEG findings are not elaborated on (Musisi et al. 2011).
Kaiser et al. (Kaiser et al. 2000) also analyzed three patients with head nodding, concluding that different types of seizure are probably subsumed under this entity. One of the three cases was probably suffering from myoclonic-astatic seizures, another from complex partial seizures.

Table 7: Electroencephalographic findings in patients with Nodding syndrome

Country	References	Study population	Interictal findings	Ictal findings
Uganda	(Idro et al. 2013b)	n=22	Diffuse background slowing, generalized sharp waves, pronounced frontotemporal epileptiform discharges in 2/22	
	(Sejvar et al. 2013)	n=12 (ictal EEG: n=2)	Diffuse background slowing, generalized spike-and-wave-complexes	Generalized electrodecrement, loss of activity in cervical paraspinal EMG
	(Musisi et al. 2013)	n=3	"Non-specific epileptic pattern" in 1/3	

Tanzania	(Winkler et al. 2008)	n=10	Diffuse background slowing, generalized sharp waves	
	(Winkler et al. 2014)	n=25 (ictal EEG: n=2)	Diffuse background slowing, generalized spike-and-wave-complexes, polyspike-wave-complexes	Generalized 2.5 Hz spike-and-wave activity
	(Spencer et al. 2016a)	n=3		Atypical absences, tonic and atonic seizures
South Sudan	(Tumwine et al. 2012)	n=32 (ictal EEG: n=3)	Recurrent pathological discharges	Delta- theta slow-wave activity, followed by a brief and small fast discharge
	(Polo et al. 2015)	n=21 (ictal EEG: n=3)	In 18/ 21 spike-and-wave discharges often intermingled with sharp waves	In 3/3: nodding episodes apparent in clusters during hyperventilation, high-amplitude, bi- or triphasic slow wave with an inverse phase reversal over the vertex region repeated every 3-10 seconds
Cameroon	(Prischich et al. 2008)	n=4	Focal epileptiform activity and non-specific focal slow wave activity	

4.3.3.3 Interpretation

The ictal EEGs during head nodding in Ugandan NS patients in combination with loss of activity in paraspinal EMG are suggestive of atonic seizures (Sejvar et al. 2013), whereas in Tanzania, ictal EEG showed generalized 2.5 Hz spike-and-wave-activity (Winkler et al. 2014) and in South Sudan, diffuse delta-theta slow-wave activity was observed (Tumwine et al. 2012). Wagner et al. also found nodding episodes to resemble a mixture of atypical absences and tonic seizures (Spencer et al. 2016a).
As for the interictal findings, background slowing and slow spike-wave-complexes are indicative of atypical absences (Winkler et al. 2014). The variety of other interictal findings (polyspike-wave-complexes, focal epileptiform discharges, etc.) may hint to multiple different seizure types like complex partial and generalized seizures, including atonic and tonic-clonic seizures.

The International Scientific Meeting Report (WHO 2012) on NS summarized EEG results available to them and highlighted

- Diffuse background slowing
- Spike-and-wave-complexes
- During nodding episodes:
    - electrodecrement followed by a burst of spikes
    - loss of muscle tone in EMG (representing atonic seizures).

While purely psychiatric disorders usually present little change in EEG, marked EEG alterations as observed in NS are typical for many neurological diseases, including encephalopathies (metabolic or toxic), endocrine disorders, hypoxia, dementia and neurological infections (Smith 2005).

4.3.4 Magnetic resonance imaging and computed tomography

MRI investigation was performed on NS patients by several authors (Sejvar et al. 2013; Winkler et al. 2008; Winkler et al. 2013; Idro et al. 2013b; Musisi et al. 2011). Sejvar et al. analyzed five NS patients, of which four showed cerebral (most pronounced in parieto-occipital regions) and / or cerebellar atrophy (two of them involving the hippocampus) and one showed encephalomalacia and calcified lesions consistent with previous CNS infection.

Idro et al. also found varying degrees of cerebral and cerebellar atrophy in 19 patients, these were more pronounced in occipital and parieto-occipital regions. In contrast to results from Tanzania, no hippocampal lesions were observed.

Winkler et al. analyzed 12 NS patients, these findings were published in two different papers (Winkler et al. 2008; Winkler et al. 2013). They detected both symmetrical and asymmetrical MRI abnormalities consisting of gliosis and hippocampal sclerosis and atrophy (three out of seven patients with “head nodding only” presented with abnormalities, while in the group “head nodding plus”, which also showed other forms of epileptic seizures, five of five MRIs were abnormal). Compared with MRI findings of 20 patients with epilepsy but without head nodding, the “head nodding plus” group showed significantly more pathologic findings, especially hippocampal changes and gliosis. These findings were also present in three out of seven patients with “head nodding only”. Atrophy was more common in patients with epilepsy (eight out of 20) than in those with “head nodding only” (one out of seven) and “head nodding plus” (one out of five). Arachnoid cysts were found in one out of 12 patients with head nodding and one out of 20 patients with epilepsy.

Musisi et al. performed computed tomography (CT) scans on eight in-patients referred to Mulago Hospital. They mention one case with nonspecific brain atrophy, but do not comment on the other cases (Musisi et al. 2013). Cranial CT in one further case series showed global cortical atrophy (Musisi 2011).

4.3.4.1 Interpretation

Findings in patients with NS revealed cerebral and cerebellar atrophy (Sejvar et al. 2013; Idro et al. 2013b), hippocampal atrophy and gliosis (Winkler et al. 2013).
Diffuse cerebral atrophy is a common finding in malnutrition (Odabaş et al. 2005; Atalabi et al. 2010; Gunston et al. 1992; Roma et al. 1979). Gliotic lesions as seen by Winkler et al. may be caused by cerebral ischemia, inflammation and trauma (Yu et al. 1998). Positive skin snip PCR for *O. volvulus* was significantly associated with intraparenchymal pathologies on MRI (Winkler et al. 2008). Particularly in light of raised auto-antibodies in NS cases (Johnson et al. 2017b), MRI pathology might be compatible with an autoimmune process triggered by infection with *O. volvulus*. Leiomodin-1, the target of auto-antibodies significantly elevated in NS cases, is present in cerebral cortex, cerebellum and hippocampus (Johnson et al. 2017b), regions which also seem affected by the described focal

pathologies on MRI. MRI results are not indicative of acute disseminated encephalomyelitis, which can be observed after infection with various bacteria/viruses or immunization (Dowell et al. 2013).

4.3.5 Histopathologic findings

Under examination by polarized light microscopy, intracellular crystalline-like structures have reportedly been observed by CDC-researchers in histological sections of the pons in six out of nine NS patients in 2014 (Idro et al. 2016; Spencer et al. 2017; Butagira 2014). However, unfortunately, the findings have not yet been officially published.

4.3.6 Other findings

4.3.6.1 Routine blood examinations

Routine blood examinations (including liver function tests, and screening for various toxins) were normal in 23 cases (Sejvar et al. 2013). As summarized by the International Scientific Meeting on NS, hematological examinations, levels of creatinine and transaminases had yielded no pathological results (WHO 2012), nor was blood urea nitrogen elevated (Kitara D. et al. 2013). Winkler et al. found eosinophilia in 28/51 cases (Winkler et al. 2008). This may be due to helminth infections.

4.3.6.2 Metabolic parameters

Concerning metabolic parameters, low electrolytes were measured in one out of three NS cases by Musisi et al. (Musisi et al. 2013).
A study on 101 patients with probable NS (Kitara D. et al. 2013) detected metabolic acidosis (though the authors do not offer mean values for pH) with low serum bicarbonate, decreased levels of sodium, potassium and chloride, and a resulting high anion gap as calculated by $[Na^+] – [Cl^-] – [HCO3^-]$. A subset of cases and controls were also examined for pyruvate and lactate levels, which were significantly higher in cases.

4.3.6.3 Vitamin B6

Vitamin B6 has been suggested as a cause of epilepsy in light of the existence of pyridoxine-dependent seizures (Stockler et al. 2011). Vitamin B6 levels were low in both cases and controls in a study from Uganda and one from Tanzania (Foltz et al. 2013; Dietmann et al. 2014). An as yet unpublished study at the NIH supports these findings in three further NS cases (Soldatos et al. 2015). Recently, further investigations in Uganda have demonstrated significantly lower plasma concentrations of vitamin B6 in NS cases than controls, and correspondingly elevated plasma concentrations of the neurotoxic metabolite 3-hydroxykynurenine (Obol et al. 2016). It must be kept in mind that these findings may result from an unbalanced diet and not be pathophysiologically linked to NS.

4.3.6.4 Desoxyribonucleic acid analysis

Using the technique of deep exome sequencing in a Ugandan and a Sudanese child, no known epilepsy genes could be demonstrated (unpublished data, reported by Dowell et al. (Dowell et al. 2013)).

4.3.6.5 Negative findings

As illustrated in a review from 2013 (Dowell et al. 2013), no association could be shown between NS and toxic environmental factors including pesticides, cassava/thiocyanates (cassava is a much-consumed plant responsible for neurological disorders such as konzo), homocysteine (which may be elevated as a side effect of treatment with antiepileptic drugs (AEDs), or might accumulate in the absence of vitamin B6), mercury, copper, lead, or arsenic. No different water sources (rivers versus boreholes, shallow wells, piped water, etc.) had been used in cases and controls (Foltz et al. 2013). Toxic nutritional factors, which have also been held responsible for the appearance of NS, including spoiled relief foods, river fish or rodent brain were not associated either in a review from 2013

(Dowell et al. 2013), though an association between families with NS case status and the intake of moldy maize could be demonstrated in 2016 (Spencer et al. 2016b). The same can be said for bush meat, monkey meat and sorghum (WHO 2012). As for deficiency of vitamins and trace elements in the course of malnutrition, no significant difference in the levels of vitamin B12, folate, vitamin A, zinc and selenium could be demonstrated (Dowell et al. 2013).
Initially, a weak association was shown between NS and the consumption of red sorghum (Serena) (Spencer et al. 2013b), baboon brain (for which the association was never statistically significant) (Tumwine et al. 2012) and absence of measles history (Tumwine et al. 2012; Spencer et al. 2013b), but this could not be confirmed in subsequent studies (Dowell et al. 2013). The same is true for crushed roots (Foltz et al. 2013) and exposure to munitions, which was found to be associated with mechanical weapons instead of chemicals, as originally suspected (Dowell et al. 2013). Regarding measles, a subsequent study from Uganda even showed a significant association between NS case status and prior measles infection (Spencer et al. 2016b).

4.4 Treatment

Without any known cause, NS can only be treated symptomatically. Recommendations concerning treatment were drawn up in 2012 (WHO 2012). Re-evaluation at the Gulu Conference in 2015 showed that treatment has proven to be effective, achieving a reduction of seizure frequency, improved nutritional status and positive emotional change in NS patients. Still, to date, there is no known cure for NS (Spencer et al. 2016a).

4.4.1 Antiepileptic drugs

Reducing seizure frequency is considered a major issue, both to avoid injuries caused by accidents and to limit the destructive effect of seizures on the brain. Early and regular treatment is reported by South Sudanese health workers to reduce the frequency of seizures and, as a consequence, complications due to accidents, as well as ensuring normal growth (Nyungura 2011). Several AEDs have been proposed.

4.4.1.1 Phenobarbitone, phenytoin and sodium valproate

As a drug which has been in use for a long time, phenobarbitone has been tried in NS. Winkler et al. conducted a study evaluating the outcome of 39 NS patients treated at the Mahenge epilepsy clinic, where they found phenobarbitone to be more effective than carbamazepine against head nodding spells. However, in 30 out of 32 patients on phenobarbitone, some forms of epileptic seizure (generalized tonic-clonic seizures or head nodding) persisted, though in decreased frequency (Winkler et al. 2014).

Apart from phenobarbitone, phenytoin is also affordable and readily available, and therefore broadly used in NS (WHO 2012). In three out of four Tanzanian patients with head nodding who were treated with phenytoin (alone or in combination with other drugs), nodding episodes stopped or decreased in frequency (Winkler et al. 2014).

The International Scientific Meeting on NS 2012 has declared sodium valproate, which is employed in various forms of generalized epilepsy including absence epilepsy, West Syndrome and Lennox-Gastaut-Syndrome, “potentially the AED of choice” (WHO 2012). It is used as standard therapy in the NS Screening and Treatment Centers set up by the Ugandan Ministry of Health.
In patients in whom seizure control under sodium valproate starting doses of 10 mg/kg/day is not achieved, guidelines envisage an increase in dosage up to a maximum of 40 mg/kg/day.

Idro et al. report a 57% decrease in frequency of nodding attacks in 22 patients at Mulago National Referral Hospital in Uganda 14 days after starting treatment with sodium valproate. The patients had initially been treated with various AEDs including carbamazepine, phenobarbitone and phenytoin (though this treatment was administered discontinuously and at sub-therapeutic doses, so the maximum effect of these drugs might have been higher under correct dosage). Patients treated with sodium valproate still suffered a median of 2 seizures per day (Idro et al. 2013a).

4.4.1.2 Alternative treatment options

Alongside its advantages (including amelioration of behavioral problems), sodium valproate also has several disadvantages: It is teratogenic, causing spina bifida in 1-2% of cases and learning disabilities in many more. Sodium valproate must therefore be strictly avoided in women of reproductive age. (Gerlach et al. 2004, 219). Substitution of folic acid before the onset of pregnancy can limit these effects. Liver toxicity can be deadly, thrombopenia and leukopenia occur. (Gerlach et al. 2004, 186). Phenobarbitone is also teratogenic (Gerlach et al. 2004, 212). Sedation is a strong adverse effect of treatment with phenobarbitone, it is also present but less pronounced in sodium valproate and phenytoin (Gerlach et al. 2004, 212, 213, 219). In the case of already withdrawn, lethargic children, these properties might be problematic.
Phenytoin is also known to cause a number of side effects regarding the central nervous system, including ataxia, confusion and cerebral atrophy, but is less sedative than phenobarbitone(Schachter 2017).
In patients with serious adverse events after use of sodium valproate and women of reproductive age, the Ugandan Ministry of Health proposes several alternative options (Idro et al. 2013a):

Lamotrigine is considered the drug of choice for girls of reproductive age. Another option is levetiracetam, which is effective in all epileptic encephalopathies (Panayiotopoulos 2005). In cases of sudden, sharp increase in seizure activity, short-term use of benzodiazepines is recommended. Carbamazepine is not considered a valid option for treatment of NS and was not evaluated by the Ugandan Ministry of Health due to its risk of inducing myoclonic jerks. Other sources, however, report it to be effective (Richer et al. 2008).

The guidelines by the Ugandan Ministry of Health do not yet include recommendations for the duration of treatment, weaning is not envisaged. In cases of unsatisfactory seizure control, dosages of AEDs should be increased. However, as pharmacokinetics of AEDs in NS patients, particularly with malnutrition, are not well understood, the risk of causing severe side effects is not negligible. If occurring, cases of status epilepticus should be treated with intravenous benzodiazepines (Idro et al. 2013a).

Substituting sodium valproate with other AEDs can be difficult: NS shows similar clinical features as some epileptic syndromes (e.g. Lennox-Gastaut-Syndrome), where treatment with conventional anti-epileptic drugs shows poor results (Dulac and Kaminska 1997).
In some of these syndromes, ketogenic diet, corticosteroids/adrenocorticotropic hormone (ACTH) and possibly intravenous immunoglobulin may be effective (Panayiotopoulos 2005).

4.4.2 Immunomodulatory therapy

Immuno-modulatory treatment options have been discussed in light of a suspected auto-immune disorder leading to NS. So far, data on this topic is scarce. Short-term treatment by means of plasmapheresis and intravenous immunoglobulins was attempted in three NS patients from Uganda (Soldatos et al. 2015), but data on clinical improvement in these patients has not been published to date. Following their discovery of elevated auto-antibodies in the CSF of NS patients, Johnson et al. recommend the application of immuno-modulatory therapies, suggesting that these may be particularly effective in early stages of the disease (Johnson et al. 2017b).

4.4.3 Other treatment goals

Apart from controlling seizures, there are other aspects of NS to be addressed:

4.4.3.1 Nutritional rehabilitation

One is providing adequate nutrition including micronutrients and vitamins. The Ugandan Ministry of Health is providing a blanket supplementary feeding program to all families of NS patients (Idro et al. 2013a) by distributing flour and beans to NS patients (Otim and Odong 2013). A problematic aspect of this approach is a possible overestimation of cases, as symptoms of NS may be feigned (van Bemmel et al. 2014).

Carbohydrate-based diets should be exchanged for ketogenic diets in some epileptic encephalopathies of childhood, as these are supposed to have neuroprotective properties (Panayiotopoulos 2005), but no studies evaluating this effect in children with NS have been published so far.

In light of low vitamin B6 levels in NS patients, CDC and WHO intended to conduct further research on the effects of high dose pyridoxine substitution (Korevaar and Visser 2013; WHO 2012), but no results have been published so far. Of the currently known enzyme defects that may lead to pyridoxine dependent seizures, one (pyridoxamine 5'-phosphate oxidase deficiency) does not respond to pyridoxine, but only to its activated form pyridoxal phosphate (Wang and Kuo 2007). As all other forms may also be treated with pyridoxal phosphate and it is not more expensive than pyridoxine, pyridoxal phosphate is recommended by Wang et al. for use in children with epilepsy (Wang and Kuo 2007).
At present, no high dose vitamin B6 substitution, but initial addition of vitamin B complex along with vitamin A and vitamin D (whose levels are likely to be decreased by AEDs) is proposed by the Ugandan Ministry of Health (Ministry of Health Uganda 2012).

4.4.3.2 Psychological help and psychotropic drugs

Psychosocial support for patients and their families is essential. Psychological assessment should be part of standard diagnostic procedure.

Attitudes toward causal relevance of psychiatric disorders for the generation of NS, and consequently also attitudes towards psychiatric treatment of NS patients differ broadly. This is certainly due to limited diagnostic tools and a broad case definition of NS which may encompass different entities. Thus, it is not clear whether (sole) treatment with psychotropic drugs is adequate for NS patients. In terms of drug use, sodium valproate is reported to have a positive effect on behavior (Idro et al. 2013a).

In Uganda, Musisi et al. address this issue by proposing a classification of NS into "Nodding Syndrome Neurological type" (consisting of patients with an abnormal EEG/EMG), "Nodding Syndrome Psychiatric type" (consisting of patients without pathological findings in EEG / EMG), "Nodding Syndrome Mixed type" (implying neurological and psychiatric symptoms) and "Nodding Syndrome Atypical type" (Musisi et al. 2013). There are reports of dramatic improvement (gain of weight, better mood and stop of head nodding and other seizures) after treatment with imipramine and family supportive counseling (in addition to supervised feeding) in eight Ugandan patients referred to Mulago National Hospital with the diagnosis of NS (Musisi et al. 2011). The patients had undergone EEG, CT and MRI and were diagnosed with different types of epilepsy (generalized tonic-clonic seizures and Lennox-Gastaut-Syndrome). These findings would suggest that psychiatric therapy (anti-depressants, anti-psychotics and counselling) may benefit not only "Nodding Syndrome psychiatric type" but also "Nodding Syndrome mixed type" categories according to the classification proposed by Musisi et al. (Musisi et al. 2013). In other words, a positive impact of psychiatric treatment on seizure characteristics could imply a causal role of psychiatric disturbances in the generation of nodding episodes.

Other experts fear negative effects of psychotropic drugs (Schenck 2012). Tricyclic antidepressants should not be used in patients with epilepsy, as they lower the seizure threshold (Castaño-Monsalve 2013).

4.4.3.3 Anti-helminthic substances

4.4.3.3.1 Insecticides

In 2012, the Ugandan Ministry in collaboration with the regional intergovernmental organization "Desert Locust Control Organization" embarked on an operation to diminish the distribution of simulium (= black fly) along major rivers in northern Uganda (NTV Uganda). This form of vector control was achieved by aerial spraying of an insecticide (Temephos (Abate EC500)). Collaboration with neighboring regions of South Sudan was envisaged (NTV Uganda). After the spraying, a marked decrease in new NS case reports was remarked (Colebunders et al. 2016a).

4.4.3.3.2 Ivermectin

Though the link between onchocerciasis and NS has not been explained so far, it is nevertheless a recurring trend which justifies the use of ivermectin even in light of its potentially neurotoxic effects (Mealey et al. 2001; Lankas et al. 1989).

Ivermectin reduces transmission through the elimination of mf, it does not, however, affect macrofilariae. In order to eliminate onchocerciasis, mass treatment must thus be applied for 14 years, after which mf reach the end of their life span (WHO/APOC 2013).

In Uganda, ivermectin mass distribution programs have already been established in most parts. The drug is distributed to the entire population once every six months (Idro et al. 2013a). Until 2009, distribution programs reportedly did not fully cover NS-endemic areas, as Kitgum and Pader districts were inaccessible to ivermectin distribution campaigns due to rebel activity during this time (Wakabi 2009). WHO reports estimated the therapeutic coverage (meaning the percentage of the population

reached by distribution programs) to be 76% in 2006 (WHO/APOC 2007). Geographic coverage was above 99% in 2013, yet therapeutic coverage was still restricted to 72% of the population (WHO/APOC 2013).

In South Sudan, early interventions include a regional ivermectin campaign to control onchocerciasis which was conducted in Mundri County in 1995 (Spencer et al. 2013b). On a larger basis, efforts have been made since the creation of the Republic of South Sudan 2005 to enable mass distribution of ivermectin (Wakabi 2009), however, the results are still far from covering the entire population. Geographic coverage ranged at 60% in 2013, therapeutic coverage reached merely 43% of the population (WHO/APOC 2013).

In Tanzania, therapeutic coverage was at 72% in 2006 according to WHO reports (WHO/APOC 2007). In 2013, geographic coverage reached 98%, therapeutic coverage attained 79% (WHO/APOC 2013).

4.4.4 Treatment according to severity of disease

As the complications of NS are many, the guidelines proposed by the Ugandan Ministry of Health include a classification of patients according to severity of disease:

- Requiring emergency care are patients with severe protein energy malnutrition, status epilepticus or severe comorbidities e.g. anemia or heart failure.
- Requiring inpatient care are patients with multiple injuries/burns, pronounced behavioral problems or comorbidities e.g. heart failure.
- Requiring outpatient care are patients without severe comorbidities, showing only mild malnutrition. They should be kept on AEDs, occupational and language therapy, nutritional therapy and nursing care for burns, etc. (Idro et al. 2013a)

4.5 Prognosis/natural history

The prognosis of NS patients seems to differ between affected areas. Anecdotally, the disease progresses much faster in Uganda and South Sudan (Grosse 2012). Idro et al. describe NS to be more severe in South Sudan and Uganda than in Tanzania.
Over time, additional types of epileptic seizures including absence, generalized tonic-clonic (grand-mal) and partial complex seizures (WHO 2012; Winkler et al. 2008; Winkler et al. 2010; Winkler et al. 2014) often develop in NS patients.

4.5.1 Tanzania

Spencer et al. analyzed the natural history of 150 epilepsy patients of the Wapogoro tribe (affected by NS in Tanzania, initial presentation 1934-1962, re-evaluation in 1971 (Spencer et al. 2013a)). 33/150 initially presented with head nodding episodes, 14/33 had died at the time of re-evaluation (mean age at time of death: 20 years). Grand-mal-seizures set in after a period of up to 12 months following the onset of head nodding. Other neurological disorders (e.g. psychomotor impairment) were also observed.

In 2010, Winkler et al. analyzed 62 Tanzanian NS patients, 59 of whom were on different treatment regimes. They reported a reduction in seizure frequency by 50% from an average of 22 per month to 11 per month. However, 13 of 59 still had daily seizures(Winkler et al. 2010).
In another publication by Winkler et al., a four-year-follow-up examination of these cases, who were treated with phenobarbitone, phenytoin or carbamazepine, revealed a case fatality rate of 9-36 per 1000 patient years (58/62 were available for follow-up, 2/58 had died). In 11 out of 23 patients who had initially presented with head nodding only (no other seizure types), additional seizure types had developed, in five of these 11, head nodding had stopped. In patients with “head nodding plus” (head

nodding in combination with other seizure types reported initially), nine out of 30 were still classified as “head nodding plus”, while in 15 of 30, head nodding had stopped, but other seizure types were still present. In four out of 58 patients, both head nodding and other seizure types had abated (Winkler et al. 2014).

80% of NS patients developed additional seizures after onset of head nodding. There was a median “overlap time” of two years, after which nodding would generally disappear (median duration of five years). The median age at which head nodding stopped was 15 years (Winkler et al. 2014).

Taken together, these findings suggest head nodding episodes are prodromal signs announcing the imminent onset of other epileptic seizure types. However, head nodding may also persist, other seizure types may regress after onset or never appear in the first place, or there may be a free interval between nodding and onset of generalized seizures. Some patients also appear to have recovered from seizure-activity of any kind.

4.5.2 Uganda

In a Ugandan study, 14/23 children with NS were suffering from additional types of epileptic seizures, which had started at about the same time as nodding in 10/14. In 3/14, nodding preceded other seizures by several months. 12 out of 23 NS patients were re-assessed after eight months of treatment with either phenytoin, phenobarbitone or carbamazepine. During this time, 6/12 reported an increase in seizure frequency (head nodding or other epileptic seizures), while in the other 6/12, the condition had remained stable. 2/12 had developed additional seizure types. As 11 of 23 patients were lost to follow-up, these results are difficult to interpret. The missing patients might have recovered, they might also have died (Sejvar et al. 2013).

Idro et al. analyzed 22 patients, of whom 18 had developed other seizure types (myoclonic, absence, generalized tonic-clonic) one to three years after onset of head nodding (Idro et al. 2013b).

4.5.3 South Sudan

In South Sudan, data concerning the clinical evolution of NS patients is rare.

Locals report that NS “progresses over months to years to include seizures, severe wasting, stunting and mental retardation”.

A very fatalistic view of the outcome of NS was expressed in the beginnings of media coverage on NS, where the spokesman for the UN humanitarian coordinator for Sudan reported NS to be “100% fatal” (Santosh 2004). Authors of the Morbidity and Mortality Weekly Report (MMWR) deliver the following statement regarding NS in South Sudan state: „No child is known to have recovered from Nodding syndrome, and the long-term outcomes of illness are not known.“ (Reik et al. 2012, 53).

Though life expectancy of NS patients is probably significantly reduced, judging by case fatality rates for patients with epilepsy (Kaiser et al. 2007; Kamgno et al. 2003), its fatality is often overestimated. Inhabitants of Lui and Amadi villages perceived head nodding as an “invariably fatal” disease, beginning with head nodding and progressing to include other seizure types, wasting and stunting due to malnutrition, and cognitive decline (Tumwine et al. 2012). In Uganda, the head of Atanga Health Care Center III states that “Parents are neglecting their children because they think they will not survive” (Okino 2013).

4.5.4 Conclusion

NS often progresses to include other types of epileptic seizures and may be accompanied by cognitive decline. Overly fatalistic views are common and should be treated with care. The prognosis of Tanzanian patients seems to be better than that of patients from Uganda and South Sudan.

4.6 Management at national and international level

4.6.1 South Sudan

Reports from 2010 depict limited access to AEDs and a lack of experienced/trained health workers to deal with the burden of NS in Lui/Amadi, the disease`s epicenter (Nyungura 2011).

4.6.2 Uganda

An International Meeting on NS, organized by the WHO, was held in Kampala in August 2012, where leading researchers agreed upon a standardized case definition, summarized present knowledge of NS and outlined topics for further research (WHO 2012). This conference was followed by the Gulu Conference in 2015, where further research data and proposals to future research and treatment strategies were discussed (Spencer et al. 2016a).
Treatment centers were created by the Ugandan Ministry of Health from 2012 onwards (Buchmann 2014). By 2016, 17 such treatment centers had been established for NS in northern Uganda (Idro et al. 2016). Additionally, a model rehabilitation system has been introduced by the NGO "Hope for Humans" (Idro et al. 2016). Still, considering the rate of one doctor and 13 nurses per 10.000 people in Uganda, additional resources could help to further enhance available treatment for NS patients (Burton 2016).

4.7 Community perspective

4.7.1 Nodding syndrome in Tanzania

Onset of head nodding before puberty was diagnosed by the Wapogoro community as a precursor of epilepsy (Jilek-Aall 2004, 1964) indicative of an especially poor prognosis (Jilek-Aall et al. 1979; Jilek-Aall 2004).

Winkler et al. (Winkler et al. 2010) note, however, that patients with NS present in hospital earlier than those with generalized epilepsy (after a median of one year as opposed to two to three years), this finding might be attributable to them carrying less social stigma than patients with generalized seizures.

Still, school attendance among NS patients is even lower than in patients with generalized epilepsy: Over 40% (27/62) of patients treated for NS were found never to have attended school, compared to only 22% in a comparable sample of patients with generalized epilepsy. Another 34% (21/62) had dropped out of school later on, mainly due to epilepsy or cognitive impairments (Winkler et al. 2010).

4.7.2 Nodding syndrome in South Sudan

According to Tumwine et al. (Tumwine et al. 2012), NS is perceived as an invariably fatal illness by the communities in Lui and Amadi in South Sudan. There are various reports depicting the stigmatization and social isolation of NS patients, who are shunned and excluded from public life for fear of contagion (Nyungura 2011). The suspicion that NS might be transmissible may be sustained among others by the fact that siblings of NS patients run a higher risk of getting NS as well.

4.7.3 Nodding syndrome in Uganda

In Uganda, NS spreads epidemically, turning into a "popular disease" after the civil war. Parents first heard about it through the radio, through posters or Village Health Teams from 2003 on. It has even been suggested that symptoms may be feigned in order to benefit from free treatment, including food (Ndeezi 2012).

4.7.3.1 Local concepts of etiology

Interviews with over 50 parents of affected children revealed various etiological hypotheses that were drawn up to explain the sudden appearance of NS and its temporal relationship with the civil war. Among others, they incriminated food poisoned by chemicals or munitions (poisoned water on the other hand was not considered likely). Black flies (simulium) were not thought to be associated with NS in this study, but spiritual beliefs also constituted an important factor in the local mindset (Mitchell et al. 2013).
NS carries a strong stigma and is often causally attributed to evil spirits (van Bemmel et al. 2014). Even among health workers from Kitgum, Lamwo and Pader district, such ideas are common: 27/40 interviewed in a study from 2013 believed NS to be attributable to evil spirits or curses. Such implication of punishment by a deity may cause stigmatization of the affected children (Mutamba et al. 2013; Buchmann 2014). This is especially disastrous, as a general fear of transmission is already prevailing, resulting in isolation of NS patients (Buchmann 2015). School attendance of children affected by NS is reduced due to these factors (Buchmann 2014).

In another study (Kitara and Amone 2012), health workers mostly held psychological trauma experienced during the war responsible for the emergence of NS, combined with poor food supply and the bite of the black fly. A small percentage of health care workers also incriminated gold mining practices in Karamoja for poisoning Aswa, Agago and Pager rivers with mercury or other metals. Community members in this study focused instead on evil spirits dwelling in the forest (which might indicate an association with the forest-dwelling simulium species). Other suspected causes were eating meat from black cows of Karamoja region, seeds intended for planting, or food contaminated by the World Food Program, munitions, and dead bodies left unburied (Kitara and Amone 2012). The association with the civil war seemed to be very strong in this study, with the condition exclusively affecting children who had lived in IDP camps. No accounts of NS occurring in children born after the civil war are mentioned (Kitara and Amone 2012).

4.7.3.1.1 Fear of contagion

There is apparently a wide-spread fear of transmission between affected children and their healthy schoolmates voiced by many community members including health workers (van Bemmel et al. 2014; Mitchell et al. 2013). Local schools were also reported to have embraced this attitude, leading to a separation of children with NS from the rest (Mitchell et al. 2013), e.g. in Okidi primary school, where teachers at one point aimed to isolate sick children but met with criticism (Muhumuza 2012).

4.7.3.1.2 Attitudes towards Western medicine and government initiatives

Despite the many unsolved questions and the lack of causal treatment of NS, the predominant attitude towards modern medicine in the interviews conducted by Mitchell was a positive one. Parents embraced Western medicine as the only effective treatment option (Mitchell et al. 2013). Other reports, however, illustrate a loss of trust in it among parents (Kitara and Amone 2012).
The population remains reserved and distrustful of the government's actions, a feeling of being left uninformed seems to prevail (Buchmann 2014).

4.7.3.1.3 Fatalistic views

Interviews with caregivers in Kitgum district point towards a condition of learned helplessness, acquired during the time spent in IDP camps, which may be similarly adopted in dealing with NS. A feeling of distrust among the Acholi people against the current Ugandan government may further promote feelings of hopelessness and despair (van Bemmel et al. 2014). Attitudes promoted by health workers may greatly contribute to such convictions: According to a study in northern Uganda, 33/40 health care workers believed NS to be invariably fatal, and many held these children to be a burden for society, preventing their parents from working (Mutamba et al. 2013).

This attitude is reflected among others in school attendance of children with NS: Accounts from Uganda suggest that reduced school attendance may be due to actual cognitive impairment or to the

parents' feeling that their children lack the necessary capacity (Stein and Nalugya 2013).
Stigmatization is a major problem in NS (Buchmann 2014).
Recent reports demonstrate how an attitude of hopelessness may cause parents to neglect their children after onset of NS for fear of a greatly reduced life span (Okino 2013). This behavior, which may help reduce attachment, could be interpreted as a defense mechanism, preventing excessive emotional turmoil after the death of the beloved children. This emotional detachment may reach extreme dimensions, resulting in isolation and neglect to the extent of children dying from starvation (Kitara and Amone 2012).

4.7.3.1.4 Conclusion

NS has turned into a political issue in northern Uganda. Caregivers of the affected children tend to feel uninformed and suspicious of the Ugandan government (Buchmann 2014). Still, the efforts undertaken to effectively treat NS definitely show an effect – communities see some improvement achieved by current treatment practices (Mwaka et al. 2015), and approximately 80% of NS patients and their families have been found to seek help primarily in a health-care facility as opposed to traditional or faith based healers (Atim et al. 2016).

5. Discussion of potential pathomechanisms in Nodding syndrome

5.1 Onchocerciasis

A persistent association with onchocerciasis has been demonstrated in NS (chapter 4.3.2.1). Its causal contribution to the pathogenesis of NS is as yet unclear.

5.1.1 The fight to control onchocerciasis

Treatment options for onchocerciasis apart from the surgical removal of onchocercomata were suggested, e.g. in the form of piperazine derivatives in 1947 by Hewitt (Puyuelo and Holstein 1950). However, onchocerciasis was long considered manageable only by vector control. From 1975 on, the Onchocerciasis Control Program (OCP) was initiated by the WHO, the World Bank and UN agencies – the program's goal was the elimination of *O. volvulus'* vector (simulium flies) through larviciding (Babalola 2011).

In 1982, the efficacy of ivermectin, a drug derived from the mold *Streptomyces avermectilis* which dwells in soil, against *O. volvulus* was first reported (Babalola 2011). Before, treatment had consisted of suramine and diethylcarbamazine, which both caused multiple adverse effects (Babalola 2011). In 1995, the new initiative the African Program for Onchocerciasis Control (APOC) consisting of ivermectin mass treatment campaigns in hyperendemic areas was established by the WHO to be implemented in 19 African countries including Sudan, Tanzania and Uganda (WHO 2013). As ivermectin has a solely microfilaricidal effect, an individual may only be cured of infection after the natural death of residing adult worms. According to simulations, in order to achieve eradication, regular (annual) ivermectin treatment is required for at least 65% of the population over 25 years (Winnen et al. 2002).

In Uganda, regular distribution of ivermectin once per year was implemented from 2008 on. Biannual distribution and, additionally, larviciding by aerial spraying could be achieved from 2012 onwards (Colebunders et al. 2016c). A geographic coverage of over 99% was achieved in Uganda in 2013 (WHO 2013). These measures of controlling onchocerciasis have been suggested as the cause of a marked decrease of new NS cases from 2008 on (Wamala et al. 2015).

In South Sudan, ivermectin distribution was initiated in 1996, however, many interruptions took place in the following years. Thus, ivermectin coverage remains low to date (Colebunders et al. 2016a). In 2013, a geographic coverage of 60% was achieved (WHO 2013). Larviciding measures have not been implemented (Wamala et al. 2015). The continuous appearance of new NS cases in South Sudan, in contrast to northern Uganda, have been attributed to insufficient efforts to control onchocerciasis in South Sudan (Wamala et al. 2015).

In Tanzania, a geographic coverage with ivermectin of over 97% was achieved in 2013 (WHO 2013). However, ivermectin application has not been known to influence the incidence of NS in this region (Spencer et al. 2017).

5.1.2 Strains of *O. volvulus* and clinical manifestations of onchocerciasis

Onchocerciasis has a considerable clinical variability, with manifestations including mainly skin lesions and ocular damage. *O. volvulus* has also been found in lymphatic tissue (Connor et al. 1970), blood (Botto et al. 1984), urine (Botto et al. 1984), sputum (Fazen et al. 1975) and ascites (Couzineau 1973).
The existence of a "neurological type" of onchocerciasis has been evoked and neurological symptoms have repeatedly been attributed to onchocerciasis (Duke et al. 1976; Hissette 1932).

In the 1970s, the existence of a "savanna strain" and a "forest strain" of *O. volvulus* could be shown (Picq and Albert 1979; Anderson et al. 1974), of which the savanna-strain seems to cause far more marked ocular pathology than the forest strain (Duke and Anderson 1972; Duke and Garner 1975). The existence of a wider variety of strains apart from these two main types has been described in Uganda (Fischer et al. 1996) and Sudan (Kron and Ali 1993). These types also differ in the amount of endosymbionts they harbor, e.g. *Wolbachia* (Higazi et al. 2005). *Wolbachia* are intracellular bacteria essential to the development of onchocercal mf (Pearlman and Gillette-Ferguson 2007). They also play an essential role in determining a host's response to infection with *O. volvulus* (Brattig 2004; Pearlman and Gillette-Ferguson 2007).

Furthermore, clinical manifestations of onchocerciasis seem to depend not only on the involved strain of *O. volvulus*, but also on differing forms of immune response to infection (Hoerauf and Brattig 2002). It has been proposed that NS (and epilepsy in general) may also be a manifestation of onchocerciasis (Colebunders and Titulaer 2017). An autoimmune mechanism triggered by *O. volvulus* may be involved in its pathogenesis (chapter 4.3.2.1.3).

5.1.3 Pathogenetic concepts regarding the link between onchocerciasis and Nodding syndrome

Different mechanisms of pathogenicity have been evoked in an attempt to explain the intriguing link between the two conditions.

5.1.3.1 Direct damage to the central nervous system

The presence of *O. volvulus* mf in the CSF has been described (Duke et al. 1976; Hissette 1932; Mazzotti 1959). However, due to the persistent absence of *O. volvulus* mf in the CSF of patients with NS in recent studies (Winkler et al. 2008; Spencer et al. 2013b; Tumwine et al. 2012), invasion of mf into the CNS of patients with NS seems highly unlikely, and it has been suggested that the presence of mf in the CSF is most likely due to contamination.

5.1.3.2 Association with another pathogenic agent

Other pathogenic agents have been implied as the "culprits" causing NS (Spencer et al. 2017). Such agents might either be

- associated with *O. volvulus* due to similar environmental factors
- associated with *O. volvulus* due to the identical use of the simulium fly as a vector organism (Colebunders et al. 2014)
- using *O. volvulus* mf in a parasitic or symbiotic way (e.g. neurotropic viruses or endosymbionts such as *Wolbachia* (Colebunders et al. 2014))

5.1.3.3 Onchocerciasis as an epiphenomenon

Immunosuppression in NS may make an organism susceptible to many forms of infection. Malnutrition or other infectious diseases such as measles have been held accountable for a reduced function of the immune system in NS. Thus, the association with onchocerciasis might simply constitute an opportunistic infection in this context, comparable to nematode infection in Human Immunodeficiency Virus (HIV) patients, facilitated by population displacement and poor living conditions (Spencer et al. 2017).

5.1.3.4 Autoimmune mechanisms

In light of recent findings describing antibodies cross-reacting to *O. volvulus* in NS patients' CSF (Soldatos et al. 2015; Johnson et al. 2017b), the conclusion has readily been drawn that NS must be due to an autoimmune reaction against *O. volvulus* (Colebunders et al. 2016b).

However, there are considerable reasons for doubt, which should be considered before adopting this hypothesis prematurely.

5.1.3.4.1 Refutations

- Onchocerciasis is a widespread condition across the African continent. To date, there is no conclusive evidence to account for the fact that NS occurs only within specific regional boundaries in South Sudan, northern Uganda and Tanzania and not in other onchocerciasis-infested areas. The existence of conditions similar to NS in other countries, e.g. the Democratic Republic of Congo (DRC), has been mentioned in light of this discussion (Colebunders et al. 2016a), however, to our knowledge, cases meeting the WHO definition of confirmed NS have not been registered outside Uganda, Tanzania and South Sudan.
- The widespread use of ivermectin in Tanzania (WHO/APOC 2013) has not put an end to NS in this area.
- A significant proportion of NS patients is negative for *O. volvulus* infection even in the absence of past ivermectin use (chapter 4.3.2.1).
- The detection of antileiomodin-1-antibodies was possible not only in NS patients, but also in approximately one third of healthy controls (Johnson et al. 2017b) .
- In an autoimmune disorder, one would expect signs of an inflammatory response in the CSF. These could repeatedly not be demonstrated in NS (chapter 4.3.1), although the presence of oligoclonal bands in the CSF possibly pointing toward an autoimmune mechanism has been reported (Soldatos et al. 2015).
- The confirmation of an autoimmune cause of NS was attempted ex juvantibus by means of intravenous immunoglobulins and plasmapheresis, which produced no short-term effect (Spencer et al. 2017).

It therefore seems possible that an autoimmune reaction to *O. volvulus* is not causative of NS despite the exciting data provided by Johnson et al. (Johnson et al. 2017b). Instead, the antibodies detected might be interpretable as a result of seizure activity. Leiomodin-1 is an intracellular protein, which could be exposed during seizures and thus cause the formation of anti-leiomodin-1-antibodies as an epiphenomenon (Spencer et al. 2017).

5.2 Measles

An association of NS and prior measles infection has been shown (Spencer et al. 2016b). In a Ugandan study, the measles virus was not detectable by PCR in the CSF of NS patients (Foltz et al. 2013), measles serology was not performed. However, oligoclonal bands as a sign of possible auto-immune disease have been demonstrated in NS (Soldatos et al. 2015).

The similarities between NS and SSPE as a result of measles infection and persistence of the virus have been pointed out in this context. SSPE has been known to cause behavioral changes, cognitive impairment, seizures and even head nodding spells (Spencer et al. 2016b). Epidemiological data has been interpreted to support the hypothesis that NS may constitute a clinical entity very similar to SSPE, arguing that SSPE usually occurs with a delay of 5-6 years after primary measles infection. Accordingly, peaks in the incidence of measles (1998-2002) and the incidence of NS (2004/2005 and 2008) can be observed in Uganda. The onset of a measles vaccination campaign from 2002 on is held accountable by the authors for the decrease in NS incidence after 2008. Similarly, in South Sudan, the NS incidence peak in 1991 might also be attributable to a peak in the incidence of measles 6-9 years earlier (from 1982 to 1985 (Spencer et al. 2016b)).

To further support this hypothesis, crystal-like inclusion bodies have been reported in post-mortem studies in brains of NS-affected children (Idro et al. 2016). These may resemble inclusion bodies representing viral nucleocapsid inclusions (Spencer et al. 2016b), which are a known finding in SSPE (Dhib-Jalbut and Liwnicz 1984).

Measles have thus been held accountable for causing NS as a form of viral reactivation in the context of malnutrition and consequent immunodeficiency. It has also been suggested that the presence of related viruses, such as rinderpest in cattle, may have contributed to immunity before the recent epidemic appearance of NS in Uganda and South Sudan. This protective factor may have been lost due to population displacement and eradication of rinderpest (Spencer et al. 2016b). The low prevalence of NS among the cattle-herding Dinka tribe in South Sudan (Spencer et al. 2013b) has also been attributed to their elevated exposure to this measles-related virus (Spencer et al. 2016b).

5.3 Other infectious diseases

There is epidemiological data concerning other infectious agents. A significant association was demonstrated in South Sudan between NS and *Mansonella perstans* (Spencer et al. 2013b), a filarial nematode which has been shown to invade the CNS (Fernando et al. 2001).
A childhood history of severe malaria was also significantly more prevalent among 101 Ugandan NS cases than controls (16% vs 2%) (Kitara D. et al. 2013).
However, none of these findings seem pronounced and consistent enough to be held accountable for causing the disease, they must rather be considered an epiphenomenon due to immunosuppression in NS.

5.4 Toxins

Studies on the community perspective towards NS in Uganda have shown that locals commonly attribute the disease to the consumption of spoiled or poisoned relief food and / or contamination with chemicals during warfare (Buchmann 2014).
A case-control study by the CDC from 2009 could not demonstrate an association of NS with various environmental factors, including pesticides, dietary components (cassava, river fish, rodent brain, red sorghum etc.) and diverse heavy metals. There was no significant difference in the water sources used for consumption (Foltz et al. 2013). Exposure to munitions was reported significantly more frequently in NS cases than in controls, however, this was later found to be an association with gun raids instead of chemicals, as originally suspected (Dowell et al. 2013).
Two case-control studies from Uganda were able to demonstrate a significant association of NS with the consumption of relief food in IDP camps (Spencer et al. 2016b; Obol et al. 2016). One of these also detected significantly more frequent consumption of moldy maize in NS cases (Spencer et al. 2016b). The uptake of mycotoxins via spoiled relief food was suggested by the authors to enhance infection with measles by means of immunosuppression (Spencer et al. 2016b). However, possible recall bias must be considered in these findings, as the investigation was conducted years after residence in IDP camps, and local beliefs may in the meantime have strongly influenced the caregivers of NS patients.

5.5 Malnutrition and vitamin B6 deficiency

Malnutrition is a common finding in NS and, in general, an important comorbidity in patients with epilepsy in Sub-Saharan Africa (Kariuki et al. 2014). It may lead to a reduced seizure threshold (Palencia et al. 1996; Pezzani 2006; Stern et al. 1974) and may also account for cerebral atrophy in MRI (Andrade and Paula-Barbosa 1996) as observed in NS.

Epidemiologically, it is interesting to observe that NS has not been described amongst children abducted by the LRA in Uganda, a fact that might be linked to better food supplies (Landis et al. 2014). The markedly lower prevalence of NS among the Dinka tribe (Tumwine et al. 2012; Spencer et al. 2013b) might also be rooted in a better nutritional status of these cattle-herders as compared to the sessile, farming Acholi tribe. Peaks in NS incidence in 2004/5 and in 2008 have been attributed to malnutrition in IDP camps, the authors note that peak camp influxes had occurred in 1997 and 2003,

thus, five to seven years prior to both peaks in NS incidence (Landis et al. 2014). From 2009 on, many started leaving IDP camps (Buchmann 2014), which could explain the decrease in new NS cases after the NS incidence peak of 2008 (Colebunders et al. 2016a).

The link between malnutrition and NS has mainly been explained by facilitated infection with a possible pathogenic agent causing NS due to immunosuppression in the context of a poor nutritional status.
It should be taken into account that not only malnutrition in general, but also a lack of certain specific dietary components may be crucial to the development of NS. Low vitamin B6 levels and elevated plasma concentrations of the neurotoxin 3-hydroxykynenurine have been observed in NS (see 4.3.6.3). Vitamin B6 deficiency is known to cause cognitive impairment and epilepsy in form of "pyridoxine-dependent seizures" (Stockler et al. 2011) as well as pronounced immunosuppression (Chandra 1997). As substitution of pyridoxine / pyridoxal phosphate is an effective treatment option in pyridoxine-dependent seizures (Gospe 2006; Naasan et al. 2009), this should constitute part of NS treatment strategies until the significance of vitamin B6 levels to the development of NS has been clarified.

Opposing these hypotheses, it has also been suggested that malnutrition merely constitutes an epiphenomenon in NS, due to social stigma (Crepin et al. 2009) or reduced uptake of calories caused by food-triggered seizures (Korevaar and Visser 2013). Some also consider malnutrition in NS to be a manifestation of anorexia in psychiatric diseases such as depression and post-traumatic stress disorder (Musisi et al. 2013).

5.6 Metabolic causes and mitochondriopathy

With regard to the etiology of NS, the question of an underlying metabolic disorder has been raised.

Metabolic acidosis with low serum bicarbonate, low sodium, low chloride and low potassium levels, resulting in a high anionic gap, could be demonstrated in NS. Lactate and pyruvate levels were elevated in a subset of cases (Kitara D. et al. 2013).

Metabolic acidosis is known to cause peripheral growth hormone insensitivity and decreased levels of insulin-like-growth-factor 1 (IGF-1), mild forms of hypothyroidism and hyperglucocorticoidism (Wiederkehr and Krapf 2001). These conditions would offer an explanation for several clinical findings in NS, such as stunting, immunosuppression, increased sensitivity to cold and apathy.

The cause of metabolic acidosis in NS remains unclear and might conceivably lie either in ketoacidosis due to malnutrition, toxin intake or lactic acidosis due to an enzymatic or mitochondrial pathology.

5.7 Psychiatric disorders

Psychiatric disorders are an important feature in NS. Different pathologies including episodic major depression, PTSD, generalized anxiety disorder and pervasive developmental disorder are common in children suffering from NS in Uganda (Spencer et al. 2016a). Treatment with imipramine is reported to have positively impacted not only social behavior, but also the frequency of nodding episodes and generalized seizure activity in a small sample of NS cases (Musisi 2011).

It has been suggested that NS may indeed primarily constitute a psychiatric disease brought about by the terrible experiences made during times of war, with nodding spells representing psychogenic non-epileptic seizures (PNES).
Differentiating between PNES and epileptic seizures can be problematic due to clinical overlap between the two conditions (Devinsky et al. 2011) and lack of EEG-specificity (Mellers 2005).

PNES may result from factitious, dissociative or conversion disorders (Mellers 2005). Conversion disorders are found in PTSD and depression (Owens and Dein 2006). They are significantly associated with a history of childhood abuse and recent adverse life events (Mellers 2005).

Thus, NS has been interpreted as a cultural manifestation of PTSD, a condition which is very common in the war-torn regions of Uganda (Musisi 2011). It has also been suggested to constitute a form of anaclitic depression, involving autism-like behavior using motor stereotypy (head nodding) as an expression of self-comforting behavior. A classification in "NS of the neurological type" and "NS of the psychiatric type" has been proposed (Musisi et al. 2013).

Obviously, there is a considerable overlap between NS and psychiatric disorders in Uganda, and there may have been a wide variety of diseases, psychiatric and otherwise, locally described as "Nodding syndrome" (Musisi et al. 2013) before the application of the WHO case definition (WHO 2012). Presumably due to this overlap, many Ugandan patients with epilepsy are treated in psychiatric institutions (Wilmshurst et al. 2014).

However, psychiatric disorders cannot be assumed as the origin of NS in general. In Tanzanian NS cases, no armed conflicts or other reasons of great emotional distress are evident (though, intriguingly, psychiatric disorders then known as "hysteria" were evoked to explain epilepsy even in the patients treated by Louise Jilek-Aall (Rollins 1976)). She herself, however, readily differentiated "hysterical" conditions from epilepsy ("kifafa") (Jilek-Aall 1964). Furthermore, also within war-torn northern Uganda, there is a marked absence of NS among children abducted by the LRA as compared to those living in IDP camps (Landis et al. 2014). This interesting fact cannot be explained by emotional trauma, which must be considered, if anything, even more pronounced in abducted children forced to witness atrocities of the highest level.

Recently, it has been suggested that an autism spectrum disorder might be involved in the pathogenesis of NS (Spencer et al. 2016a). Further studies regarding the role of nutrition in the development of autism spectrum disorders provide evidence for an association between autism spectrum disorders and certain nutritional deficiencies (Fujiwara et al. 2016). Whether such mechanisms contribute to the development of NS remains to be shown.

5.8 Genetic predisposition

Familial clustering is a common finding in the epidemic appearance of NS (Spencer et al. 2016b; Colebunders et al. 2016a; Idro et al. 2013b). This is also true for cases of "endemic" epilepsy among the Wapogoro tribe in Tanzania (Neuman et al. 1995), where NS was first described.

In combination with the limited age group affected by NS and the clustering of cases in time and space, this may be interpreted as a consequence of common exposure to environmental factors (Colebunders et al. 2015).
However, familial clustering was noteworthy in NS cases even when compared to controls with identical exposure (Kitara D. et al. 2013) and has been investigated in the Wapogoro tribe in Tanzania (Neuman et al. 1995).

Considering the resemblance between NS and certain genetic epilepsy syndromes, a genetic background for the disease has been suggested (Winkler et al. 2008). To date, no known epilepsy genes have been detected in NS patients (Dowell et al. 2013).
Pathogenetic mechanisms to account for familial clustering could conceivably include altered predispositions regarding immunological pathways, metabolic pathways e.g. vitamin B6 metabolism, or responsiveness to treatment options, e.g. ivermectin (DeMott 2013).

5.9 Proposed approach to future research and treatment

In the quest to solve the mystery of NS, the results of histopathological examinations on nine brain specimens from NS patients are anxiously anticipated. Further postmortem studies should be undertaken to determine the nature of the crystalline structures which have been reported (Idro et al. 2016).

Concerning a possible auto-immune cause of NS, long-term evaluation of healthy controls with positive antibody status cross-reacting to *O. volvulus* antigens should be envisaged. These have been suggested to constitute an asymptomatic pre-stage of NS. Also, the development of disease after induction of autoantibodies in an animal model should be evaluated for proof of molecular mimicry in NS (Johnson et al. 2017b).

For clarification of a possible mitochondriopathy, muscle biopsies should be obtained in NS.

As to a possible infectious cause, anti-streptolysin-O would be of interest, as the various aftermaths of streptococcal infections include different neurological and psychiatric disorders.

In light of a possible psychogenic component, additional clinical investigations could provide evidence as to occurrence of nodding episodes during sleep, the presence of an aura and voluntary suppression of nodding episodes (as observed in basal ganglia disorders, e.g. tics).

An occurrence of NS has repeatedly been reported in various African countries apart from Uganda, South Sudan and Tanzania (Colebunders et al. 2014). A strict application of the WHO definition criteria for NS would help to further clarify these accounts.

Concerning treatment, clinical trials to evaluate the effect of doxycycline for depletion of *Wolbachia* in *O. volvulus* have been proposed (Idro et al. 2016). Furthermore, as suggested by Johnson and colleagues in light of their findings (Johnson et al. 2017b), the long-term effects of immuno-modulatory treatment should be part of a future research agenda in NS.

Part II: Landscape review on Nakalanga syndrome and a comparison to Nodding syndrome

6. Nakalanga syndrome

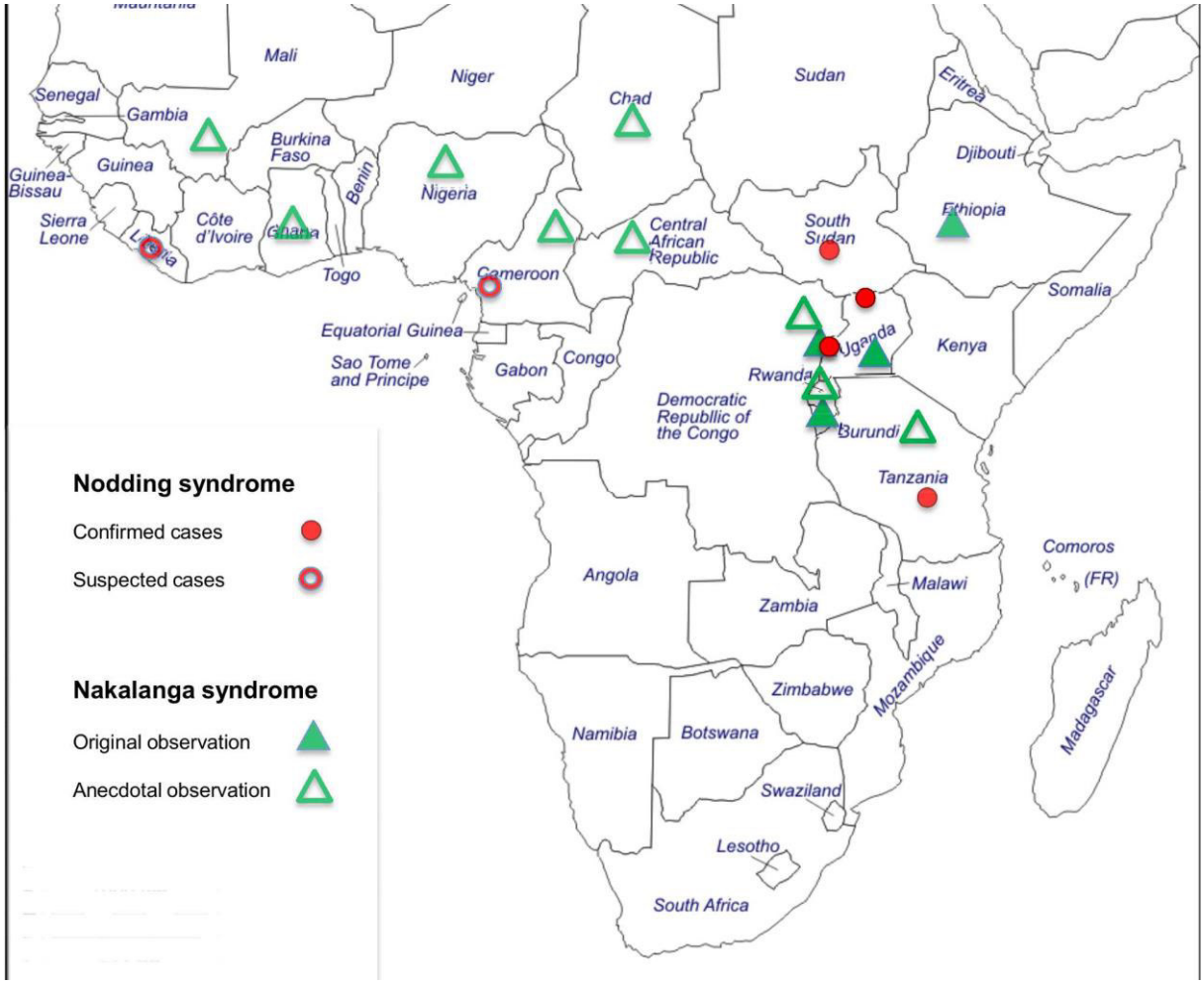
During the literature research for NS (chapter 3.1), the previously anecdotally reported resemblance between NS and another syndrome, termed „Nakalanga syndrome“, became apparent. In cooperation with various authors who had significantly contributed to research on this condition, foremost Dr. Christoph Kaiser and Prof. Dr. Dr. Andrea Winkler, we were able to publish an article focusing on the relationship of Nakalanga syndrome with NS.
The following passages (chapter 6.1 -6.5) are taken verbatim from this publication (Föger et al. 2017). Of note, the search procedure for Nakalanga syndrome was completed and published before the latest update of our search on NS was conducted, and thus does not include some of the most recent publications regarding NS. Among these, there is evidence suggesting the involvement of an autoimmune mechanism in the generation of NS (Johnson et al. 2017a). We were therefore not able to include these findings in our publication (Föger et al. 2017), but consider them highly relevant (chapter 5.1.3.4).

6.1 “The terms of „Nakalanga“ and „Nodding syndrome“

“The term Nakalanga is first found in an anthropological account published by John Roscoe (Roscoe 1911) in 1911, mentioning it as the name of a god recognized by a clan of the Buganda kingdom living in the area of the Mabira forest located 60 km east of today`s Ugandan capital city, Kampala. Up to today, Nakalanga is still the name of a god in the conceptual world of the Baganda (Bukuluki 2006). In addition to this meaning, in a 1934 geographical article about the Mabira forest, the word is found used to designate a person characterized by a condition of short stature („dwarfism“), which was frequently seen in the area (Pitman 1934). It was suggested that these persons were descendants of a pygmy tribe that in bygone times would have inhabited the Mabira forest (Pitman 1934; Johnston 1902).
During the late 1940s, Raper and Ladkin (Raper and Ladkin 1950) carried out an extensive investigation in the Mabira forest on patients affected by the Nakalanga phenomenon. They gave a thorough description of the condition and concluded that their patients were affected by a medical disorder, which they called Nakalanga syndrome. Up to 1965, two additional case series were published from the same area (Jelliffe et al. 1962; Bagenda et al. 1964). Thereafter, no more studies were undertaken, and when the Mabira forest became accessible again in the 1980s, no more cases were found. Instead, patients with a condition conforming with Nakalanga syndrome were observed in other locations, namely western Uganda (Ovuga et al. 1992; Kaiser et al. 2007; Kipp et al. 1996; Höfer 1999), Burundi (Newell et al. 1997), and Ethiopia (Oomen 1967). This is complemented by anecdotal observation from other areas of sub-Saharan Africa (Marshall and Cherry 1961; Boussinesq et al. 2002; Duke 1998), suggesting that the syndrome is probably not confined to Mabira and southeastern Uganda (Figure 1: Map of sub-Saharan Africa. Cases of Nakalanga and Nodding syndrome are reported from onchocerciasis endemic areas throughout West, Central, and East Africa.). As early as 1938, from an area in Mexico where a high endemicity of onchocerciasis and an elevated epilepsy prevalence were found, Casis Sacre described patients affected at a young age by a severe disorder characterized by growth failure, mental retardation, generalized weakness, and disturbed pubertal development (Casis-Sacre 1938). Although the similarity of this observation with the above-

mentioned reports was recognized (Jilek-Aall 2004), no further investigations from this area are available to more precisely assess its possible connection with Nakalanga syndrome.

Figure 1: Map of sub-Saharan Africa. Cases of Nakalanga and Nodding syndrome are reported from onchocerciasis endemic areas throughout West, Central, and East Africa.



Because patients with NS frequently display signs and symptoms that have also been described in Nakalanga syndrome, it has been questioned if both these conditions represent different manifestations of a common underlying pathology (Tumwine et al. 2012; Spencer et al. 2013b; Kaiser et al. 2013; Idro et al. 2013a; Ndeezi 2012; van Bemmel et al. 2014).
In this article, we focus on the following aspects:

- Based on a thorough literature search, we summarize the characteristic clinical features of Nakalanga syndrome as they were originally described in different areas, and we propose a working medical definition.
- We summarize available information on the etiology and possible causation of Nakalanga syndrome.
- We examine the question of whether the symptoms and signs found in Nakalanga syndrome are also present in cases of NS.
- We give suggestions as to how the relationship between the two entities could be further studied.

6.2 Characterization of Nakalanga syndrome and a proposed definition

In their pivotal study in the Mabira forest, Raper and Ladkin (Raper and Ladkin 1950) collected information from various community members about the local concept of the Nakalanga phenomenon. As a second step, in a convenience sample of characteristic patients, a list of signs and symptoms was established, and this was completed by more detailed investigations in seven selected patients, who were taken to a nearby hospital. Similar studies were carried out by Jellife et al. (Jelliffe et al. 1962) and Bagenda et al. (Bagenda et al. 1964) in areas neighboring Mabira forest.
As an overall result of these studies, Nakalanga syndrome was specified as a disorder affecting previously healthy children during the first ten years of their life. Growth retardation was described as the most prominent feature. When available, we applied height data from the original publications (Raper and Ladkin 1950; Jelliffe et al. 1962; Bagenda et al. 1964; Marshall and Cherry 1961) to the currently used WHO growth standards (WHO; Onis et al. 2007; Onis et al. 2012) and found strikingly similar median z-scores between -4.54 and -4.80 in the case series from these three closely neighboring areas (Raper and Ladkin 1950; Bagenda et al. 1964; Jelliffe et al. 1962), indicating an overall severe degree of stunting (Table 8). Generally, a height-for-age z-score of more than 2.0 standard deviations below the growth standard median is considered to indicate stunted growth (WHO). Yet, in each of the three studies (Raper and Ladkin 1950; Jelliffe et al. 1962; Bagenda et al. 1964), one patient with a height measurement corresponding to a z-score above the -2.0 standard deviation threshold was found (z-scores: -1.08, -1.52, and -1.98; Table 8), indicating a normal stature even when related to the current WHO standard. This is evidence that stunted growth, although reported as a frequent symptom, was not a mandatory criterion in the concept of the local communities to classify a person as a Nakalanga patient. The height of 53 local control children was measured by Raper and Ladkin (Raper and Ladkin 1950) and, expectedly, was found at z-scores below the current WHO standard (median: -2.14; range: +1.4 to -5.3). Twelve of these 53 children had height-for-age z-scores below -3.0, but their overall height was still taller than that of Nakalanga patients. Emaciation, delayed sexual development, and mental impairment were described as additional characteristic symptoms of Nakalanga syndrome, although these were not invariably found in all cases. Some patients also showed facial dysmorphia, deformation of the vertebral spine, or epileptic seizures (Table 8).
In 1992, Ovuga et al. (Ovuga et al. 1992) for the first time described the unusually frequent occurrence of a condition similar to Nakalanga syndrome in the Itwara onchocerciasis focus, situated in the Kabarole district, western Uganda (Table 8). The Itwara forest has no contiguity to Mabira forest in southeastern Uganda, where Raper and Ladkin had made their primary investigations 40 years earlier (Raper and Ladkin 1950). The study of Kipp et al. (Kipp et al. 1996) demonstrated that „Ekihuruka“, as the disorder was named by the population in the local Rutoro language, was consistent in its clinical picture with Nakalanga syndrome (Table 8). In 1999, a detailed analysis of 36 patients with Nakalanga (Ekihuruka) syndrome examined in the mentioned area of the Kabarole district was reported (Höfer 1999). A subgroup of 12 of these patients, who in addition were suffering from epilepsy, were also followed in the study of Kaiser et al. (Kaiser et al. 2007; Kaiser et al. 1998). In accordance with the earlier reports from southeastern Uganda, the study of Höfer (Höfer 1999) demonstrated that patients affected by Nakalanga (Ekihuruka) syndrome were not solely characterized by growth retardation or another single sign or symptom alone but rather by the combination of several distinct signs and symptoms. Consistent with the anthropometric results from southeastern Uganda (Raper and Ladkin 1950), the height measured in a control group of healthy children in western Uganda overlapped with the upper range of Nakalanga (Ekihuruka) patients (Höfer 1999), although the height-for-age z-score

of the control group (median: -1.09; range: +0.96 to -2.8) was by far higher than that of the patient group (median: -4.02; range: -1.36 to -6.62; Table 8).

Table 8: Clinical case series and case reports on Nakalanga syndrome: Southeast Uganda 1950-64, Ethiopia 1967, West Uganda 1991-95, Burundi 1995.

Publication [Reference]	Age	Anthropometry		Clinical Features					Onchocer-ciasis[ii]
	at onset[i]/ examination	Stunting[i]	Wasting[i]	Pubertal Development	Mental Development	Facial Dysmorphia	Kyphosis Scoliosis	Epileptic Seizures	
Southeast Uganda 1950 – 64									
Raper & Ladkin (Raper and Ladkin 1950)	n.r.[iii] (2-4)/ 11.5 (6-18)	-4.54[iv] (-1.52 - -6.15)	-6.21[iv] (-3.12 - -9.84)	delay; small genitalia; some cases retarded [v]	not severely impaired; appearance younger[v]	small mandible; protuberant skull; large lips[v]	prone to deve-lop scoliosis[v]	epilepsy in 2/7	positive in all cases
Marshall & Cherry (Marshall and Cherry 1961)[vi]	n.r.[iii]/ 30	-5.06 [iv]	n.r.[iii]	few pubic hair; normal testes, small penis	mentally dull	prognathic jaw; protruding teeth	n.r.[iii]	no epilepsy	positive
Jeliffe et al. (Jelliffe et al. 1962)	n.r.[iii]/ 14 (10-19)	-4.80 [iv] (-1.08 - -5.58)	-3.53 [iv] (-1.46 - -6.54)	reduced sexual activity; poor pubic hair[v]	Mild to moderate apathy; 2/ 5 "mental torpor"	prognatic jaw, forward angulated incisors in 2/ 5	2/5 marked kyphosis	epilepsy in 1/5	positive in all
Bagenda et al. (Bagenda et al. 1964)	n. r. (0-7)/ 20 (13-25)	-4.72 [iv] (-1.98 - -8.52)	n. r.[iii]	delay; cases $\geq$ 20 y in puberty or post-puberty	7/ 19 normal life; 10 doing simple jobs; 2 looked after	deep-set eyes; teeth protruding; small chin[v]	8/19 kypho-scoliosis	epilepsy in 7/19	positive in 18/19
Ethiopia 1967									
Oomen(Oom en 1967)[vi]	n.r.[iii]/ 35	-5.74[iv]	cachectic[v]	small genitalia	n.r.[iii]	n.r.[iii]	kyphoscoliosis	epilepsy	positive
West Uganda 1993 – 94									
Ovuga et al. (Ovuga et al. 1992)[vii]	n.r.[iii]	growth arrest[viii]	emaciation[v,viii]	poorly developed[v]	31/91 cognitive impair-ment; some apathetic[v]	distorted dentition[v]	pigeon chest; kyphosis[v]	epilepsy in 24/91	positive in 82/91
Kipp et al.(Kipp et al. 1996) [vii]	7 (1 - >8)/ 18 (15-32)	-4.9[ix]	-1.9[ix]	27 of 31 pre-pubertal, versus 2 of 28 controls	several cases mentally subnormal[v]	n.r.[iii]	deformed spine in 8/31	n. r.[iii]	positive in all
Höfer (Höfer 1999)[vii]	n.r.[iii] (1-11)/ 15 (7-20)	-4.02 [iv] (-1.36 - -6.62)	-2.53[iv] (+0.51 - -10.7)	delay, in comparison with local controls	14/36 mentally retarded	6/36 protruding forehead, flat nasal bridge	kyphoscoliosis in 6/36	epilepsy in 16/36	positive in 13/16
Burundi 1995									

Newell et al.(Newell et al. 1997)	n.r.[iii] / 17 (12-20)	-4.83[iv] (-2.59 - -5.19)	-1.11[iv] (+1.18 – 3.64)	delay in 2/9	n.r.[iii]	n.r.[iii]	n.r.[iii]	all with epilepsy	positive in all

[i] median (range)
[ii] detection of microfilaria of *Onchocerca volvulus* in skin biopsy, or of antibodies in serology (Newell et al. (Newell et al. 1997))
[iii] n.r. = not reported
[iv] z-score for height-for-age (stunting) and body mass index (BMI) (wasting), referring to 2006 WHO growth standard(Onis et al. 2012; Onis et al. 2007). Available: http://www.who.int/childgrowth/en/
[v] no quantified information
[vi] case report
[vii] overlap of study populations in studies of Ovuga et al. (Ovuga et al. 1992), Kipp et al. (Kipp et al. 1996) and Höfer (Höfer 1999)
[viii] growth arrest as mandatory symptom, defined as < 80% of average height of local population; emaciation as characteristic symptom, not specified
[ix] mean z-score of height-for-age and BMI, referring to 1977 NCHS (National Center for Health Statistics) growth reference (National Center for Health Statistics 1977). Available: http://www.cdc.gov/nchs/data/series/sr_11/sr11_165.pdf ; Range not reported

In 1997, Newell et al. (Newell et al. 1997) in a study from an onchocerciasis endemic area in Burundi reported cases with retarded growth, mental impairment, and delayed sexual development among a group of patients identified in an epilepsy survey (Table 8), and they pointed out the similarity of this observation with Nakalanga syndrome. In a study on clinical features of onchocerciasis in Ethiopia, Oomen described an individual patient showing a striking similarity with Nakalanga syndrome as found in southeastern Uganda (Oomen 1967).
The consistent syndromic pattern found in the mentioned noncontingent areas indicates that the reported patients may be affected by the same neurological disorder. Based on these findings, we propose that Nakalanga syndrome can be defined as a disorder affecting young children and youths who were born healthy and have passed through an initial phase of healthy development (Table 9). Patients present with at least one of the following predominant symptoms: retardation of growth (stunting), emaciation (wasting), delayed sexual development, or mental impairment. Less frequently, facial dysmorphia with small mandible, large lips, protruding front teeth, kyphoscoliosis, or epileptic seizures are encountered along with the mentioned major signs and symptoms. In the environment of a patient with Nakalanga syndrome, an accumulation of other cases with similar features is found.

Table 9: Proposed criteria for definition of Nakalanga syndrome compared to criteria for definition of a probable case of Nodding syndrome consented in Kampala 2012 (adapted from ref. (Dowell et al. 2013; WHO 2012)).

Proposed criteria for Nakalanga syndrome	Consented criteria for Nodding syndrome
I. Major criteria (obligatory) 1. Born healthy 2. Onset in childhood 3. No alternative explanatory condition 4. Plus one or several symptoms of developmental disturbance: – a) Stunting, growth failure – b) Wasting, emaciation – c) Retardation of sexual development – d) Mental impairment	**I. Major criteria** 1. Reported head nodding in a previously healthy person 2. Age 3-18y at onset of head nodding 3. Nodding frequency 5-20 times/min
II. Minor criteria (additional) 5. Facial dysmorphia: Small and protuberant mandible, large lips, protruding front teeth 6. Kyphoscoliosis 7. Epileptic seizures 8. Occurrence of similar cases in the surroundings	**II. Minor criteria** 4. Other neurological abnormalities (cognitive, school dropout, other seizures or neurological abnormalities) 5. Clustering in space or time with similar cases 6. Delayed sexual or physical development 7. Psychiatric manifestations

6.3 Information on etiology and possible causes of Nakalanga syndrome

In view of the clinical picture and the epidemiologic distribution, Raper and Ladkin (Raper and Ladkin 1950) excluded the hypothesis that people with Nakalanga syndrome could belong to a pygmy tribe. The combination of their clinical observations with the finding of a low urinary excretion of the 17-ketosteroids led them to assume that Nakalanga syndrome should be induced by defects in pituitary and adrenal gland function. In 1961, Marshall and Cherry (Marshall and Cherry 1961) reported on an

autopsy case which revealed no major changes of the histological appearance of the adrenal gland compatible with major adrenal dysfunction. In the histology of the pituitary gland of this case, they described some alterations in the composition of acidophil, basophil, and chromophobe cells, but the vascular supply was not disturbed, and there was no major lesion found that could have been produced by invasion of a pathogenic agent, e. g., *Onchocerca volvulus* microfilaria. It was concluded that „the primary affection may have been either in the pituitary portal system or the hypothalamus“, and the authors speculated that the „humoral transmission through the pituitary portal system was possibly jeopardized by circulating products of dead microfilaria“ (Marshall and Cherry 1961). In a series of ten Nakalanga patients, Leonard and Stanfield (Leonard and Stanfield 1965) found normal levels of morning plasma cortisol and a normal protein binding fraction of cortisol. They also reported normal results of fasting serum growth hormone (GH) in two patients and a normal rise of GH in a third case following stimulation with injected insulin (Leonard and Stanfield 1965). In the studies from Burundi (Newell et al. 1997) and from western Uganda (Höfer 1999), thyroid-stimulating hormone (TSH) as well as total thyroxine (T4) and triiodothyronine (T3) levels were measured and normal values were found in 31 of 32 cases. Höfer (Höfer 1999) also investigated the serum concentration of IGF-I and IGF-binding-protein-3 (IGF-BP-3) in a group of 23 severely stunted Nakalanga patients and found slightly lower concentrations in patients than controls, but IGF-I levels were not compatible with GH deficiency in 16 cases. When the remaining seven patients were assessed case-by-case with GH determination after physical strain and a follow-up of their growth rate over one year, GH deficiency was excluded in three more patients. In agreement with the findings of Leonard and Stanfield (Leonard and Stanfield 1965), and contrasting with the earlier assumptions of Raper and Ladkin (Raper and Ladkin 1950), the results of Höfer (Höfer 1999) disprove the hypothesis that a primary pituitary lesion plays a causative role in the pathophysiology of Nakalanga syndrome.

When Nakalanga syndrome was first recognized in the 1950s as a regional medical entity (Raper and Ladkin 1950; Jelliffe et al. 1962; Bagenda et al. 1964), a search on the cause of the condition was undertaken with the resources available at the time. On the ground of their clinical, laboratory, and epidemiological findings, the authors of the three studies from Southeast Uganda widely excluded a number of chronic disorders that elsewhere in Uganda or tropical Africa had been found related with growth failure (Bagenda et al. 1964; Jelliffe et al. 1962; Raper and Ladkin 1950). Explicitly, they found no connection with malaria, malnutrition, tuberculosis, rickets, syphilis, blood dyscrasias, intestinal parasites, and chronic diseases of the liver or other organs, but viral etiologies or auto-immune disorders were not mentioned. In view of the sporadic distribution of patients in different ethnic groups and families, a genetic disorder was considered unlikely, although this was not fully excluded (Jelliffe et al. 1962). Consistent with the findings from southeastern Uganda, no known disorder could be identified which possibly caused growth failure in Nakalanga (Ekihuruka) patients in western Uganda (Kipp et al. 1996; Höfer 1999). As a consistent observation, all study areas were found highly infested with onchocerciasis (Table 8).

Little is known about the natural history and the prognosis of Nakalanga syndrome. According to Raper and Ladkin (Raper and Ladkin 1950), after the onset in early childhood, the symptoms progress to reach a peak during adolescence. In some patients, the physical and mental condition visibly deteriorates to the extent of severe wasting and progressive loss of mental function. It seems likely that Nakalanga syndrome results in increased mortality, and this is supported by the observation that few, if any, Nakalanga patients older than 30 years were reported in the various studies (Table 8). In the cohort of 12 patients in western Uganda, who in addition to Nakalanga (Ekihuruka) syndrome were also suffering from epilepsy, a high mortality was found (Kaiser et al. 2007). No comparable data have been assessed from Nakalanga patients without associated epilepsy. Contrasting with the observation of an obviously severe course of the disease in many patients, it has also been stated that some Nakalanga patients „may reach an advanced age“ (Raper and Ladkin 1950) or „appear to live a normal life“ (Jelliffe et al. 1962).

6.4 Comparison between Nakalanga syndrome and Nodding syndrome

The age of NS patients at examination in cross-sectional studies, as well as the reported age at onset of the disorder, coincided well with that of patients affected by Nakalanga syndrome. Growth retardation and wasting as the most prominent features of Nakalanga syndrome were reported in the majority of

published studies on NS, although exact measurements were only provided in two studies (Piloya-Were et al. 2014; Kaiser et al. 2015). All studies on the clinical characteristics of NS also found mental impairment of varying degrees in a part of their patients, and all found patients with other epileptic seizures in addition to head nodding seizures. Disturbance of pubertal development, spine deformity, or facial dysmorphia were documented only exceptionally in patients with NS, but these features were not systematically investigated in all studies. The findings of Table 10 document the intriguing overlap between Nakalanga syndrome and NS, but hitherto available data are fragmentary and, in part, were established with poorly defined methods.

A recent study from northern Uganda (Piloya-Were et al. 2014) determined various endocrinological parameters in a series of eight patients with NS with different degrees of stunted growth and delayed puberty. Normal values were found for morning cortisol, TSH, and T4 in all patients. IGF-1 levels were generally low but within the normal range in five of eight patients, and serum GH - determined without stimulation - was normal. Gonadotropin levels were within the range of the clinically delayed stages of puberty. These results are consistent with those from patients with Nakalanga syndrome examined in southeastern Uganda (Leonard and Stanfield 1965), western Uganda (Höfer 1999), and Burundi (Newell et al. 1997). As the authors state, pituitary stimulation tests are needed to better differentiate the role of hypothalamic and pituitary factors in inducing growth failure and hypogonadism in NS patients (Piloya-Were et al. 2014).

Table 10: Clinical features of Nakalanga syndrome according to the proposed definition found in patients with Nodding syndrome.

Publication [Reference]	Age[i]	Clinical Features						
	At onset of NS / at examination	Stunting	Wasting	Delayed Puberty	Mental Retardation	Facial Dysmorphia	Kyphosis Scoliosis	Epileptic seizures other than head nodding
South Sudan								
Lacey (Lacey 2003)[ii]	n. r.[iii] / 18	+[iv,v]	+[iv,v]	n. r.[iii]	+[iv]	n. r.[iii]	n. r.[iii]	+[iv]
Nyungera et al. (Nyungura 2011)	n. r.[iii] / 15	+[iv,v]	+[iv,v]	n. r.[iii]	+[iv]	n. r.[iii]	n. r.[iii]	+[iv]
Tumwine et al.(Tumwine et al. 2012)	12 / 12	+[iv,v]	+[iv,v]	+[4]	+[iv]	n. r.[iii]	n. r.[iii]	+[iv]
De Polo et al. (Polo et al. 2015)	9 / 12	n. r.[iii]	n. r.[iii]	n. r.	all, different degree	n. r.[iii]	n. r.[iii]	all
Northern Uganda								
Idro et al. (Idro et al. 2013b)	6 / 14	9/22 cases[v]	16/22 cases[v]	n. r.[iii]	10/22 severely impaired	5/22 unspecified lip changes	1/22 kyphosis	18/22 cases
Sejvar et al. (Sejvar et al. 2013)	8 / 12	n. r.[iii]	n. r.[iii]	n. r.[iii]	test score of cases lower than controls[vi]	n. r.[iii]	n. r.[iii]	6/23 cases
Kitara et al.(Kitara et al. 2013)	11 / 13	n. r.[iii]	+[v]	n. r.[iii]	school faillure	n. r.[iii]	n. r.[iii]	+[iv]
Piloya-Were et al. (Piloya-Were et al. 2014)	7 / 15	-2.41[vii] (-0.10 - -4.04)	n. r.[iii]	obvious delay[viii]	n. r.[iii]	n. r.[iii]	n. r.[iii]	5/8 cases
Southern Tanzania								
Winkler et al. (Winkler et al. 2010)	n.r.[iii] / 14	n. r.[iii]	n. r.[iii]	n. r.[iii]	12/62 impaired	n. r.[iii]	n. r.[iii]	34/62 cases
Spencer et al. (Spencer et al. 2013a)	10 / 13	11/33 with small stature	18/33 poorly nourished	n. r.[iii]	8/33 impaired	n. r.[iii]	n. r.[iii]	29/33 cases
Western Uganda								
Kaiser et al. (Kaiser et al. 2015)[ii]	7 / 15	z-score[ix] -7.3	n. r.[iii]	infantile at age of 15 years	severely impaired	n. r.[iii]	not present	present

[i] median age in years
[ii] case report
[iii] n. r. = not reported

[iv] + = feature reported without more specific information
[v] no anthropometrical data reported
[vi] clinical neurological assessment in 23 cases; Neurocognitive evaluation in 65 pairs of children and controls
[vii] median (range) of z-score for height-for-age (stunting) referring to 2000 CDC growth standard (Kuczmarski et al. 2002). Available: http://www.cdc.gov/growthcharts/cdc_charts.htm
[viii] Tanner maturity stage (TS) for breast or testis development in 8 patients aged 13 to 18 years: TS1 in two patients (infantile), TS2 in five, TS3 in one
[ix] z-score for height-for-age (stunting) referring to 1977 NCHS growth standard (National Center for Health Statistics 1977). Available: http://www.cdc.gov/nchs/data/series/sr_11/sr11_165.pdf

(Adapted from Föger et al. 2017)

Our working definition of the Nakalanga syndrome shows an intriguing similarity to that of NS (WHO 2012): both conditions have their onset from an early age, are frequently combined with mental retardation, and there is a striking overlap in the symptom of growth failure as the predominant feature in Nakalanga patients. The patient with NS reported by Kaiser et al. (Kaiser et al. 2015) was also found severely stunted and considered by the community to suffer from Nakalanga syndrome, locally known as „Ekihuruka“ (Höfer 1999; Kipp et al. 1996). This case report illustrates that Nakalanga syndrome and NS occur concomitantly in this area in western Uganda (Kipp et al. 1996; Höfer 1999; Ovuga et al. 1992; Kaiser et al. 2007; Kaiser et al. 2015). Possibly, some of the patients with Nakalanga syndrome reported 40 years earlier from southeastern Uganda were also affected by head nodding attacks. This is indicated by the description of Raper and Ladkin (Raper and Ladkin 1950) that „inability to hold up the head is taken as a sign of a severe affection“ and „certain cases would let the head fall forwards while eating and be quite incapable of raising it again.“
Another shared trait between NS and Nakalanga syndrome is the association with onchocerciasis, although this does not necessarily imply causality. All study areas where cases of either condition were reported were also highly endemic for onchocerciasis, and, when this was investigated, infection with *O. volvulus* was consistently more frequent in patients than in controls (Kipp et al. 1996; Höfer 1999; Tumwine et al. 2012; Spencer et al. 2013b; Foltz et al. 2013; Reik et al. 2012). The isolated observation of a disorder reminiscent of Nakalanga syndrome from an onchocerciasis endemic area in Mexico could also be seen as corroboration of this association (Casis-Sacre 1938). A close relationship between onchocerciasis and convulsive epilepsy has also been found in areas with and without confirmed NS (Kaiser et al. 2013; Pion et al. 2009), and there is indication that in these areas intensity of infection is involved in the induction of epilepsy (Boussinesq et al. 2002; Kaiser et al. 2013; Pion and Boussinesq 2012). So far, the issue of *O. volvulus* infection intensity has not been specifically examined in studies on NS or Nakalanga syndrome, but Raper and Ladkin pointed out their impression that Nakalanga patients „were more early and more heavily parasitised than their fellows“ (Raper and Ladkin 1950).
As a limitation to the assumption of a possible causative relationship between Nakalanga syndrome/NS and onchocerciasis, it is highly interesting that in many *O. volvulus* endemic areas, a single case of one of these two disorders was never reported. It has also not been clarified whether infection with *O. volvulus* actually precedes the onset of head nodding or growth retardation, because the relationship between onchocerciasis was so far investigated solely with cross-sectional studies. It may well be that NS and/or Nakalanga syndrome are due to an alternative pathogenic agent, potentially transferred by the same vector as *O. volvulus*. Affected children could be particularly susceptible to infection with onchocerciasis, which would then be a natural consequence rather than the cause of these disorders. As far as possible pathological mechanisms were investigated, the presence of the parasite, or evidence on an inflammatory or immune reaction to the parasite in the central nervous system, could not be verified neither in patients with NS (Winkler et al. 2008; Tumwine et al. 2012; Sejvar et al. 2013; Idro et al. 2013b; König et al. 2010; Idro et al. 2016) nor in the mentioned autopsy case affected by Nakalanga syndrome (Marshall and Cherry 1961).

6.5 Conclusions and recommendations

Many aspects of Nakalanga syndrome and NS and their possible interrelation remain unsolved. One important question that needs to be addressed is the determination of the hitherto unknown frequency and the extent of growth failure in patients with NS in those areas where it was first confirmed - South Sudan, northern Uganda, and Tanzania. It is also unclear why in these areas no patients presenting with growth failure, delayed puberty, and mental retardation but without head nodding were reported, as this was demonstrated in southeastern as well as in western Uganda. We suggest that the characteristic features of Nakalanga syndrome should be more systematically investigated in patients with NS. It would also be of interest to find out whether the communities affected by NS also know about an illness in their area which is primarily characterized by growth failure and which might correspond to Nakalanga syndrome. We consider it of importance that studies on this issue uniformly refer to the generally consented 2012 Kampala case definition of NS (Spencer et al. 2017; WHO 2012) and that the effective ILAE guidelines for epidemiologic studies are followed (Thurman et al. 2011).

Although sophisticated diagnostic tools such as video monitoring including electroencephalography (EEG) or brain imaging are not readily available in the setting of rural sub-Saharan Africa, seizures could be documented with mobile phone video and mobile EEG machines. These tools would be useful to confirm the diagnosis of NS in suspected cases. We want to encourage more neurological researchers to seek the collaboration of interested local colleagues to establish a dataset for neurophysiological records that could be reevaluated remotely by African and non-African experts alike.

Our proposed definition of the Nakalanga syndrome deliberately does not formulate specific criteria for confirmation of the disorder in the individual patient. We hope that our proposal will further develop on the basis of future research, and the contributions of others will help to improve its practicality. At present, we consider it of importance that the major features configuring Nakalanga syndrome - stunting, wasting, delayed sexual development, and mental impairment - should be assessed with clearly defined methodological approaches. Anthropometric measurements of height and weight should be carried out in patients, and in local controls, and should be related to the current standards of WHO (WHO; Onis et al. 2007; Onis et al. 2012). These were developed with recent multicenter surveys and are recommended to replace earlier reference databases (Kuczmarski et al. 2002; National Center for Health Statistics 1977). Definite clinical methods for the assessment of pubertal stages were developed with the basic studies of Marshall and Tanner (Marshall and Tanner 1969, 1970), and these have been successfully applied in northern Uganda (Piloya-Were et al. 2014; Odongkara Mpora et al. 2014). Because of the great diversity of regulating influences on the development of puberty (Abreu and Kaiser 2016; Juul et al. 2006; Frisch and McArthur 1974; Perry et al. 2014; Lomniczi et al. 2015), universal standards on the age at onset and the chronological sequence of pubertal stages are not available. It would therefore be crucial to always include carefully matched local controls in study protocols. The development and validation of more diagnostic tools on mental function would help to generate comparable results in different studies.

Taken together, we find evidence that Nakalanga syndrome and NS are closely related and may even be two manifestations of one underlying, yet unclear, pathology. According to the metaphoric hypothesis formulated by Wamala et al. (Wamala et al. 2015) that „Nodding syndrome may be only the ears of the hippo“, Nakalanga syndrome may emerge to be one of these ears, i.e., the other end of a disease continuum. However, we want to caution against adoption of the premature conclusion that onchocerciasis is confirmed as the cause of Nodding – or Nakalanga - syndrome (Colebunders et al. 2016b). A multidisciplinary approach of researchers from various fields will be needed to find answers to the many unsolved questions connected with this (these) mysterious brain disorder(s).” (Föger et al. 2017).

7. Summary

- Nakalanga syndrome and NS are neurological/developmental disorders of unknown cause affecting children and adolescents in onchocerciasis endemic areas of sub-Saharan Africa.
- NS presents mainly with paroxysmal head nodding, often in combination with cognitive decline, stunted growth, delayed puberty and convulsive seizures (Föger et al. 2017).
- Nakalanga syndrome is characterized by stunted growth, delayed puberty and mental impairment (Föger et al. 2017).
- A subset of children with Nakalanga syndrome present with epileptic seizures, but as opposed to NS, this is not a leading symptom.
- There are many possible causes for NS, which include infectious agents, toxic influences and auto-immune mechanisms.
- Nodding and Nakalanga syndrome seem to be closely linked.

Future research should focus on these aspects and aim to elucidate the pathomechanism of NS in order to develop effective treatment options.

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9. Addendum

PLOS | NEGLECTED TROPICAL DISEASES

REVIEW

Nakalanga Syndrome: Clinical Characteristics, Potential Causes, and Its Relationship with Recently Described Nodding Syndrome

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Citation: Föger K, Gora-Stahlberg G, Sejvar J, Ovuga E, Jilek-Aall L, Schmutzhard E, et al. (2017) Nakalanga Syndrome: Clinical Characteristics, Potential Causes, and Its Relationship with Recently Described Nodding Syndrome. PLoS Negl Trop Dis 11(2): e0005201. doi:10.1371/journal.pntd.0005201

Editor: Uwem Friday Ekpo, Federal University of Agriculture, NIGERIA

Published: February 9, 2017

Funding: The authors received no specific funding for this work.

Competing Interests: The authors have declared that no competing interests exist.

Abstract

Nakalanga syndrome is a condition that was described in Uganda and various other African countries decades ago. Its features include growth retardation, physical deformities, endocrine dysfunction, mental impairment, and epilepsy, amongst others. Its cause remains obscure. Nodding syndrome is a neurological disorder with some features in common with Nakalanga syndrome, which has been described mainly in Uganda, South Sudan, and Tanzania. It has been considered an encephalopathy affecting children who, besides head nodding attacks, can also present with stunted growth, delayed puberty, and mental impairment, amongst other symptoms. Despite active research over the last years on the pathogenesis of Nodding syndrome, to date, no convincing single cause of Nodding syndrome has been reported. In this review, by means of a thorough literature search, we compare features of both disorders. We conclude that Nakalanga and Nodding syndromes are closely related and may represent the same condition. Our findings may provide new directions in research on the cause underlying this neurological disorder.

The Terms of "Nakalanga" and "Nodding Syndrome"

The term Nakalanga is first found in an anthropological account published by John Roscoe [1] in 1911, mentioning it as the name of a god recognized by a clan of the Buganda kingdom living in the area of the Mabira forest located 60 km east of today's Ugandan capital city, Kampala. Up to today, Nakalanga is still the name of a god in the conceptual world of the Baganda [2]. In addition to this meaning, in a 1934 geographical article about the Mabira forest, the word is found used to designate a person characterized by a condition of short stature ("dwarfism"), which was frequently seen in the area [3]. It was suggested that these persons were descendants of a pygmy tribe that in bygone times would have inhabited the Mabira forest [3,4].

During the late 1940s, Raper and Ladkin [5] carried out an extensive investigation in the Mabira forest on patients affected by the Nakalanga phenomenon. They gave a thorough description of the condition and concluded that their patients were affected by a medical disorder, which they called Nakalanga syndrome. Up to 1965, two additional case series were published from the same area [6,7]. Thereafter, no more studies were undertaken, and when the Mabira forest became accessible again in the 1980s, no more cases were found. Instead, patients with a condition conforming with Nakalanga syndrome were observed in other locations, namely western Uganda [8–11], Burundi [12], and Ethiopia [13]. This is complemented by anecdotal observation from other areas of sub-Saharan Africa [14–16], suggesting that the syndrome is probably not confined to Mabira and southeastern Uganda (Fig 1). As early as 1938, from an area in Mexico where a high endemicity of onchocerciasis and an elevated epilepsy prevalence were found, Casis Sacre described patients affected at a young age by a severe disorder characterized by growth failure, mental retardation, generalized weakness, and disturbed pubertal development [17]. Although the similarity of this observation with the above-

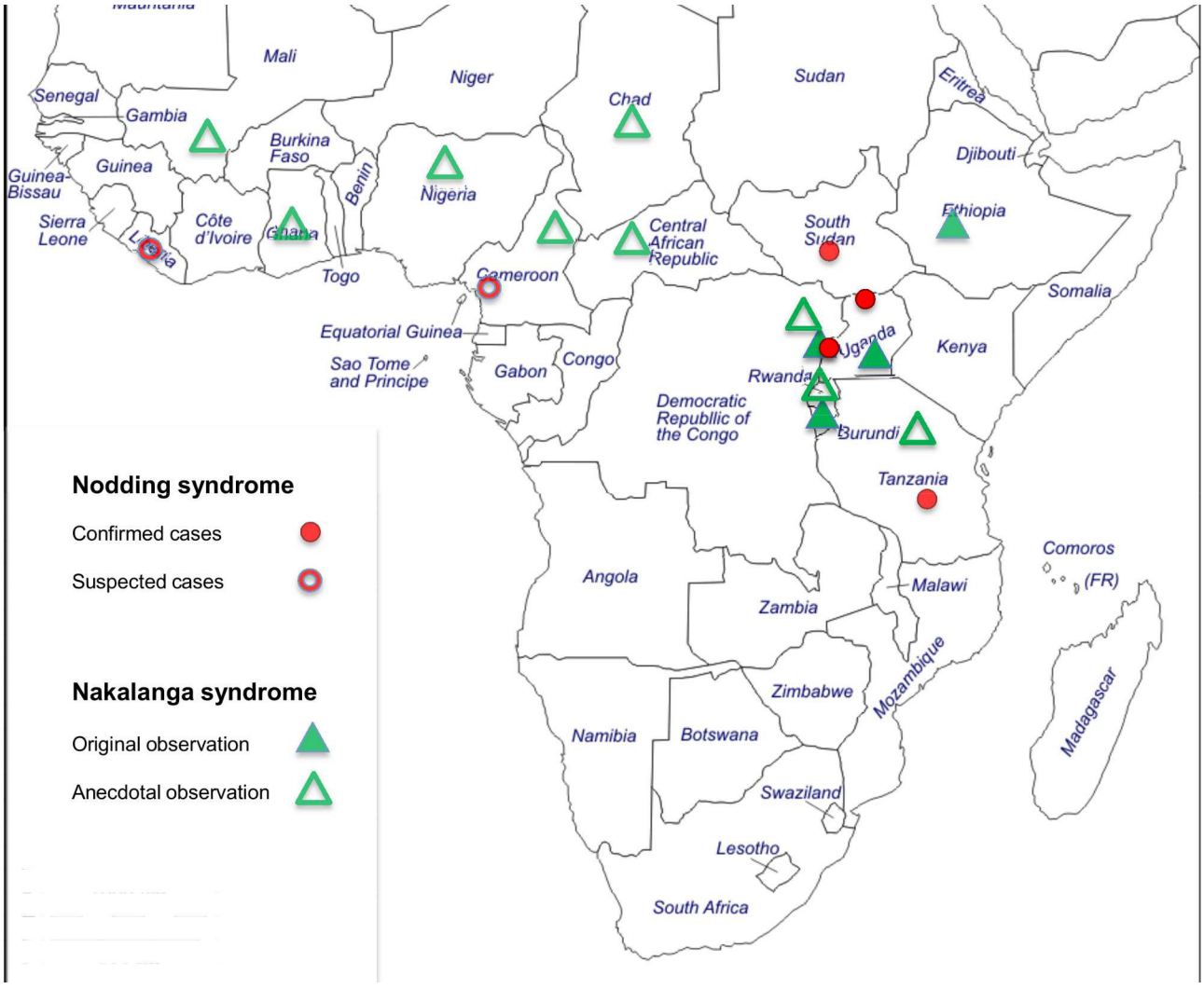

Fig 1. Map of sub-Saharan Africa. Cases of Nakalanga and Nodding syndrome are reported from onchocerciasis endemic areas throughout West, Central, and East Africa.

doi:10.1371/journal.pntd.0005201.g001

mentioned reports was recognized [18], no further investigations from this area are available to more precisely assess its possible connection with Nakalanga syndrome.

Nodding syndrome is an unexplained neurological disorder with the clinical core feature of a paroxysmal spell in which the head repeatedly bobs forward for several minutes or longer [19]. It emerged during the last two decades in then southern Sudan and northern Uganda [20–26] and, in retrospect, was documented in Tanzania since the 1960s [27,28] and in western Uganda in 1994 [29]. Reports from Grand Bassa County, Liberia [30], from the Littoral Province of Cameroon [31], and from the Ituri District in the Orientale Province of the Democratic Republic of the Congo [32] also point towards the possible existence of Nodding syndrome in these areas (Fig 1). A case definition for Nodding syndrome was agreed upon at an international conference in Kampala, Uganda in 2012 [33]. Because patients with Nodding syndrome frequently display signs and symptoms that have also been described in Nakalanga syndrome, it has been questioned if both these conditions represent different manifestations of a common underlying pathology [21,22,34–37].

In this article, we focus on the following aspects:

- Based on a thorough literature search, we summarize the characteristic clinical features of Nakalanga syndrome as they were originally described in different areas, and we propose a working medical definition.
- We summarize available information on the etiology and possible causation of Nakalanga syndrome.
- We examine the question of whether the symptoms and signs found in Nakalanga syndrome are also present in cases of Nodding syndrome.
- We give suggestions as to how the relationship between the two entities could be further studied.

Characterization of Nakalanga Syndrome and a Proposed Definition

We searched several medical databases (Medline, ScienceDirect, African Neurology Database of the Institute of Neuroepidemiology of the University of Limoges) using the search term "nakalanga." Other sources, such as commercial search engines or unpublished congress proceedings, were searched without specific limits, and reference lists of retrieved articles and reviews were screened for further records of relevance (latest search: May 23, 2016). The database search identified 45 records, and 6 additional records were found from other sources. After removal of duplicate entries and assessment of relevance, 12 articles were found to present original clinical data [5–14,38,39]. Three of these were excluded because they contained redundant or insufficient information [11,38,39]. The remaining nine records [5–10,12–14] represent the evidence base for a systematic characterization of Nakalanga syndrome (Table 1). A flow diagram describing the search procedure is available as supporting information (S1 Diagram).

In their pivotal study in the Mabira forest, Raper and Ladkin [5] collected information from various community members about the local concept of the Nakalanga phenomenon. As a second step, in a convenience sample of characteristic patients, a list of signs and symptoms was established, and this was completed by more detailed investigations in seven selected patients, who were taken to a nearby hospital. Similar studies were carried out by Jellife et al. [6] and Bagenda et al. [7] in areas neighboring Mabira forest.

As an overall result of these studies, Nakalanga syndrome was specified as a disorder affecting previously healthy children during the first ten years of their life. Growth retardation was

Table 1. Clinical case series and case reports on Nakalanga syndrome: Southeast Uganda 1950–64, Ethiopia 1967, West Uganda 1991–95, Burundi 1995.

Publication [Reference]	Age	Anthropometry		Clinical Features					Onchocerciasis[ii]
	at onset[i]/ examination	Stunting[i]	Wasting[i]	Pubertal Development	Mental Development	Facial Dysmorphia	Kyphosis Scoliosis	Epileptic Seizures	
Southeast Uganda 1950–64									
Raper and Ladkin [5]	n.r.[iii] (2–4)/ 11.5 (6–18)	-4.54[iv] (-1.52–-6.15)	-6.21[iv] (-3.12–-9.84)	delay; small genitalia; some cases retarded [v]	not severely impaired; appearance younger[v]	small mandible; protuberant skull; large lips[v]	prone to develop scoliosis[v]	Epilepsy in 2/7	Positive in all cases
Marshall and Cherry [14][vi]	n.r.[iii]/ 30	-5.06 [iv]	n.r.[iii]	few pubic hair; normal testes, small penis	mentally dull	prognathic jaw; protruding teeth	n.r.[iii]	no epilepsy	positive
Jeliffe et al. [6]	n.r.[iii]/ 14 (10–19)	-4.80 [iv] (-1.08–-5.58)	-3.53 [iv] (-1.46–-6.54)	reduced sexual activity; poor pubic hair[v]	Mild to moderate apathy; 2/ 5 "mental torpor"	prognatic jaw, forward angulated incisors in 2/ 5	2/5 marked kyphosis	epilepsy in 1/5	Positive in all
Bagenda et al. [7]	n. r. (0–7)/ 20 (13–25)	-4.72 [iv] (-1.98–-8.52)	n. r.[iii]	delay; cases ≥20 y in puberty or postpuberty	7/ 19 normal life; 10 doing simple jobs; 2 looked after	deep-set eyes; teeth protruding; small chin[v]	8/19 kyphoscoliosis	epilepsy in 7/19	Positive in 18/19
Ethiopia 1967									
Oomen [13] [vi]	n.r.[iii]/ 35	-5.74[iv]	cachectic[v]	small genitalia	n.r.[iii]	n.r.[iii]	kyphoscoliosis	epilepsy	positive
West Uganda 1993–94									
Ovuga et al. [8][vii]	n.r.[iii]	growth arrest[viii]	emaciation[v,viii]	poorly developed[v]	31/91 cognitive impairment; some apathetic[v]	distorted dentition[v]	pigeon chest; kyphosis[v]	epilepsy in 24/91	Positive in 82/91
Kipp et al. [9][vii]	7 (1–>8)/ 18 (15–32)	-4.9[ix]	-1.9[ix]	27 of 31 prepubertal, versus 2 of 28 controls	several cases mentally subnormal[v]	n.r.[iii]	deformed spine in 8/31	n. r.[iii]	Positive in all
Höfer [10] [vii]	n.r.[iii] (1–11)/ 15 (7–20)	-4.02 [iv] (-1.36–-6.62)	-2.53[iv] (+0.51–-10.7)	delay, in comparison with local controls	14/36 mentally retarded	6/36 protruding forehead, flat nasal bridge	Kyphoscoliosis in 6/36	Epilepsy in 16/36	Positive in 13/16
Burundi 1995									
Newell et al. [12]	n.r.[iii] / 17 (12–20)	-4.83[iv] (-2.59–-5.19)	-1.11[iv] (+1.18–3.64)	delay in 2/9	n.r.[iii]	n.r.[iii]	n.r.[iii]	all with epilepsy	Positive in all

[i] median (range)

[ii] detection of microfilaria of *Onchocerca volvulus* in skin biopsy, or of antibodies in serology (Newell et al. [12])

[iii] n.r. = not reported

[iv] z-score for height-for-age (stunting) and body mass index (BMI) (waisting), referring to 2006 WHO growth standard [40,41]. http://www.who.int/childgrowth/en/

[v] no quantified information

[vi] case report

[vii] overlap of study populations in studies of Ovuga et al. [8], Kipp et al. [9], and Höfer [10]

[viii] growth arrest as mandatory symptom, defined as <80% of average height of local population; emaciation as characteristic symptom, not specified

[ix] mean z-score of height-for-age and BMI, referring to 1977 NCHS growth reference [62]. http://www.cdc.gov/nchs/data/series/sr_11/sr11_165.pdf; Range not reported

doi:10.1371/journal.pntd.0005201.t001

described as the most prominent feature. When available, we applied height data from the original publications [5–7,14] to the currently used WHO growth standards [40–42] and found strikingly similar median z-scores between -4.54 and -4.80 in the case series from these three closely neighboring areas [5–7], indicating an overall severe degree of stunting (Table 1). Generally, a height-for-age z-score of more than 2.0 standard deviations below the growth standard median is considered to indicate stunted growth [40]. Yet, in each of the three studies [5–7], one patient with a height measurement corresponding to a z-score above the -2.0 standard deviation threshold was found (z-scores: -1.08, -1.52, and -1.98; Table 1), indicating a normal stature even when related to the current WHO standard. This is evidence that stunted growth, although reported as a frequent symptom, was not a mandatory criterion in the concept of the local communities to classify a person as a Nakalanga patient. The height of 53 local control children was measured by Raper and Ladkin [5] and, expectedly, was found at z-scores below the current WHO standard (median: -2.14; range: +1.4 to -5.3). Twelve of these 53 children had height-for-age z-scores below -3.0, but their overall height was still taller than that of Nakalanga patients. Emaciation, delayed sexual development, and mental impairment were described as additional characteristic symptoms of Nakalanga syndrome, although these were not invariably found in all cases. Some patients also showed facial dysmorphia, deformation of the vertebral spine, or epileptic seizures (Table 1).

In 1992, Ovuga et al. [8] for the first time described the unusually frequent occurrence of a condition similar to Nakalanga syndrome in the Itwara onchocerciasis focus, situated in the Kabarole district, western Uganda (Table 1). The Itwara forest has no contiguity to Mabira forest in southeastern Uganda, where Raper and Ladkin had made their primary investigations 40 years earlier [5]. The study of Kipp et al. [9] demonstrated that "Ekihuruka," as the disorder was named by the population in the local Rutoro language, was consistent in its clinical picture with Nakalanga syndrome (Table 1). In 1999, a detailed analysis of 36 patients with Nakalanga (Ekihuruka) syndrome examined in the mentioned area of the Kabarole district was reported [10]. A subgroup of 12 of these patients, who in addition were suffering from epilepsy, were also followed in the study of Kaiser et al. [11,43]. In accordance with the earlier reports from southeastern Uganda, the study of Höfer [10] demonstrated that patients affected by Nakalanga (Ekihuruka) syndrome were not solely characterized by growth retardation or another single sign or symptom alone but rather by the combination of several distinct signs and symptoms. Consistent with the anthropometric results from southeastern Uganda [5], the height measured in a control group of healthy children in western Uganda overlapped with the upper range of Nakalanga (Ekihuruka) patients [10], although the height-for-age z-score of the control group (median: -1.09; range: +0.96 to -2.8) was by far higher than that of the patient group (median: -4.02; range: -1.36 to -6.62; Table 1).

In 1997, Newell et al. [12] in a study from an onchocerciasis endemic area in Burundi reported cases with retarded growth, mental impairment, and delayed sexual development among a group of patients identified in an epilepsy survey (Table 1), and they pointed out the similarity of this observation with Nakalanga syndrome. In a study on clinical features of onchocerciasis in Ethiopia, Oomen described an individual patient showing a striking similarity with Nakalanga syndrome as found in southeastern Uganda [13].

The consistent syndromic pattern found in the mentioned noncontingent areas indicates that the reported patients may be affected by the same neurological disorder. Based on these findings, we propose that Nakalanga syndrome can be defined as a disorder affecting young children and youths who were born healthy and have passed through an initial phase of healthy development (Table 2). Patients present with at least one of the following predominant symptoms: retardation of growth (stunting), emaciation (wasting), delayed sexual development, or mental impairment. Less frequently, facial dysmorphia with small mandible, large

Table 2. Proposed criteria for definition of Nakalanga syndrome compared to criteria for definition of a probable case of Nodding syndrome consented in Kampala 2012 (adapted from ref. [26,33]).

Proposed criteria for Nakalanga syndrome	Consented criteria for Nodding syndrome
Major criteria (obligatory)	**Major criteria**
1. Born healthy	1. Reported head nodding in a previously healthy person
2. Onset in childhood	2. Age 3–18 y at onset of head nodding
3. No alternative explanatory condition	3. Nodding frequency 5–20 times/min
4. Plus, one or several symptoms of developmental disturbance:	
a) Stunting, growth failure	
b) Wasting, emaciation	
c) Retardation of sexual development	
d) Mental impairment	
Minor criteria (additional)	**Minor criteria**
5. Facial dysmorphia: small and protuberant mandible, large lips, protruding front teeth	4. Other neurological abnormalities (cognitive, school dropout, other seizures, or neurological abnormalities)
6. Kyphoscoliosis	5. Clustering in space or time with similar cases
7. Epileptic seizures	6. Delayed sexual or physical development
8. Occurrence of similar cases in the surroundings	7. Psychiatric manifestations

doi:10.1371/journal.pntd.0005201.t002

lips, protruding front teeth, kyphoscoliosis, or epileptic seizures are encountered along with the mentioned major signs and symptoms. In the environment of a patient with Nakalanga syndrome, an accumulation of other cases with similar features is found.

Information on Etiology and Possible Causes of Nakalanga Syndrome

In view of the clinical picture and the epidemiologic distribution, Raper and Ladkin [5] excluded the hypothesis that people with Nakalanga syndrome could belong to a pygmy tribe. The combination of their clinical observations with the finding of a low urinary excretion of the 17-ketosteroids led them to assume that Nakalanga syndrome should be induced by defects in pituitary and adrenal gland function. In 1961, Marshall and Cherry [14] reported on an autopsy case which revealed no major changes of the histological appearance of the adrenal gland compatible with major adrenal dysfunction. In the histology of the pituitary gland of this case, they described some alterations in the composition of acidophil, basophil, and chromophobe cells, but the vascular supply was not disturbed, and there was no major lesion found that could have been produced by invasion of a pathogenic agent, e. g., *Onchocerca volvulus* microfilaria. It was concluded that "the primary affection may have been either in the pituitary portal system or the hypothalamus," and the authors speculated that the "humoral transmission through the pituitary portal system was possibly jeopardized by circulating products of dead microfilaria" [14]. In a series of ten Nakalanga patients, Leonard and Stanfield [39] found normal levels of morning plasma cortisol and a normal protein binding fraction of cortisol. They also reported normal results of fasting serum growth hormone (GH) in two patients and a normal rise of GH in a third case following stimulation with injected insulin [39]. In the studies from Burundi [12] and from western Uganda [10], thyroid-stimulating hormone (TSH) as well as total thyroxine (T4) and triiodothyronine (T3) levels were measured and normal values were found in 31 of 32 cases. Höfer [10] also investigated the serum concentration of insulin-like growth factor I (IGF-I) and IGF-binding-protein-3 (IGF-BP-3) in a group of 23 severely stunted Nakalanga patients and found slightly lower concentrations in patients than

controls, but IGF-I levels were not compatible with GH deficiency in 16 cases. When the remaining seven patients were assessed case-by-case with GH determination after physical strain and a follow-up of their growth rate over one year, GH deficiency was excluded in three more patients. In agreement with the findings of Leonard and Stanfield [39], and contrasting with the earlier assumptions of Raper and Ladkin [5], the results of Höfer [10] disprove the hypothesis that a primary pituitary lesion plays a causative role in the pathophysiology of Nakalanga syndrome.

When Nakalanga syndrome was first recognized in the 1950s as a regional medical entity [5–7], a search on the cause of the condition was undertaken with the resources available at the time. On the ground of their clinical, laboratory, and epidemiological findings, the authors of the three studies from Southeast Uganda widely excluded a number of chronic disorders that elsewhere in Uganda or tropical Africa had been found related with growth failure [5–7]. Explicitly, they found no connection with malaria, malnutrition, tuberculosis, rickets, syphilis, blood dyscrasias, intestinal parasites, and chronic diseases of the liver or other organs, but viral etiologies or auto-immune disorders were not mentioned. In view of the sporadic distribution of patients in different ethnic groups and families, a genetic disorder was considered unlikely, although this was not fully excluded [6]. Consistent with the findings from southeastern Uganda, no known disorder could be identified which possibly caused growth failure in Nakalanga (Ekihuruka) patients in western Uganda [9,10]. As a consistent observation, all study areas were found highly infested with onchocerciasis (Table 1).

Little is known about the natural history and the prognosis of Nakalanga syndrome. According to Raper and Ladkin [5], after the onset in early childhood, the symptoms progress to reach a peak during adolescence. In some patients, the physical and mental condition visibly deteriorates to the extent of severe wasting and progressive loss of mental function. It seems likely that Nakalanga syndrome results in increased mortality, and this is supported by the observation that few, if any, Nakalanga patients older than 30 years were reported in the various studies (Table 1). In the cohort of 12 patients in western Uganda, who in addition to Nakalanga (Ekihuruka) syndrome were also suffering from epilepsy, a high mortality was found [11]. No comparable data have been assessed from Nakalanga patients without associated epilepsy. Contrasting with the observation of an obviously severe course of the disease in many patients, it has also been stated that some Nakalanga patients "may reach an advanced age" [5] or "appear to live a normal life" [6].

Comparison between Nakalanga Syndrome and Nodding Syndrome

A second literature search for records presenting original clinical information on patients with Nodding syndrome retrieved 20 publications [19–25,28,29,44–54]. Nine of these were excluded from the analysis [19,22,24,25,46–48,51,52] because they presented incomplete data or redundant information, which was found in more detail in another article. The remaining 11 articles were systematically screened for symptoms and signs, which beforehand had been identified as characteristic for Nakalanga syndrome (Table 3). Details of the search procedure and a flow diagram is available as supporting information (S2 Diagram).

The age of Nodding syndrome patients at examination in cross-sectional studies, as well as the reported age at onset of the disorder, coincided well with that of patients affected by Nakalanga syndrome. Growth retardation and wasting as the most prominent features of Nakalanga syndrome were reported in the majority of published studies on Nodding syndrome, although exact measurements were only provided in two studies [29,50]. All studies on the clinical characteristics of Nodding syndrome also found mental impairment of varying degrees in a part of their patients, and all found patients with other epileptic seizures in addition to head nodding

seizures. Disturbance of pubertal development, spine deformity, or facial dysmorphia were documented only exceptionally in patients with Nodding syndrome, but these features were not systematically investigated in all studies. The findings of Table 3 document the intriguing overlap between Nakalanga and Nodding syndromes, but hitherto available data are fragmentary and, in part, were established with poorly defined methods.

A recent study from northern Uganda [50] determined various endocrinological parameters in a series of eight patients with Nodding syndrome with different degrees of stunted

Table 3. Clinical features of Nakalanga syndrome according to the proposed definition found in patients with Nodding syndrome.

Publication [Reference]	Age[i]	Clinical Features						
	At onset of NS / at examination	Stunting	Wasting	Delayed Puberty	Mental Retardation	Facial Dysmorphia	Kyphosis Scoliosis	Epileptic seizures other than head nodding
South Sudan								
Lacey [20] [ii]	n. r.[iii] / 18	+[iv,v]	+[iv,v]	n. r. [iii]	+[iv]	n. r. [iii]	n. r. [iii]	+[iv]
Nyungera et al. [45]	n. r.[iii] / 15	+[iv,v]	+[iv,v]	n. r. [iii]	+[iv]	n. r. [iii]	n. r. [iii]	+[iv]
Tumwine et al. [21]	12 / 12	+[iv,v]	+[iv,v]	+[4]	+[iv]	n. r. [iii]	n. r. [iii]	+[iv]
De Polo et al. [53]	9 / 12	n. r. [iii]	n. r. [iii]	n. r.	all, different degree	n. r. [iii]	n. r. [iii]	all
Northern Uganda								
Idro et al. [24]	6 / 14	9/22 cases[v]	16/22 cases[v]	n. r. [iii]	10/22 severely impaired	5/22 unspecified lip changes	1/22 kyphosis	18/22 cases
Sejvar et al. [23]	8 / 12	n. r. [iii]	n. r. [iii]	n. r. [iii]	test score of cases lower than controls[vi]	n. r. [iii]	n. r. [iii]	6/23 cases
Kitara et al.[49]	11 / 13	n. r. [iii]	+[v]	n. r. [iii]	school failure	n. r. [iii]	n. r. [iii]	+[iv]
Piloya-Were et al. [50]	7 / 15	-2.41[vii] (-0.10–-4.04)	n. r. [iii]	obvious delay[viii]	n. r. [iii]	n. r. [iii]	n. r. [iii]	5/8 cases
Southern Tanzania								
Winkler et al. [44]	n.r. [iii] / 14	n. r. [iii]	n. r. [iii]	n. r. [iii]	12/62 impaired	n. r. [iii]	n. r. [iii]	34/62 cases
Spencer et al. [28]	10 / 13	11/33 with small stature	18/33 poorly nourished	n. r. [iii]	8/33 impaired	n. r. [iii]	n. r. [iii]	29/33 cases
Western Uganda								
Kaiser et al. [29][ii]	7 / 15	z-score[ix] -7.3	n. r. [iii]	infantile at age of 15 years	severely impaired	n. r. [iii]	not present	present

[i] median age in years

[ii] case report

[iii] n. r. = not reported

[iv] + = feature reported without more specific information

[v] no anthropometrical data reported

[vi] clinical neurological assessment in 23 cases; Neurocognitive evaluation in 65 pairs of children and controls

[vii] median (range) of z-score for height-for-age (stunting) referring to 2000 CDC growth standard [61]. http://www.cdc.gov/growthcharts/cdc_charts.htm

[viii] Tanner maturity stage (TS) for breast or testis development in eight patients aged 13 to 18 years: TS1 in two patients (infantile), TS2 in five, TS3 in one

[ix] z-score for height-for-age (stunting) referring to 1977 NCHS growth standard [62]. http://www.cdc.gov/nchs/data/series/sr_11/sr11_165.pdf

doi:10.1371/journal.pntd.0005201.t003

growth and delayed puberty. Normal values were found for morning cortisol, TSH, and T4 in all patients. IGF-1 levels were generally low but within the normal range in five of eight patients, and serum GH—determined without stimulation—was normal. Gonadotropin levels were within the range of the clinically delayed stages of puberty. These results are consistent with those from patients with Nakalanga syndrome examined in southeastern Uganda [39], western Uganda [10], and Burundi [12]. As the authors state, pituitary stimulation tests are needed to better differentiate the role of hypothalamic and pituitary factors in inducing growth failure and hypogonadism in Nodding syndrome patients [50].

Our working definition of the Nakalanga syndrome shows an intriguing similarity to that of Nodding syndrome [33]: both conditions have their onset from an early age, are frequently combined with mental retardation, and there is a striking overlap in the symptom of growth failure as the predominant feature in Nakalanga patients. The patient with Nodding syndrome reported by Kaiser et al. [29] was also found severely stunted and considered by the community to suffer from Nakalanga syndrome, locally known as "Ekihuruka" [9,10]. This case report illustrates that Nakalanga and Nodding syndromes occur concomitantly in this area in western Uganda [8–11,29]. Possibly, some of the patients with Nakalanga syndrome reported 40 years earlier from southeastern Uganda were also affected by head nodding attacks. This is indicated by the description of Raper and Ladkin [5] that "inability to hold up the head is taken as a sign of a severe affection" and "certain cases would let the head fall forwards while eating and be quite incapable of raising it again."

Another shared trait between Nodding and Nakalanga syndrome is the association with onchocerciasis, although this does not necessarily imply causality. All study areas where cases of either condition were reported were also highly endemic for onchocerciasis, and, when this was investigated, infection with *O. volvulus* was consistently more frequent in patients than in controls [9,10,21,22,25,46]. The isolated observation of a disorder reminiscent of Nakalanga syndrome from an onchocerciasis endemic area in Mexico could also be seen as corroboration of this association [17]. A close relationship between onchocerciasis and convulsive epilepsy has also been found in areas with and without confirmed Nodding syndrome [34,55], and there is indication that in these areas intensity of infection is involved in the induction of epilepsy [16,34,56]. So far, the issue of *O. volvulus* infection intensity has not been specifically examined in studies on Nodding or Nakalanga syndrome, but Raper and Ladkin pointed out their impression that Nakalanga patients "were more early and more heavily parasitised than their fellows" [5].

As a limitation to the assumption of a possible causative relationship between Nakalanga syndrome/Nodding syndrome and onchocerciasis, it is highly interesting that in many *O. volvulus* endemic areas, a single case of one of these two disorders was never reported. It has also not been clarified whether infection with *O. volvulus* actually precedes the onset of head nodding or growth retardation, because the relationship between onchocerciasis was so far investigated solely with cross-sectional studies. It may well be that Nodding and/or Nakalanga syndrome are due to an alternative pathogenic agent, potentially transferred by the same vector as *O. volvulus*. Affected children could be particularly susceptible to infection with onchocerciasis, which would then be a natural consequence rather than the cause of these disorders. As far as possible pathological mechanisms were investigated, the presence of the parasite, or evidence on an inflammatory or immune reaction to the parasite in the central nervous system, could not be verified neither in patients with Nodding syndrome [19,21,23,24,57,58] nor in the mentioned autopsy case affected by Nakalanga syndrome [14].

Conclusions and Recommendations

Many aspects of Nakalanga and Nodding syndromes and their possible interrelation remain unsolved. One important question that needs to be addressed is the determination of the hitherto unknown frequency and the extent of growth failure in patients with Nodding syndrome in those areas where it was first confirmed—South Sudan, northern Uganda, and Tanzania. It is also unclear why in these areas no patients presenting with growth failure, delayed puberty, and mental retardation but without head nodding were reported, as this was demonstrated in southeastern as well as in western Uganda. We suggest that the characteristic features of Nakalanga syndrome should be more systematically investigated in patients with Nodding syndrome. It would also be of interest to find out whether the communities affected by Nodding syndrome also know about an illness in their area which is primarily characterized by growth failure and which might correspond to Nakalanga syndrome. We consider it of importance that studies on this issue uniformly refer to the generally consented 2012 Kampala case definition of Nodding syndrome [33,59] and that the effective ILAE guidelines for epidemiologic studies are followed [60]. Although sophisticated diagnostic tools such as video monitoring including electroencephalography (EEG) or brain imaging are not readily available in the setting of rural sub-Saharan Africa, seizures could be documented with mobile phone video and mobile EEG machines. These tools would be useful to confirm the diagnosis of Nodding syndrome in suspected cases. We want to encourage more neurological researchers to seek the collaboration of interested local colleagues to establish a dataset for neurophysiological records that could be reevaluated remotely by African and non-African experts alike.

Our proposed definition of the Nakalanga syndrome deliberately does not formulate specific criteria for confirmation of the disorder in the individual patient. We hope that our proposal will further develop on the basis of future research, and the contributions of others will help to improve its practicality. At present, we consider it of importance that the major features configuring Nakalanga syndrome—stunting, wasting, delayed sexual development, and mental impairment—should be assessed with clearly defined methodological approaches. Anthropometric measurements of height and weight should be carried out in patients, and in local controls, and should be related to the current standards of WHO [40–42]. These were developed with recent multicenter surveys and are recommended to replace earlier reference databases [61,62]. Definite clinical methods for the assessment of pubertal stages were developed with the basic studies of Marshall and Tanner [63,64], and these have been successfully applied in northern Uganda [50,65]. Because of the great diversity of regulating influences on the development of puberty [66–70], universal standards on the age at onset and the chronological sequence of pubertal stages are not available. It would therefore be crucial to always include carefully matched local controls in study protocols. The development and validation of more diagnostic tools on mental function would help to generate comparable results in different studies.

Taken together, we find evidence that Nakalanga syndrome and Nodding syndrome are closely related and may even be two manifestations of one underlying, yet unclear, pathology. According to the metaphoric hypothesis formulated by Wamala et al. [71] that "Nodding syndrome may be only the ears of the hippo," Nakalanga syndrome may emerge to be one of these ears, i.e., the other end of a disease continuum. However, we want to caution against adoption of the premature conclusion that onchocerciasis is confirmed as the cause of Nodding—or Nakalanga—syndrome [72]. A multidisciplinary approach of researchers from various fields will be needed to find answers to the many unsolved questions connected with this (these) mysterious brain disorder(s).

Key Learning Points

- Nakalanga and Nodding syndromes both are developmental disorders of unknown cause affecting children and adolescents in onchocerciasis endemic areas of sub-Saharan Africa.
- Predominant features of Nakalanga syndrome are stunted growth, delayed pubertal development, and mental impairment—and epileptic seizures in a proportion of cases.
- Nodding syndrome is characterized by paroxysmal head nodding, frequently accompanied by mental decline—and stunted growth, delayed puberty, and convulsive seizures in a proportion of cases.
- Our review provides evidence that both syndromes are closely related and may represent manifestations of one underlying disease.
- We propose the use of clearly described multidisciplinary methods to clarify the relationship between these enigmatic disorders and their underlying pathology.

Top Five Papers

1. Raper AB, Ladkin RG. Endemic dwarfism in Uganda. East Afr Med J. 1950;27: 339–359.
2. Kipp W, Burnham G, Bamuhiiga J, Leichsenring M. The Nakalanga syndrome in Kabarole District, Western Uganda. Am J Trop Med Hyg 1996;54: 80–83.
3. Winkler AS, Friedrich K, König R, Meindl M, Helbok R, Unterberger I, et al. The head nodding syndrome—clinical classification and possible causes. Epilepsia. 2008;49: 2008–2015.
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Supporting Information

S1 Diagram.
(PDF)

S2 Diagram.
(PDF)

Acknowledgments

We are grateful to Mrs. Mary Holmes, Drs. Christian and Felix Benninger (Heidelberg, Germany), and Prof. emeritus Walter Kipp (Edmonton, Canada) for review of the manuscript.

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