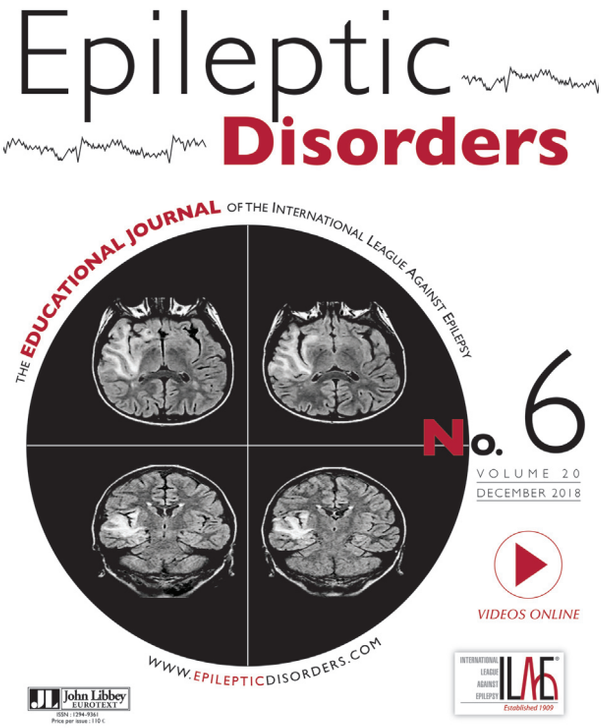

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The natural history of nodding syndrome

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ABSTRACT – *Aims.* Nodding syndrome is a poorly understood acquired disorder affecting children in sub-Saharan Africa. The aetiology and pathogenesis are unknown, and no specific treatment is available. Affected children have a distinctive feature (repeated clusters of head nodding) and progressively develop many other features. In an earlier pilot study, we proposed a five-level clinical staging system. The present study aimed to describe the early features and natural history of nodding syndrome and refine the proposed clinical stages.

Methods. This was a retrospective study of the progressive development of symptoms and complications of nodding syndrome. Participants were a cohort of patients who had been identified by community health workers and were referred for treatment. A detailed history was obtained to document the chronological development of symptoms before and after onset of head nodding and a physical examination and disability assessment performed by a team of clinicians and therapists.

Results. A total of 210 children were recruited. The mean age at the onset of head nodding was 7.5 (SD: 3.0) years. Five overlapping clinical stages were recognised: prodromal, head nodding, convulsive seizures, multiple impairments, and severe disability stages. Clinical features before the onset of head nodding (prodromal features) included periods of staring blankly or being inattentive, complaints of dizziness, excessive sleepiness, lethargy, and general body weakness, all occurring two weeks to 24 months before nodding developed. After the onset of head nodding, patients progressively developed convulsive seizures, cognitive and psychiatric dysfunction, physical deformities, growth arrest, and eventually, in some patients, severe disability.

Conclusion. The description of the natural history of nodding syndrome and especially the prodromal features has the potential of providing a means for the early identification of at-risk patients and the prompt initiation of interventions before extensive brain injury develops. The wide spectrum of symptoms and complications emphasises the need for multidisciplinary investigations and care.

Key words: head nodding, neuro-inflammation, head drops, atonic seizures, *Onchocerca volvulus*

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Nodding syndrome (NS) is a poorly understood acquired neurological disorder affecting previously normally developing children in geographically-bound regions in sub-Saharan Africa. Northern Uganda, Southern Tanzania and South Sudan have the highest burden of disease. There are an estimated 10,000 cases in these three countries (CDC, 2012; Idro *et al*., 2014; Landis *et al*., 2014). Recently, there have also been reports of similar patients in The Democratic Republic of Congo and the Central African Republic (Robert Colebunders, personal communication). In the affected districts of northern Uganda, the prevalence of nodding syndrome among the affected age group is 6.8 (95% CI: 5.9-7.7) per 1,000 (Iyengar *et al*., 2014). The aetiology is unclear (Spencer *et al*., 2013) but there has been a consistent epidemiological association with infection with the filarial worm, *Onchocerca volvulus* (Kaiser *et al*., 1996; Ngugi *et al*., 2013; Colebunders *et al*., 2015). Recent pilot studies suggest that nodding syndrome may be a neuroinflammatory disorder with antibodies to *Onchocerca volvulus*-specific proteins cross-reacting with host proteins (Idro *et al*., 2016; Johnson *et al*., 2017). Definitive studies to confirm these findings are ongoing.

Affected individuals develop symptoms between the ages of three and 18 years and present with a distinct feature, head nodding. Head nodding is characterised by repeated vertical drops of the head onto the chest, 5-20 times/minute, at the sight of food, spontaneously or in association with cold weather (Edwards, 2012; Wamala *et al*., 2015). The head nods have been characterised as atonic seizures (Sejvar *et al*., 2013) but in many children are associated with myoclonic jerks and/or atypical absence seizures. Progressively, patients develop convulsive seizures, behaviour difficulties and psychiatric disorders, declining cognitive function, wasting and growth failure, delayed development of secondary sexual characteristics, and physical and motor disability (Idro *et al*., 2013a). Diagnostic EEGs show generalized slow-wave activity with or without interictal epileptiform discharges. The brain MRI shows varying degrees of cortical and cerebellar atrophy and hippocampal changes in a minority (Idro *et al*., 2013a; Van Bemmel *et al*., 2014).

The natural history of nodding syndrome is inadequately described (Idro *et al*., 2013b; Winkler *et al*., 2014). To date, there are no specifically designed prospective studies. There is no biological diagnostic test and the early symptoms that may help guide on prompt recognition are unknown. Potentially, description of these early features will facilitate prompt initiation and implementation of interventions to arrest progression. In an earlier cases series of 22 untreated patients, we proposed that the symptoms and complications of nodding syndrome probably develop over five clinical stages but this observation is yet to be confirmed (Idro *et al*., 2013a). This study aimed to describe the natural history of nodding syndrome, the early features, and the progressive development of symptoms and complications of the disease. We also sought to examine if the symptoms and complications progressively clustered in the five proposed stages and if so, whether these stages were distinct enough to allow recognition.

Materials and methods

Study design

This study was part of a larger epidemiologic study of nodding syndrome in Uganda. For this study, between October and November 2013, we conducted a cross-sectional survey of a retrospective cohort of patients in Pader district, obtained detailed history of the progressive development of symptoms, and performed clinical testing to describe the functional state, co-morbidities, and complications of the disease.

Setting

Northern Uganda has only recently recovered from the devastating effects of the Lord's Resistance Army insurgency against the Government of Uganda. The region has high levels of poverty, high malaria transmission (Okello *et al*., 2006) and is endemic for *Onchocerca volvulus* (Oguttu *et al*., 2014; World Health Organization, 2017). The study was conducted in Pader; the district with the highest burden of nodding syndrome. Of the over 3,000 registered patients in the country in the year 2013, about 1,200 lived in Pader. Other affected districts included Kitgum, Lamwo, Gulu, Amuru, Oyam and Lira.

Participants

A case of nodding syndrome was defined according to the World Health Organization criteria (2012) (World Health Organization, 2012) as:

– a child or adolescent with head nodding on two or more occasions;

– symptom onset between the ages of three and 18 years;

– head nodding occurring at a frequency of 5-20/minute and in whom head nodding has been observed by a trained health worker or documented on EEG/EMG;

– plus, any one of:

- Triggered by food or cold weather;
- Presence of other seizure types, other neurological abnormalities, or decline in cognitive function and;
- Clustering of cases in space (on a population basis) or time.

All suspected cases had been registered by the local Village Health Worker and at the local health centre and had only recently been initiated on symptomatic treatments at the nodding syndrome treatment centres in the district (Idro *et al.*, 2016). These symptomatic treatments included provision of sodium valproate, plus nutritional, physical, and psychological therapy (Idro *et al.*, 2013b).

Ethical approval and informed consent procedures

Ethical approval for the study was obtained from Makerere University School of Medicine Research and Ethics Committee. Written informed consent was obtained from parents or the primary caregiver if the parent was unavailable. Because of challenges of severe cognitive impairment in some children, no formal assent was obtained in most age-appropriate children. This requirement had been waived by the ethics committee.

Recruitment

Participants were recruited from two highly affected sub-counties in Pader district: Atanga and Awere. These two were purposively chosen because of the large number of patients and close geographical location. In each sub-county, only the most affected villages, with at least five probable patients, were selected. A total of 11 villages were included. All probable nodding syndrome patients in each selected village were invited to participate.

Data collection

The study was conducted by a large multidisciplinary team comprised of clinicians, nurses, therapists, psychologists, and a social worker. Each village was allocated a day and in villages with many patients, up two days. Participants were informed about the study at least two weeks earlier and were assessed at any of the village meeting places, the home of the village chair, or the local health centre. Two days before the survey, the study nurses went back to the villages and reminded the village health workers and parents about the study.

On the morning of the survey, the village health worker helped gather parents and the patients at the agreed place. Patients who could not move were assessed in their homes. A joint general discussion was held on study procedures with all parents, and prospective participants followed by individual written consent. Specifically developed case record forms were administered to consenting parents/patients and used to carefully document the history of each patient. This included history of the pregnancy, birth and early development, the past medical history, timing of the onset of head nodding, and clinical features prior to this. Symptoms after the onset of head nodding were then documented on a timeline together with the intervals up to the onset. The type, frequency, and severity of seizures, treatments received, schooling, visual, hearing and cognitive difficulties, ability to perform age-appropriate activities of daily living, and independence in self-care were all documented. A full physical examination, standard neurological testing, and functional assessment of the patients were then performed. Motor function was assessed using the Gross Motor Classification System (McDowell, 2008) while the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997) was used to screen for behavioural difficulties. Children screening positive for behavioural difficulties on the SDQ had psychiatric assessments using specific domains of the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI KID) (Sheehan *et al.*, 2010).

Data and statistical analysis

Completed Case Record Forms were double entered into a Microsoft Access database and exported to STATA (Version 13.0, College Station, TX). The time at onset of head nodding was defined as the time the parent or primary caregiver first noticed head nodding in the participant. To delineate the stages, the timing of the symptoms and development of the complications were all related to the onset of head nodding. To establish clustering of symptoms within a time range, the lower and upper quartiles were used. For each symptom, the median, lower (25%), and upper (75%) quartile time at onset of the symptoms, either prior to or after the onset of head nodding, was determined. Symptoms with similar values of the 25% and 75% quartiles were taken to cluster together.

Results

General description

Altogether, there were 243 patients with suspected nodding syndrome registered in the 11 villages surveyed. Four were unavailable (three travelled to different relations and one was attending school in another village) at the time of the study and so, were not assessed. On screening, 16 children were found to have been misdiagnosed with nodding syndrome. They had other forms of epilepsy and were excluded. Thirteen other children, who had data on demographic characteristics but were missing information for several other variables, were also excluded. The remaining

Table 1. The early or prodromal features of nodding syndrome.

Symptoms	Yes/ *n* (%)	No/ *n* (%)	Missing/ *n* (%)	No. reporting duration / *n* (%)*	Median (IQR) time from the onset of the symptom to development of heading nodding (months)
Dizziness	34 (16.2)	175 (83.3)	1 (0.5)	30	0.96 (0.23, 2.00)
Periods of staring or gazing blankly	25 (11.9)	185 (88.1)	0 (0.00)	21	1.00 (0.46, 2.00)
Periods of being inattentive	31 (14.8)	179 (85.2)	0 (0.00)	29	1.00 (0.23, 12.00)
Decline in comprehension	27 (12.9)	183 (87.1)	0 (0.00)	22	2.50 (1.00, 12.00)
Lethargy	29 (13.8)	181 (86.2)	0 (0.00)	26	10.0 (1.00, 12.00)
Excessive sleepiness	36 (17.1)	174 (82.9)	0 (0.00)	31	2.00 (0.46, 24.00)
General body weakness	36 (17.1)	174 (82.9)	0 (0.00)	34	2.50 (0.46, 24.00)

*Participants who reported the presence of the symptom and the duration before head nodding.

210 children were available for the study. There were no sex differences; just over half were male. The mean age at the onset of head nodding was 7.5 (SD: 3.0) years and the mean duration with head nodding at the time of the survey was 6.2 (SD: 2.7) years. The majority of patients, 163/210 (77.6%), developed head nodding after the age of five years.

The prodromal or early features of nodding syndrome

The early or prodromal features of nodding syndrome were defined as symptoms that developed before the onset of head nodding. These included what parents and primary caregivers described as periods of staring blankly or being inattentive, complaints of dizziness, excessive sleepiness, lethargy, and general body weakness (*table 1*). One hundred and thirty participants (61.9%) reported at least one of these symptoms. Overall, the features developed between two weeks and 24 months before the onset of head nodding. Of the group, excessive sleepiness and general body weakness were the most common (17.1%), followed by dizziness (16.2%). Using the 25% and 75% quartiles of the time at onset, lethargy (median time: 10 months before onset of head nodding), general body weakness, and decline in comprehension (median time: 2.5 months before onset of head nodding) were the earliest symptoms to develop. Dizziness with periods of staring blankly and being inattentive, with a median period of a month before the onset of head nodding, were the last prodromal features to develop (*figure 1*). No EEGs or brain imaging of patients at this stage were obtained.

The head nodding stage

Head nodding is the pathognomonic feature of the syndrome. In the initial stages, the head nods were reported mostly in the early hours of the morning but also while eating food and with a cold bath or breeze. The head would drop forward repeatedly at a characteristic frequency of 5-20 Hz initially for brief moments, but with time, the episodes lasted several minutes. Earlier EEG studies showed that these head nods are atonic seizures, but some patients also have concurrent myoclonic jerks and atypical absences. Initially, the patients maintained awareness but again with time, they would stare blankly, drool, and then progress to develop other seizure types including tonic-clonic and myoclonic seizures. With continued disease progression and the development of other types of seizures, the head nodding seized in some patients.

Features developing after the onset of head nodding

After the onset of head nodding, almost all progressively developed other features (*table 2*). The most common were convulsive seizures, cognitive dysfunction, behavioural difficulties and psychiatric disorders, slowing or arrested growth, and motor difficulties. Others were malnutrition (wasting), delayed development of secondary sexual characteristics, and unique facies.

Features suggestive of cognitive dysfunction were the most prevalent. These included a perceived decline in understanding or comprehension of instructions (86.8%), recent onset of learning difficulties (73.8%), poor attention (69.1%), and memory (64.8%).

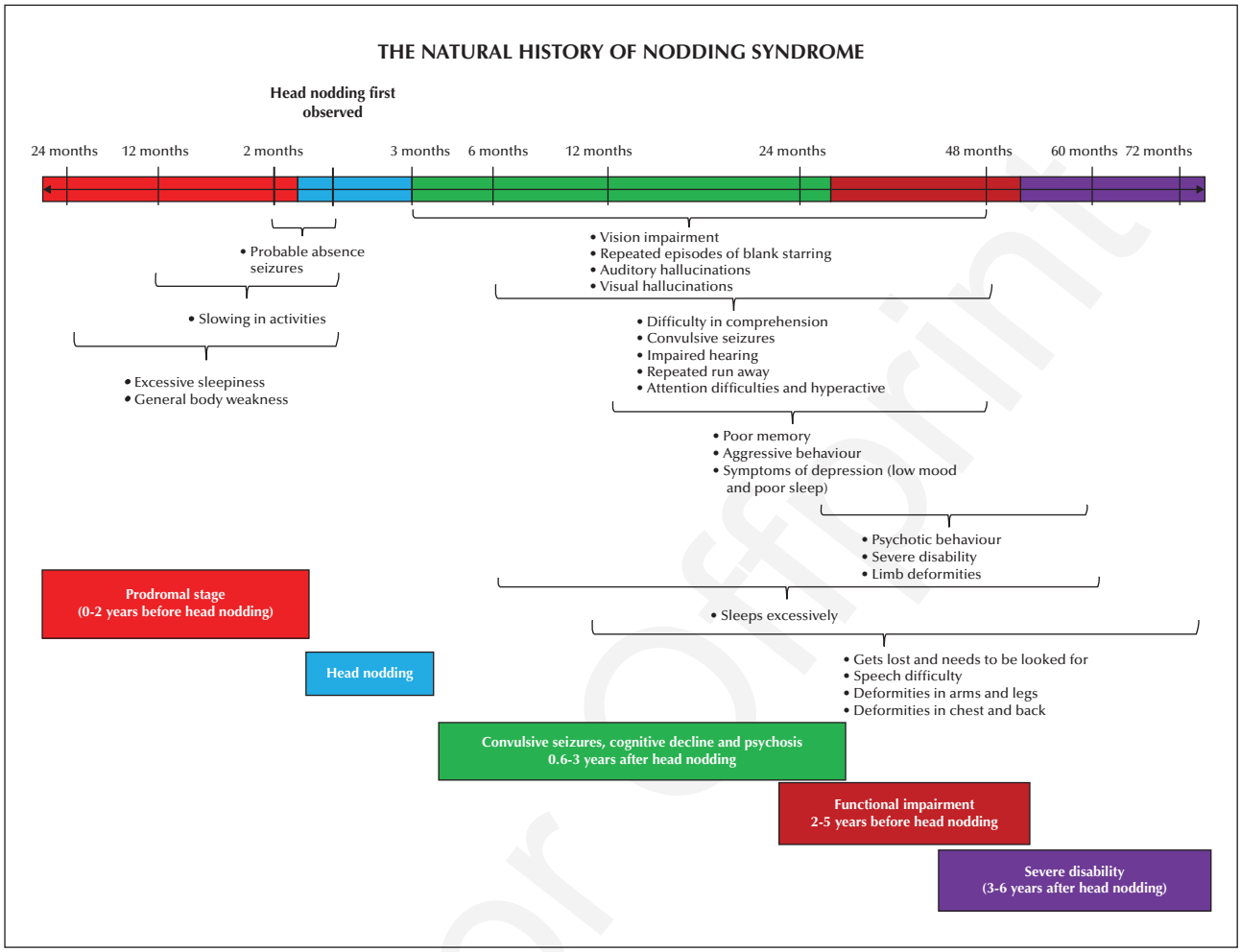

Figure 1. The natural history of nodding syndrome.

Convulsive (focal, generalized tonic-clonic and myoclonic jerks) and non-convulsive seizures (absences) in 62.4% were the other leading features to develop. Behavioural difficulties and psychiatric disorders included aggression, hyperactivity, auditory and visual hallucinations, and clinical depression. Progressively, some patients developed physical disability and deformities of the limbs; deformities around the knees and ankles, flat feet and hands, and deformities of the chest and spine (pectus deformities, kyphosis, and scoliosis). Severe disability with inability to walk was less frequently reported (*table 2*). A timeline of these symptoms is also shown in *figure 1*. Symptoms reported by less than 10 children (<5%) were not included in the time line.

Discussion

This study aimed to describe the natural history of nodding syndrome and in particular, the early features and the progressive development of symptoms and complications. It also examined if symptoms and complications clustered as proposed earlier, in five stages. The study found that the features of untreated nodding syndrome progressively develop across five overlapping stages over several years. *Head nodding (the head nodding stage)* is preceded by a *prodromal period* in at least two thirds of patients. However, unlike what was reported in the earlier small case series (Idro *et al.*, 2013a), the prodromal period has a variable length of up to two years. Although non-specific and easily confused with other conditions (*table 3*), early recognition of the prodromal features in children of the affected age group and living in the affected regions potentially provides a means for the identification of at-risk patients and the prompt initiation of interventions before extensive brain injury develops. Unfortunately, we do not have electrographic and structural brain imaging of this stage.

One to three years after the onset of head nodding, patients develop an increasing number and

Table 2. The symptoms and complications of nodding syndrome, and their duration after head nodding was first observed.

Symptom	Yes /*n* (%)	No /*n* (%)	No. reporting duration/ *n**	Duration to developing symptom / median (IQR) (months)
Decline in comprehension	191 (86.8)	19 (13.2)	191	24.0 (8.0, 48.0)
Poor attention	145 (69.1)	65 (30.9)	139	24.0 (12.0, 48.0)
Poor memory	136 (64.8)	74 (35.2)	123	24.0 (12.0, 48.0)
Learning difficulties	155 (73.8)	55 (26.2)	140	36.0 (12.0, 48.0)
Visual impairment	35 (16.7)	175 (83.3)	33	36.0 (3.0, 48.0)
Hearing impairment	12 (5.7)	198 (94.3)	12	24.0 (7.5, 48.0)
Repeated episodes of blank staring	115 (54.7)	95 (45.3)	107	24.0 (3.0, 48.0)
Convulsive seizures	131 (62.4)	79 (37.6)	130	24.0 (6.0, 48.0)
Repeatedly runs away	57 (27.1)	153 (72.9)	53	24.0 (6.0, 36.0)
Gets lost and needs to be looked for	47 (22.4)	163 (77.6)	43	24.0 (12. 0, 72.0)
Hyperactive	70 (33.3)	140 (66.7)	62	24.0 (6.0, 48.0)
Aggressive behaviour	70 (33.3)	140 (66.7)	70	24.0 (12.0, 48.0)
Prolonged periods of low mood or sadness	110 (52.4)	100 (47.6)	110	24.0 (12.0, 48.0)
Sleeps poorly	37 (17.6)	173 (82.4)	30	30.0 (12.0, 48.0)
Eats poorly	14 (6.7)	196 (93.3)	10	48.0 (36.0, 60.0)
Visual hallucinations	55 (26.2)	155 (73.8)	47	24.0 (5.0, 48.0)
Auditory hallucinations	20 (9.5)	190 (90.5)	13	12.0 (4.0, 48.0)
Sleeps excessively	50 (23.8)	160 (76.2)	34	24.0 (6.0, 60.0)
Speech difficulties	30 (14.3)	180 (85.7)	30	36.0 (24.0, 72.0)
Limb deformities	29 (13.8)	181 (86.2)	21	48.0 (24.0, 60.0)
Deformities in the chest and back	44 (21.0)	166 (79.0)	37	60.0 (24.0, 72.0)
Severe disability	51 (24.3)	159 (75.7)	40	36.0 (24.0, 66.0)
Bedridden	3 (1.4)	207 (98.6)	3	24.0 (12.0, 84.0)

*Number of participants who reported the symptom and provided duration to its development after head nodding began.

intensity of convulsive seizures, as well as cognitive and emotional dysfunction; *the convulsive seizure stage*. Progressively, there are multiple functional *impairments* in behaviour and motor abilities. Some also develop deficits in speech, vision or hearing while others develop overt psychiatric disorders. Beyond this period, deformities of the limbs, chest, and spine, faltering growth or failure of growth are observed. Some become bedridden; *the severe disability stage*. However, not all patients progress to these advanced stages and in many cases, marked improvement and reversal of symptoms have been observed with antiepileptic drug treatment and rehabilitation (Idro *et al*., 2014). The wide spectrum of clinical signs involving multiple systems including the central nervous system, motor, and endocrine systems would in addition also suggest that nodding syndrome is a multisystem disease rather than a purely neurological disorder and emphasise the need for a multidisciplinary investigation of the aetiology and care provision.

Table 3. Examples of disorders that may potentially be confused with the early stages of nodding syndrome.

1	Childhood epilepsy syndromes *e.g.* Lennox- Gastaut syndrome
2	Epileptic encephalopathies
3	Childhood dementia
4	Depression in children

Table 4. The natural history of nodding syndrome; the revised clinical stages.

Stage One: The prodromal stage. Patients have increasing inattention, dizziness, lethargy; **no** head nodding, **no** convulsive seizures.
Stage Two: Head nodding stage; head nodding develops.
Stage Three: Convulsive seizures stage; other types of seizures (tonic, clonic, myoclonic, absence, tonic-clonic) develop; cognitive decline is observed.
Stage Four: Multiple impairments; patients develop impairments in motor function, speech difficulties, severe cognitive impairment, behavioural difficulties and psychiatric disorders, malnutrition, physical deformities including kyphosis, limb and pectus deformities, and growth failure.
Stage Five: Severe disability with limited independent mobility (the general picture is that of a severely wasted child with apathy and depressive features including a flat affect, poor appetite, and limited speech.)

The continued decline in the burden of seizures in individual patients with antiepileptic therapy compared to reports at the height of the epidemic points to the success and importance of antiepileptic treatment in these patients. In addition, the lower number of patients in advanced stages of the disease in Uganda today may imply halting of disease progression in some patients and possibly a reversal in poor health with application of the symptomatic treatments.

Overall, the timing of the progression of symptoms in this study correlates well with that described in the earlier proposed clinical stages (Idro *et al.*, 2013a). However, the stages are not so distinct and overlap. Beyond the prodromal and the head nodding stages, patients developed convulsive seizures within one to three years, cognitive dysfunction within one to four years, and psychiatric disorders and motor difficulties overlapped within two to five years before onset of severe disability at between three and six years (*figure 1, tables 2, 4*). Prospective studies of incident cases may more conclusively demonstrate the respective stages.

With emerging reports of nodding syndrome now in the Democratic Republic of Congo and the Central African Republic, together with the growing problem in South Sudan, the need to clearly understand the pathogenesis of this disorder and develop specific treatment and preventive interventions cannot be stronger. Furthermore, the multisystem nature of the disease demonstrated here should also be explored. The variable progression of the disease may provide some clues. In the meantime, in the absence of a specific treatment, the symptomatic treatment protocol that has been implemented in Uganda with some success could be adopted in the neighbouring countries.

The primary limitation of this study was the use of a retrospective cohort and the challenges of recall in using parental history to describe the natural history of the disease. Again, a prospective study would be ideal but since 2014, there have been no incident cases of nodding syndrome in Uganda. Prospective studies may now only be possible in the new areas reporting the disease. Despite this limitation, highly skilled clinicians screened the participants and used standardised forms adapted from the previous case series to obtain the progressive development of symptoms. Secondly, there is no specific biological marker or diagnostic test for nodding syndrome. It was therefore not possible to correlate the clinical stages to plasma or cerebrospinal fluid levels of a specific marker. We also did not specifically obtain any functional (*e.g.* EEG) or structural imaging of the brain in the prodromal stage nor in the progressive stages to correlate with the specific clinical observations. However, recent documentation of cross-reacting antibodies in some patients with nodding syndrome, which pathologically link *Onchocerca volvulus* infection to nodding syndrome, is starting to provide an insight into the possible cause of the disease, may explain disease progression, and may, in the not-so-far future, provide biological markers that may correlate with clinical observations. Stage-specific EEG and brain MRI features will be valuable additions in future studies. If indeed nodding syndrome is a neuroinflammatory disorder, as proposed, with antibodies to *Onchocerca volvulus* antigens that cross-react with host proteins, the slow progression of the disease described here – over several years – would suggest that this is really an insidious process.

In conclusion, nodding syndrome is probably a multisystem disorder in which symptoms develop over several overlapping and progressively severe stages, starting with a non-specific prodromal period of variable length. A high index of suspicion and prompt recognition of especially the early features may guide

in the early identification of at-risk patients and promote the prompt initiation of interventions before extensive brain injury develops. The wide spectrum of symptoms and complications emphasises the need for multi-disciplinary care. In addition to advancing our understanding of nodding syndrome, the clinical stages identified here will also be helpful in the development and ascertainment of end points in intervention studies. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) What is the distinctive feature of nodding syndrome? What causes it?

(2) List the clinical stages in the natural history of untreated nodding syndrome?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".