Nodding Syndrome in Ugandan Children - Clinical features, Brain imaging and Complications; an observational case series

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NODDING SYNDROME IN UGANDAN CHILDREN - CLINICAL FEATURES, BRAIN IMAGING AND COMPLICATIONS; AN OBSERVATIONAL CASE SERIES

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ABSTRACT

Objectives: Nodding syndrome is a devastating neurological disorder of uncertain aetiology affecting children in Africa. There is no diagnostic test and risk factors and symptoms that would allow early diagnosis are poorly documented. This study aimed to describe the clinical, neurophysiologic and brain imaging (MRI) features and complications of nodding syndrome in Ugandan children.

Design: Case series

Participants: 22 children with nodding syndrome brought to Mulago National Referral hospital for assessment.

Outcome measures: Clinical features, physical and functional disabilities, electro-encephalogram (EEG) and brain MRI findings and a staging system with a progressive development of symptoms and complications.

Results

The median age of symptom onset was 6(range 4-10) years and median duration of symptoms was 8.5(range 2-11) years. Sixteen of 22 families reported multiple affected children. Physical manifestations and complications included stunting, wasting, lip changes and gross physical deformities. The bone age was delayed by 2(range 1-6) years. There was peripheral muscle wasting and progressively, generalised wasting. Four children had nodding as the only seizure type; 18 in addition had myoclonic, absence and generalised tonic-clonic seizures developing 1-3years in the course of illness. Psychiatric manifestations included wandering, aggression, depression and disordered perception. Cognitive assessment in 3 children demonstrated profound impairment. The EEG was abnormal in all, suggesting symptomatic generalized epilepsy. There were different degrees of cortical atrophy on brain MRI but no hippocampal changes. Five stages with worsening physical, EEG and brain imaging features were identified: a prodrome, development of head nodding and cognitive decline, other seizure types, multiple complications, and severe debilitation.

Conclusions

Nodding syndrome is a neurologic disorder that may be characterised as probably symptomatic generalized epilepsy. Clinical manifestations and complications develop in stages which might be useful in defining treatment and rehabilitation. Studies of risk factors, pathogenesis, management, and long-term outcome are urgently needed.

ARTICLE SUMMARY

Article focus

- This paper offers detailed descriptions of the clinical features and complications of nodding syndrome in Ugandan children and the neurophysiologic and brain imaging features.
- It also proposes a clinical staging system for the disease.

Key messages

- Nodding syndrome is an epidemic neurologic disorder affecting children in parts of sub-Saharan Africa that may be characterised as probably symptomatic generalized epilepsy and with features of an epileptic encephalopathy.
- Patients progressively develop both physical and functional deficits including multiple seizure types, cognitive and physical decline, malnutrition, and psychiatric features. Five such stages could be identified.
- The proposed clinical stages are associated with worsening cortical atrophy on brain imaging and more severe epileptiform and background EEG changes. These stages may be useful in guiding treatment and rehabilitation.

Strengths and limitations of this study

- Although the sample size is small and there is no comparison group, this is the first study to carefully document a range of co-morbidities and complications in nodding syndrome, describe the natural history and provide a staging system, and combine these with extensive neurophysiology and brain imaging data.
- The study patients however may not be representative of the population as they were not randomly drawn from the community.
- The study did not investigate aetiology and the proposed staging was derived from parental descriptions rather than prospective observations and therefore suffers from recall.
- The resolution of our brain MRI images is quite low.

BACKGROUND

Nodding syndrome is an emerging and devastating neurological disorder of uncertain aetiology affecting children in sub-Saharan Africa. Current estimates suggest there are about 10,000 affected children[1]. The syndrome was first reported in Tanzania in 1960's[2] and subsequent reports have come from Liberia[3], South Sudan[4-6] and Uganda[7 8]. The syndrome is characterized by head nods, now determined as atonic seizures, often in association with feeding and development of other seizure types and cognitive decline[6 9].

In Uganda, almost all affected individuals are from the north where there are close to an estimated 3,000 cases. This region is crossed by two rivers - Aswa and Pager; with high malaria transmission and endemic for *Onchocerca volvulus.* This parasite has variously been associated with the *Nakalanga* syndrome (short stature and malnutrition)[10-12], epilepsy[13] and nodding syndrome[2 5 9]. The region has also, for the past 20 years, had instability due to rebel activity[14]. As a result, the population was internally displaced into densely populated camps. It is only in the last 5 years that peace has returned and people returned to their homes.

There are only limited descriptions of nodding syndrome[4 5 9 15]. Initial symptoms that would allow early recognition of the disease, the natural history and risk factors to identify any modifiable factors are poorly understood. There is no diagnostic test and the current case definition is based on clinical criteria only. The objective of this study was to describe the clinical, neurophysiologic and brain imaging features and complications of nodding syndrome in Ugandan children and to propose a staging system.

METHODS

Design and setting

This is a case series of 22 Ugandan children with nodding syndrome. The study was conducted in Mulago, the National Referral hospital in Uganda and teaching hospital for Makerere University College of Health Sciences in Kampala. This hospital provides tertiary level care for patients in a country in which most public healthcare services are paid for by the state.

Participants

Participants were patients with suspected nodding syndrome brought by the Ministry of Health from Kitgum district near the border with South Sudan, to Mulago Hospital in March 2012 for specialist assessments to better understand the syndrome. Kitgum district is the epicentre of the disease and one of the most affected districts in the country. Of the 25 patients one young adult (a 23 year old male found to have a brain tumour) and two adolescents (an 18 year old girl with a cerebellar hypoplasia syndrome and a 16 year old boy with history of cerebral malaria at the age of 4 years and subsequent neurologic sequelae) were excluded. The remaining 22 children had probable nodding syndrome and were included in the study. Then, a case of probable nodding syndrome was defined as:

- A child older than 2 years or adolescent who previously was developing normally,
- Presents with two or more episodes of recurrent head nodding occurring spontaneously or consequent to the sight of food or coldness
- With or without other types of seizures, neurological signs, regression in growth or mental retardation.

This case definition was revised during the International Meeting on Nodding syndrome later. All the same, all selected patients still fulfilled the revised criteria[16].

Permission for the study was obtained from Makerere University School of Medicine Research and Ethics Committee. However, we had no study protocol prior to the arrival of the patients and so, patient care and assessments followed the hospital's procedures for routine non-surgical care for children. Thus, verbal parental consent was obtained for all clinical, laboratory and imaging procedures. As is policy however, parents provided written consent for photography as this is considered over and above routine care and for surgical procedures. Parents were specifically made aware that the objective of the assessments was not cure but better

understanding of the disease and that, results of investigations will be made available to the wider scientific community in presentations and publications. To this effect, a submission was then made to the Ethics Committee and permission to use results of the investigations subsequently granted.

Study measurements and Procedures

All had detailed clinical, neurophysiologic, and brain imaging assessments and laboratory testing.

Clinical assessment

The history included an inquiry of the time from pregnancy to onset and the progressive development of symptoms, physical and functional difficulties. The physical examination included the general, nutritional, neurologic, cognitive and mental state assessment. Wasting was defined as weight for height Z score of -<2 and stunting as height for age Z score of -<2. Sexual maturity was assessed using the Tanner Sexual Maturity staging. Patients were classified as having nodding syndrome only or nodding syndrome plus if they had complications such as a report of other seizure types, neurologic and clinically evident cognitive decline, physical and functional difficulties. X-rays of the left wrist were taken for bone age and reported using a Greulich and Pyle Atlas by a blinded radiologist[17]. Bone growth was considered delayed if it was 2 years below chronological age.

Laboratory procedures

Ten millilitres of blood was drawn for full blood count, ESR, malaria parasites, electrolytes, liver and renal function tests, and HIV testing. Cerebrospinal fluid was examined for cells, glucose, protein, microscopy and bacteriologic culture. In addition, 10 children had a skin snip examined for *Onchocerca volvulus* as previously described[9].

Neurophysiology and imaging

All had a 30 minute EEG and the recording examined by a consultant neurophysiologist (SW) in UK. Brain MRI in T1, T2 and Flair sequences were obtained without contrast in 19/22 patients using a 0.5Tesla machine (BASDA Medical Apparatus, Guangzhou) and the images also examined in the UK by a Consultant Neuro-radiologist (KC).

Treatment

Patients were started on symptomatic treatment (sodium valproate for seizure control, nutritional and physical therapy, counselling and social support) according to national guidelines developed a month earlier[18]. In this management, all received sodium valproate starting at 10mg/kg/day. The dose was titrated in 5-10 mg/kg/day increases with seizure control. Nutritional rehabilitation included Ready to Use Therapeutic Foods (Plumpy'Nut®, Nutriset, Malaunay) and locally prepared food. Occupational and physiotherapy, family counselling and support were provided as appropriate.

Data analysis

Data was analysed using STATA version 12 (STATA Corp, TX). Results are summarised as frequencies, proportions and medians as appropriate. The clinical features, complications and disability were then used to describe treatment and rehabilitation needs. Clinical stages were identified and brain imaging and EEG correlated with the clinical stages.

RESULTS

General features

Nine patients (40.9%) were male. The age range was 12-18 years. The median age at onset of symptoms was 6(range 4–10) years. The median duration of symptoms was 8.5(range 2-11) years. Sixteen of the 22 families reported multiple cases; median 2(range 0–4), **Table 1**.

Striking features on physical examination included stunting, cognitive impairment (on KABC or performance of basic tasks), lip changes with or without other physical deformities. Several children had burns and scars from falls into fires. The skin was dry, thin and scaly. Extremities, especially the feet, felt cold with a temperature gradient with the trunk but a normal capillary refill time. There were striking changes of the lower lip **(Figure 1)**. In mild cases, the lower lip was enlarged with no visible or palpable localised swellings. In severe cases, the mucosa was deep purple, with soft papular growths and increasingly large, thick bands of tissue. One child, not exposed to sodium valproate previously, had unexplained alopecia.

Table 1 Characteristics of 22 patients with nodding syndrome

ID	Sex	Age (yrs)	Duration of symptoms in yrs	Admission weight in Kg	Discharge weight in Kg	Seizure based classification	Main Psychiatric morbidity	Other prominent complications	EEG Seizure classification
1	F	14	11	20.2	23.1	Head nodding plus other seizures types	Behaviour problems Hallucinations	Severe cognitive impairment Burns Lip deformity Severe stunting, with severe wasting Motor difficulties with musculoskeletal deformities and contractures	Generalised epileptiform discharges
2	F	13	5	28.1	28.3	Head nodding plus other seizures types	Hallucinations Aggressive behaviour	Moderate wasting	Generalised epileptiform discharges
3	F	15	10	23.6	24.8	Head nodding plus other seizures types	Behaviour problems Aggression Pycho-social disorder	Severe wasting Speech difficulties	Generalised epileptiform discharges
4	F	14	9	37.1	39.0	Head nodding only		Severe cognitive impairment Stunting	Generalised epileptiform discharges
5	F	16	9	36.2	37.8	Head nodding plus other seizures types	Aggressive behavior Wandering Hallucinations	Severe cognitive impairment Speech difficulties Moderate wasting	Right temporal discharges
6	F	14	5	38.4	39.9	Head nodding plus other seizures types			Generalised epileptiform discharges
7	F	14	7	21.7	21.2	Head nodding plus other seizures types		Severe cognitive impairment Lip deformity Severe wasting	Generalised epileptiform discharges
8	F	18	10	48.3	49.1	Head nodding plus other seizures types	Aggressive behaviour Hallucinations	Severe cognitive impairment Speech difficulties	Generalised epileptiform discharges
9	F	18	8	30.1	36.3	Head nodding plus other seizures types	Psychotic symptoms Behavioural problems	Severe cognitive impairment Lip deformity Speech difficulties Severe wasting	Left temporal discharges
10	M	16	11	36	34.5	Head nodding plus other seizures types		Moderate wasting Burns Marked lip	Generalised epileptiform discharges

								deformity	
11	M	15	9	17.0	19.2	Head nodding plus other seizures types	Depression	Hearing impairment Stunting Burns Musculoskeletal Deformities Severe cognitive impairment Severe wasting	Generalised epileptiform discharges
12	M	13	8	34.0	35.5	Head nodding plus other seizures types	Hallucinations		Generalised epileptiform discharges
13	F	13	3	32.0	32.9	Head nodding plus other seizures types		Moderate wasting	Generalised epileptiform discharges
14	F	14	9	34.8	38.3	Head nodding plus other seizures types	Hallucinations		Generalised epileptiform discharges
15	M	12	8	16.1	18.8	Head nodding plus other seizures types		Severe wasting Stunting Kyphosis, pectus deformity Generalised skin changes	Generalised epileptiform discharges
16	M	12	2	17.1	18.2	Head nodding alone		Stunting Severe wasting	Generalised epileptiform discharges
17	M	14	8	23.7	25.1	Head nodding plus other seizures types	Post ictal Aggression Wandering	Severe cognitive impairment Stunting Lip deformity, Ataxia Speech difficulties Motor difficulties with musculoskeletal deformities Moderate wasting	Generalised epileptiform discharges
18	M	18	6	33.3	35.3	Head nodding plus other seizures types		Moderate wasting	Generalised epileptiform discharges
19	F	12	4	21	21.4	Head nodding alone		Moderate wasting Stunting	Generalised epileptiform discharges
20	M	15	9	28.9	31.4	Head nodding alone		Stunting	Generalised symptomatic epilepsy
21	M	15	9	20.5	24.1	Head nodding plus other seizures types		Severe cognitive impairment Lip deformity	Generalised epileptiform discharges

								Speech difficulties Stunting Moderate wasting Motor disability with severe musculoskeletal deformity, wasting/dystrophy	
22	F	15	9	27.3	32.7	Head nodding plus other seizures types	Behavioural problems Aggression	Severe cognitive impairment Stunting Burns Episodes of disorientation Speech difficulties	Generalised epileptiform discharges

Growth and sexual maturity

Sixteen of the 22 children were wasted and nine stunted. Ten had sexual maturity assessed; 3/10 children (aged 12, 13, 14 years) scored Tanner Stage 3. All remaining 7 children (ages 12-17 years) were either Tanner Stage 1 or 2. The bone age was delayed by a median 2(range 1-6) years.

Musculoskeletal findings

Almost all had peripheral muscle wasting with flat feet and hands, thin cylindrical digits and progressively, more generalised wasting. Other physical changes included kyphosis and pectus deformities of the chest. Flexion limb deformities were seen in severely debilitated patients (**Figure 2).**

Neurological, cognitive and behavioural features

Seizures

Other than head nodding, a variety of other seizures including absence, complex partial, myoclonic, and tonic-clonic seizures were described in 18/22 patients.

a) Head nodding

Nodding was precipitated by food in 16/22 children. In 4/22, it was associated with cold weather or cold breeze while in 13/22, it developed spontaneously. Nodding episodes came in clusters (both day and night) and were characterised by repetitive flexion and forward drop of the head around the neck. It lasted several seconds to minutes. Some children became unresponsive and stared blankly with a cluster of nodding, stopped feeding or drooled saliva.

b) Other seizure types

Initially nodding was the predominant seizure type but as the disease progressed, generalised tonic-clonic seizures gained more prominence. Myoclonic seizures were not readily reported but were observed in several children in hospital. One such child had a prolonged cluster of nodding with concurrent myoclonic jerks involving both upper limbs lasting about 10 minutes. In a second child, similar myoclonic jerking was followed by a generalised tonic-clonic seizure. Several children reported sudden falls sustaining facial and head injuries.

Four children reported paroxysmal events associated with fear, panic and visual hallucinations. We could not obtain clear descriptions of the images seen by two. The third child would shout and run with onset of the hallucinations and the forth reported seeing a person with knives whose intention 'was to kill her'. None of these events was captured on EEG.

Other neurologic complications

Focal neurological signs were uncommon exception. There were no obvious cranial nerve palsies. However, six children were lethargic with an apathetic and expressionless face or 'myopathic facies'. Three of the six drooled saliva while two had very slow speech and repeated epileptiform (spike and wave) discharges on EEG. The deep tendon reflexes were increased in a minority of patients. In the majority however, the reflexes were either normal or reduced. Almost all these had peripheral muscle wasting manifesting with flat feet and hands and thin cylindrical fingers and progressively, generalised wasting.

Vision, hearing and speech difficulties

No parent reported visual impairment and we did not test visual acuity but hearing impairment was reported in one child. Speech difficulties were reported in 10/22 children. These included immature speech for age and slow, slurred or dysarthric speech. Two children were mute but retained gestural ability and receptive language.

Behaviour and psychiatric features and complications

The earliest psychiatric manifestation was wandering behaviour or running away. Because of concerns about injury or getting lost, some parents tied up the patients to restrain them in the home. Aggression, particularly towards familiar people, was reported in 6/22 manifesting 3-6 years after onset of nodding. In two children, the onset was concurrent with wandering

behaviour. Five children had sleep difficulties and at least 8/22 had moderate to severe mood problems with one clinically depressed.

Cognitive function

All 22 children had cognitive difficulties and were out of school. Academic performance declined with symptom onset; previously well performing pupils started getting poorer grades and were eventually withdrawn from school within 2-4 years of disease onset. Cognitive functioning, using the Kaufman Assessment Battery for Children 2nd Edition (KABC-2), was assessed in four children ages 13-15 years two weeks after initiation of sodium valproate. This test has previously been adapted to Uganda[19]. Three of the 4 children responded to the test instructions. The fourth child did not respond at all. All 3 children had severe cognitive impairment (**Table 2**).

Table 2: Cognitive function in 3 children two weeks after initiation of sodium valproate

Cognitive Domain	**Patient 1 Male 13 years**		**Patient 2 Male 15 years**		**Patient 3 Male 15 years**	
	Test Score	Age equivalent in years	Test Score	Age equivalent in years	Test Score	Age equivalent in years
Working memory	8	<5	7	<5	21	=5
Planning	7	<8	1	<5	3	<5
Learning	28	<5	25	<5	54	=5
Visual spatial	0	<5	0	<5	31	<5
Knowledge	11	<5	5	<5	52	<8

Laboratory findings

The mean haemoglobin was 12.4 (range 10.8–14.8) g/dl and the mean red cell volume was 81.4 (range 65.8-89.1)fl. Five children had iron deficiency anaemia. Total white blood cell and platelet counts were normal but 10/22 children had eosinophilia. The ESR was high in 17/22 children with a median of 28.5 (range 5-90) mm in the first hour. Other than mild elevations of gamma GGT, the liver and renal function was normal. Nine children had osteopenia on X ray but only one had hypocalcaemia and four, hypophosphataemia. Creatine kinase levels were

normal in all children and all tested HIV negative. Cerebrospinal fluid total protein, cells and glucose were all normal. Three out of 10 patients had *O.volvulus* microfilaria on the skin snip.

EEG

The diagnostic EEG was abnormal in all cases. The background showed generalised excess of slow activity. Generalised inter-ictal epileptiform activity was observed in all but two patients in whom, they were focal temporal (unilateral in one and bilateral in the second). All patients with generalised epileptiform activity had high amplitude spikes or sharp waves, some associated with slow wave activity often occurring in runs (**Figure 3)**. The discharges had bilateral fronto-temporal or fronto-centro-temporal emphasis but some were more generalised and increased in frequency in light sleep. There was a clear gradation from mild to more severe background abnormalities and epileptiform activity. No overnight recordings were performed. The EEG findings suggested symptomatic generalised epilepsy in 20 and symptomatic focal epilepsy in the remaining 2.

Brain imaging

Brain MRI without contrast was performed in 19/22 patients. The imaging showed different degrees of cortical and some cerebellar atrophy. No focal cerebral cortical or hippocampal changes were observed (**Figure 4)**.

Disease progression

Five stages with deteriorating seizures, neuro-cognitive and psychiatric disability were identified: a prodrome; development of head nodding and cognitive impairment; other seizure types; multiple complications and, severe debilitation (**Panel 1**).

Panel 1: A mum's description of the sequential chronology of symptoms and disease progression in her 18 year old daughter.

"She was growing well until the age of 8 years when symptoms of nodding began. The head nodding is triggered by food. When food is given, she freezes with it in her hand, stares blankly into space with a fixed gaze, and then nods repeatedly for a time which varies with each episode but the maximum time was initially 5 minutes. The symptoms got worse with time and about 6 years later, the nodding symptoms were immediately followed by or associated with big seizures during which the whole body shook. She would drool saliva, foam around the mouth and loses consciousness. After the big seizure, she would sleep and on waking is often weak and sometimes disoriented. On some nights, she reports seeing a figure that holds a knife and wants to kill her. She is distressed by her illness and gets embarrassed on waking if she had a seizure in public. She is very quiet but sometimes aggressive. Overtime, her speech has become sluggish. Although she is 18 years old, she still has childish behaviour which is evident as she speaks. Her father died following a febrile illness. She has six siblings two of who have similar symptoms."

Stage 1 The prodromal period

This poorly defined and short-lived period was reported in four patients. The earliest symptoms included “dizziness” and increasing inattention. The children were excessively sleepy, lethargic and would sometimes stare blankly during meals.

Stage 2 Development of head nodding

Among the four patients, head nodding developed within 6 weeks of the prodrome. In the majority however, the initial feature was an abrupt onset of nodding. Subsequently, parents reported declining cognitive abilities and behaviour difficulties. Disease progression however appeared to arrest in these four.

Stage 3 Development of other seizure types

Other than the four children with nodding only, 18 children in addition developed other seizure types including absence, complex partial, myoclonic and generalised tonic-clonic seizures. One child developed generalised tonic clonic seizures almost simultaneously with the nodding. In the others however, these developed 1-3 years after initial symptoms. It was around this time that almost all school going children dropped out of school.

Stage 4 Development of multiple complications

Multiple complications developed 4-8 years after the initial symptoms associated with marked regression in achievement. These consisted of deteriorating behaviour and psychiatric symptoms and decline in motor, speech and other cognitive functions. Some patients developed physical deformities including kyphosis, limb and pectus deformities (**Figure 2)**. Some sustained severe facial injuries with “drop attacks” and burns. Those who were still independently mobile would wander about or ran away and were prone to getting lost. Changes in the architecture of the lower lips (**Figure 1**) also occurred at this time. With disrupted and poor feeding, the children became severely wasted.

Stage 5 The severely debilitated child

These children have little if any, independent mobility. The general picture was that of a severely wasted child with apathy and depressive features including a flat affect, poor appetite and limited speech. Some had contractures around the major joints.

Patients with head nodding only had less cortical atrophy on brain MRI compared to those with multiple complications. In addition, there was a clear gradation from milder to more severe epileptiform and background EEG abnormalities in patients with suggested later clinical stages of the disease.

Response of seizures to sodium valproate

The patients had previously been on mostly small doses of different anti epileptic drugs including phenytoin, phenbarbitone and carbamazepine. In conformity with proposed national guidelines, all were started on sodium valproate and the other anti epileptic drugs weaned off. Prior to this, a 24 hour seizure count was obtained and this was repeated 14 days later. Overall, there was a 57% reduction in total seizures including clusters of nodding. The median total daily seizures reduced from 5 (range 2–14) on admission to 2 (range 0-8) 14 days after initiation of sodium valpraote. Concurrent improvements were also seen on the EEG with marked improvements or absent interictal discharges in 3/5 patients who had repeat recordings on the day of assessment **(Figure 3)**.

DISCUSSION

Recently, world media has highlighted reports of "a mysterious disease" baffling scientists – the nodding syndrome.[8 20 21] The main questions are: what is the cause, the pathogenesis, disease classification, clinical spectrum and treatment? In this paper we describe the clinical features, complications of nodding syndrome in Ugandan children together with the brain imaging features. Our results suggest that nodding syndrome is a neurologic disorder characterised as symptomatic generalised epilepsy.

Clinical features and complications

Nodding syndrome in Ugandan children manifests with head nodding, cognitive dysfunction, psychiatric features, and/or multiple other seizure types. It may be complicated by stunted growth, pubertal delay, wasting, motor decline and physical deformities. The earliest manifestations are that of a poorly defined prodrome followed within weeks by head nodding. In the later stages, there is cognitive dysfunction, psychiatric difficulties, severe muscle wasting and musculoskeletal deformity. Delayed physical growth, bone age and sexual maturity are common in affected children. This may partly be a result of delayed puberty since most were in Tanner Stage 2. Pubertal delay may be secondary to chronic illness, poor nutrition and/or

psychosocial deprivation. If so, improved nutrition, a caring environment and symptom control should lead to improved growth and the initiation of puberty.

The progressive development of symptoms and complications appears to reflect the natural progression of an epileptic encephalopathy. Stage 1 might be brief seizures, while the departure from school in Stage 3 can be explained by uncontrolled seizures. Stage 4 can be the time when a high seizure load contributes to regression which together with ensuing poor nutrient intake leaves a severely debilitated child in Stage 5, the sum effect of multiple factors on functioning.

The clinical features in Ugandan children are as severe as in South Sudanese children[6] but may be more severe than that reported in Tanzanian patients[9]. Despite similar age of onset and duration of symptoms, only 18% of Ugandan children had the milder nodding only compared to 45% in Tanzania; all our patients had abnormal interictal background EEG compared to 60% in Tanzania. Ugandan children also had severer cognitive impairment and a much higher burden and variety of seizures. These differences may suggest a variation in the presentation of the disease by region. Family clustering in all three countries however suggests a common exposure factor.

Aetiology and pathogenesis

The aetiology of nodding syndrome and pathogenesis of the complications remain unknown. A variety of viral central nervous system infections have been screened for on PCR but no association has been demonstrated[16]. The uncertain association with infestation with *Onchocerca Volvulus* however remains[5 9]. Others have postulated that nodding syndrome is a consequence of treatment of patients with heavy *Onchocerca volvulus* infestation or dual infection with other similar parasites[7 15]. Contrary evidence of any association with onchocerciasis also exists[22]. Other aetiologic considerations include toxic brain injury, an inflammatory brain disease, a slow virus infection or prion disease, an atypical mitochondrial disease or other genetic disorder. Repeated severe psycho-trauma has also been proposed[23]. Earlier studies by the Ugandan Ministry of Health and the US Centers of Disease Control demonstrated very low serum levels of vitamin B6 in cases compared to controls. Although unlikely, the question then was whether nodding syndrome is an atypical form of pyridoxine dependent epilepsy? Studies to further investigate this are awaited[24].

Children with the syndrome demonstrate some features of prion protein disease including motor and cognitive dysfunction, epilepsy, behaviour and psychiatric morbidity. However, other features such as extrapyramidal involvement and cortical blindness have not been reported. The age of onset of symptoms is much younger and progression much slower[25]. The brain imaging and EEG too are not supportive. Brain biopsy or autopsy studies would be important in excluding prion disease. Future studies should also include the auto-immune encephalitides.

The brain MRI findings may suggest viral encephalitis, a para-infectious phenomenon (an antibody mediated channelopathy) or an outside chance of a neurotoxin as possible aetiologies. Among Tanzanian patients, hippocampal gliosis, probably from inflammation, was described in some patients[9]. Although this could partly explain the cognitive difficulties, we did not observe such lesions even with the more severe cognitive impairment in our patients. Instead, we think an epileptic encephalopathy is likely. The background EEG in all 22 showed generalized excess of theta and slow activity. Interictal epileptiform activity was demonstrated in all but one patient. Prolonged EEG recording (including during sleep) with detailed neuropsychological testing and functional brain imaging may help with understanding pathogenesis of the cognitive decline.

Study limitations

Our patients may not be representative sample as they were not drawn randomly from the community. This study did not investigate aetiology and the proposed staging was mostly derived from parental descriptions rather than prospective observations and therefore suffers from recall. Third, we only performed diagnostic EEG rather than prolonged recordings important in investigating associations between seizures and cognitive dysfunction. The resolution of our MRI images is also quite low.

CONCLUSIONS

Nodding syndrome is a neurologic disorder that is complicated by multiple physical and functional disabilities and may be classified as symptomatic generalised epilepsy. Assessment and care should be provided by a multidisciplinary team. Studies of aetiology, pathogenesis, evidence based treatment and rehabilitation strategies are urgently needed.

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Author contributions

RI, ROO, AKM, HAT, TPW, PB, JN1, SBM, ADM, HN, SW, EM, JN2, SK, JRA and JKT all participated in patient care and performed the different assessments. ROO, AKM, HAT and SBN were in-charge of daily care, TPW and EM performed the growth and sexual staging assessments, JN1 the psychiatric assessments, HN the nutrition assessment, SW reported the EEG recordings, KC the brain MRI and RI wrote the first draft. All provided a critical review of the manuscript.

Conflict of Interest

The authors report no competing interests.

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Figure legends

Figure 1 Lip changes

The figure shows changes in the lips with increasing distortion. In patients with mild involvement, the lower lip is enlarged but with no visible or palpable swellings. With more severe involvement, there is deep purple discolouration of the mucosa, soft papular growths and increasingly larger and thicker bands of tissue. Other oral abnormalities included lacerations and loss of teeth from injuries.

Figure 2 Hand and foot muscle wasting, deformities and contractures

Figure 2 shows wasting of the muscles of the hand and foot, knee and foot flexion deformities and contractures, pectus deformity of the chest and kyphosis. Such marked deformities are seen with increasing symptom duration.

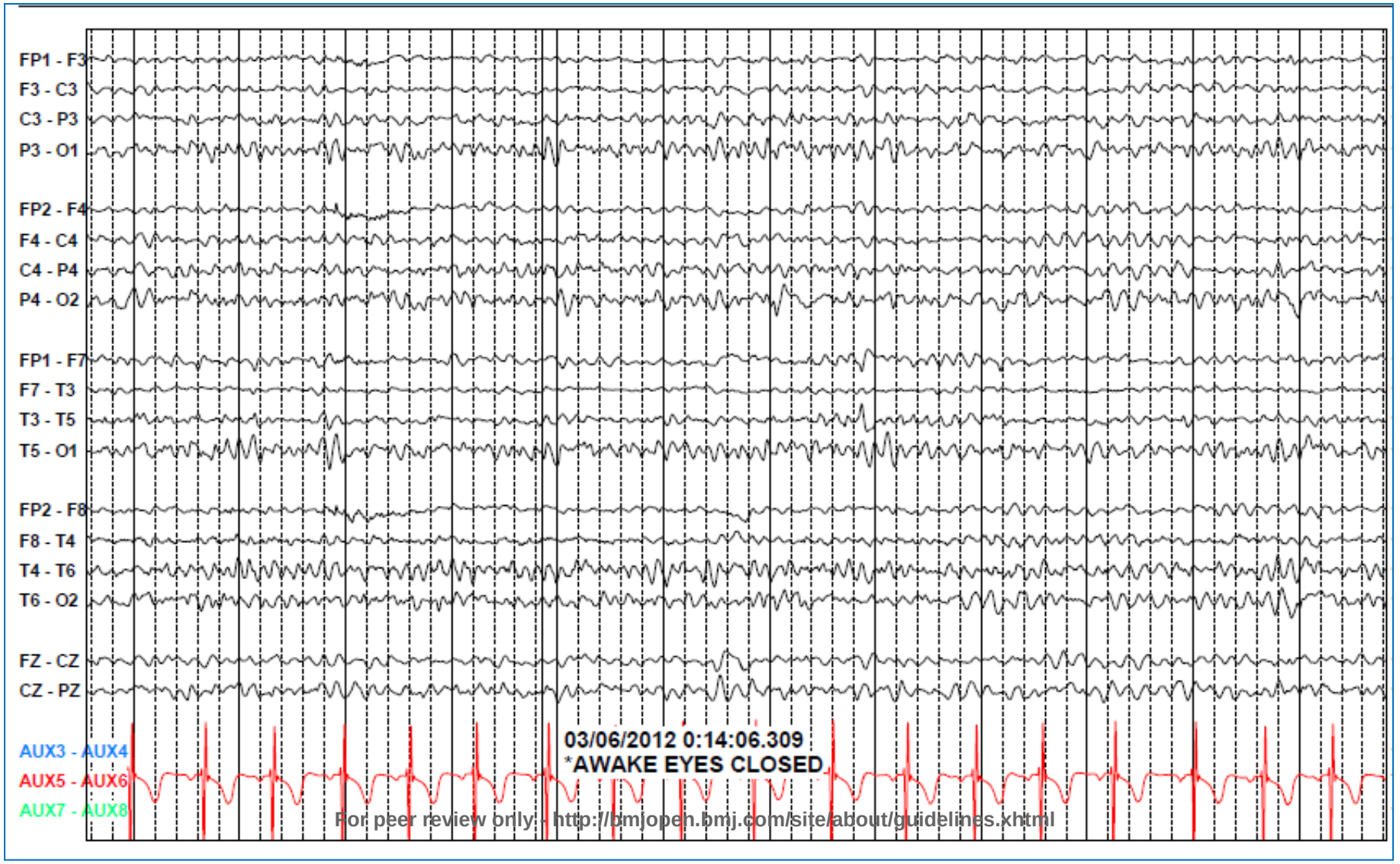
Figure 3 EEG recordings

Figure 3 is an EEG recording of a 12 year old girl. She had head nodding and cognitive impairment. During the recording, interictal epileptiform discharges (spikes and sharp waves) were observed in wakefulness (3a) and during light sleep when increasingly more florid epileptiform discharges were observed. There was no clinical event with this recording (3b).

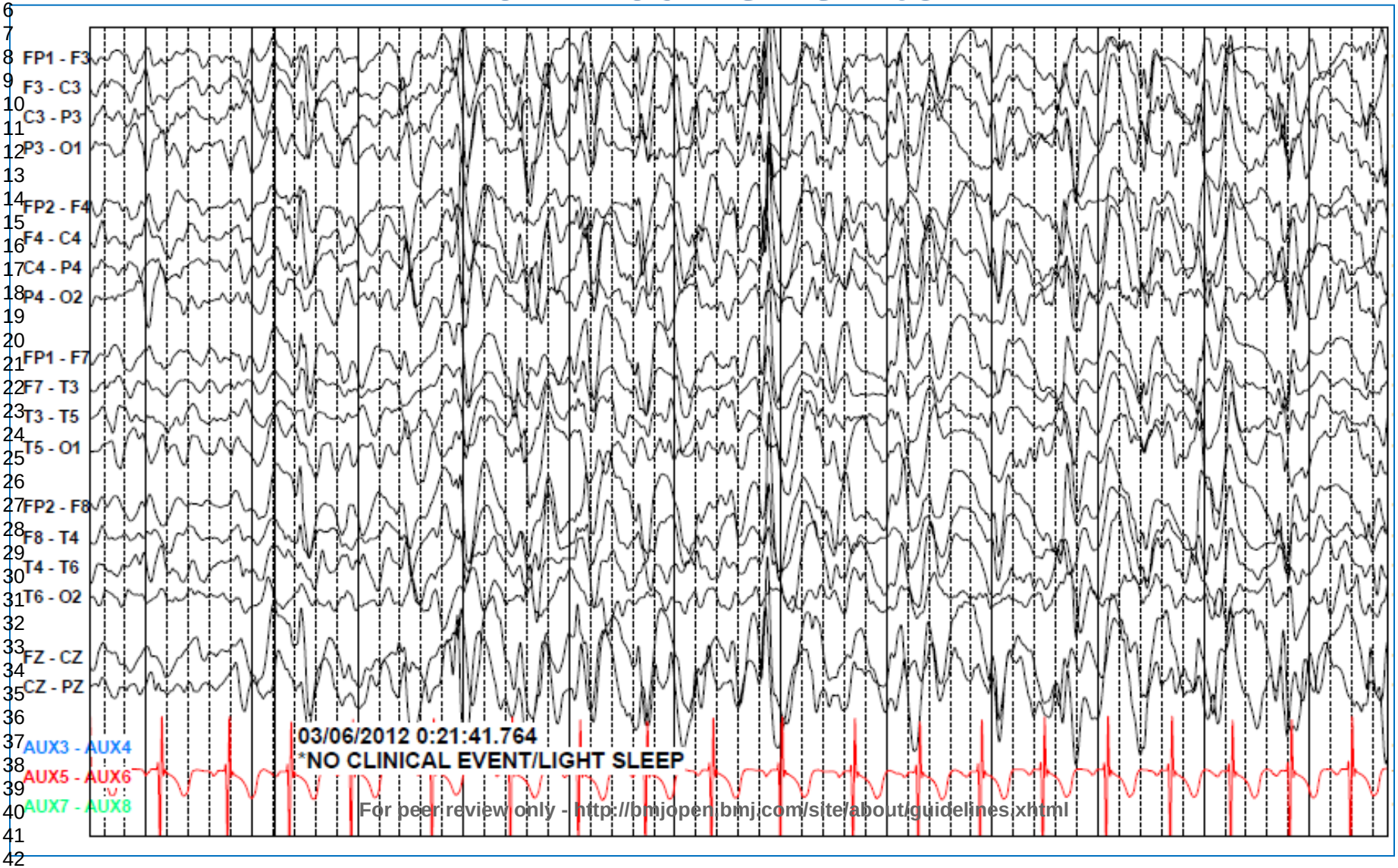
Figure 4 Brain MRI

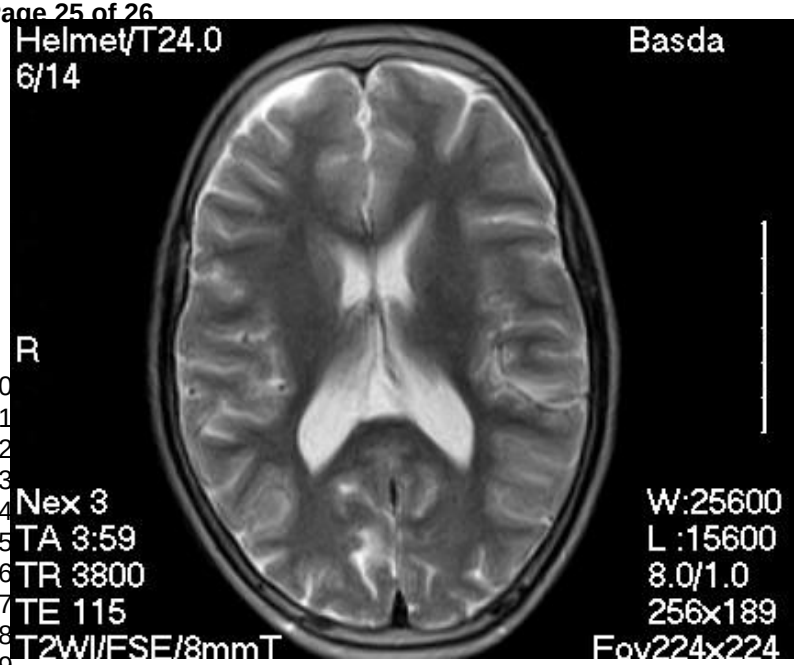
Figure 4 shows T1 and T2 brain MRI images of a 15 year old boy. He had head nodding, myoclonic and absence seizures but no tonic clonic seizures. There is cortical brain atrophy with widening of adjacent sulci but no focal lesions or obvious abnormalities in the hippocampi.

EEG at onset of recording - awake

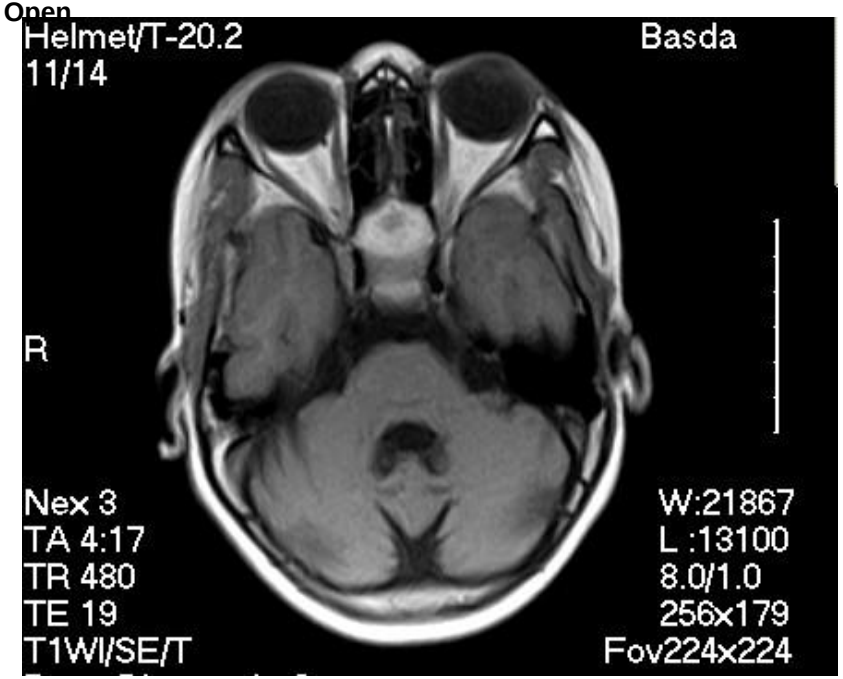


Florid discharges in light sleep, no clinical events





4a



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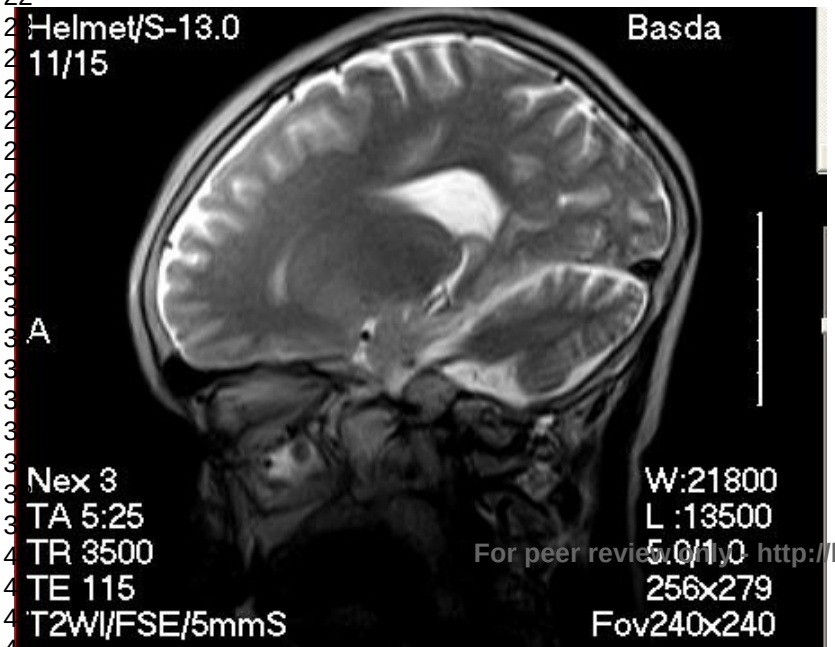

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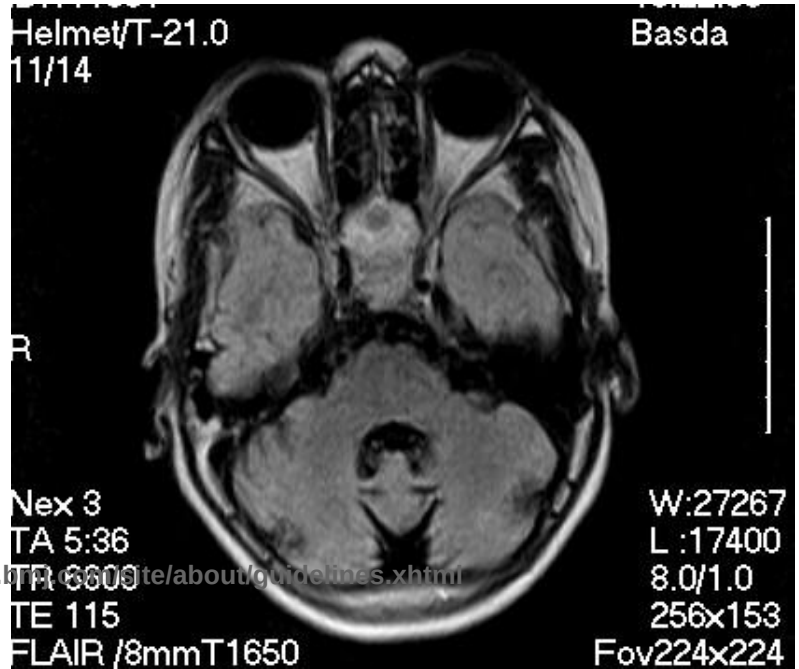

4d

R Idro et al, Nodding Syndrome in Ugandan Children

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	N/A
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	N/A

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4-5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	12-13
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	-
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	7-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-13
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Nodding Syndrome in Ugandan Children - Clinical features, Brain imaging and Complications; an observational case series

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NODDING SYNDROME IN UGANDAN CHILDREN - CLINICAL FEATURES, BRAIN IMAGING AND COMPLICATIONS; AN OBSERVATIONAL CASE SERIES

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ABSTRACT

Objectives: Nodding syndrome is a devastating neurological disorder of uncertain aetiology affecting children in Africa. There is no diagnostic test and risk factors and symptoms that would allow early diagnosis are poorly documented. This study aimed to describe the clinical, electrophysiologic and brain imaging (MRI) features and complications of nodding syndrome in Ugandan children.

Design: Case series

Participants: 22 children with nodding syndrome brought to Mulago National Referral Hospital for assessment.

Outcome measures: Clinical features, physical and functional disabilities, electro-encephalogram (EEG) and brain MRI findings and a staging system with a progressive development of symptoms and complications.

Results

The median age of symptom onset was 6(range 4-10) years and median duration of symptoms was 8.5(range 2-11) years. Sixteen of 22 families reported multiple affected children. Physical manifestations and complications included stunting, wasting, lip changes and gross physical deformities. The bone age was delayed by 2(range 1-6) years. There was peripheral muscle wasting and progressive generalised wasting. Four children had nodding as the only seizure type; 18 in addition had myoclonic, absence and/or generalised tonic-clonic seizures developing 1-3years after the onset of illness. Psychiatric manifestations included wandering, aggression, depression and disordered perception. Cognitive assessment in 3 children demonstrated profound impairment. The EEG was abnormal in all, suggesting symptomatic generalised epilepsy in the majority. There were different degrees of cortical and cerebellar atrophy on brain MRI but no hippocampal changes. Five stages with worsening physical, EEG and brain imaging features were identified: a prodrome, development of head nodding and cognitive decline, other seizure types, multiple complications, and severe disability.

Conclusions

Nodding syndrome is a neurologic disorder that may be characterised as probably symptomatic generalised epilepsy. Clinical manifestations and complications develop in stages which might be useful in defining treatment and rehabilitation. Studies of risk factors, pathogenesis, management, and outcome are urgently needed.

ARTICLE SUMMARY

Article focus

- This paper offers detailed descriptions of the clinical features and complications of nodding syndrome in Ugandan children and the electrophysiologic and brain imaging features.
- It also proposes a clinical staging system for the disease.

Key messages

- Nodding syndrome is an epidemic neurologic disorder affecting children in parts of sub-Saharan Africa that may be characterised as a probable symptomatic generalised epilepsy with features of epileptic encephalopathy.
- Patients progressively develop both physical and functional deficits including multiple seizure types, cognitive and physical decline, malnutrition, and psychiatric features. Five clinical stages could be identified.
- The proposed clinical stages are associated with worsening cortical and cerebellar atrophy on brain imaging and more severe epileptiform and background EEG changes. These stages may be useful in guiding treatment and rehabilitation.

Strengths and limitations of this study

- Although the sample size is small and there is no comparison group, this is one of the few studies so far to have carefully documented the clinical features and complications of nodding syndrome combined with extensive electrophysiology and brain imaging data, describe the natural history and the first to provide a staging system.The study patients, however, may not be representative of the population, as they were not randomly drawn from the community.
- The study did not investigate aetiology and the proposed staging was mainly derived from parental descriptions rather than prospective observations and, therefore, suffers from recall bias.
- The resolution of our brain MRI images is quite low.

BACKGROUND

Nodding syndrome is a devastating neurological disorder of uncertain aetiology described in African children[1]. It was first described in Tanzania in 1960s[2] and subsequent reports have come from Liberia[3], South Sudan[4-6] and Uganda[7 8]. The syndrome is characterized by head nodding determined to be atonic seizures[8] often occurring in association with feeding, a cold breeze or cold weather and complicated by other seizure types, malnutrition and cognitive decline[6 9 10].

In Uganda, almost all affected individuals are from the north of the country where there are an estimated 3,000 cases. The region has for the past 20 years, had instability from rebel activity[11]. As a result, the population was internally displaced into densely populated camps. It is only in the last 5 years that peace returned and population returned to their homes. This region is crossed by two rivers - the *Aswa* and *Pager* Rivers, has high malaria transmission and is endemic for *Onchocerca volvulus*. This parasite has variously been associated with the *Nakalanga* syndrome (a tropical syndrome characterised by short stature and malnutrition)[12-15], epilepsy[16 17] and nodding syndrome[5 9]. This association has, however, been indirect as no O. volvulus contamination of cerebrospinal fluid has been documented[18].

There are only limited descriptions of nodding syndrome[4 5 8-10]. Winkler et al provided the most detailed account of the syndrome to date, describing clinical features in 62 Tanzanian patients and classifying them as either head nodding only or head nodding plus, if they also had other seizure types[9]. Initial symptoms allowing early recognition of the disease, its natural history and potentially modifiable risk factors are poorly characterized. There is no diagnostic test and the current case definition is based solely on clinical criteria. The objective of this study was to describe the clinical, electrophysiologic and brain imaging features and complications of nodding syndrome in Ugandan children and to propose a staging system.

METHODS

Design and setting

This is a case series of 22 Ugandan children with nodding syndrome. The study was conducted in Mulago, the National Referral Hospital in Uganda and teaching hospital for Makerere University College of Health Sciences in Kampala. This hospital provides tertiary level care for patients in a country in which most public healthcare services are paid for by the state.

Participants

Participants were patients with suspected nodding syndrome brought by the Ministry of Health from Kitgum district near the border with South Sudan, to Mulago Hospital in March 2012 for specialist assessments to better understand the syndrome. Kitgum district is the epicentre of the disease and one of the most affected districts in the country. Of the 25 patients brought to Mulago, one young adult (a 23 year old male found to have a brain tumour) and two adolescents (an 18 year old girl with a cerebellar hypoplasia syndrome and a 16 year old boy with history of cerebral malaria at the age of 4 years and subsequent neurologic sequelae) were excluded. The remaining 22 children had probable nodding syndrome and were included in the study. A case of probable nodding syndrome was defined as:

- A child older than 2 years or an adolescent who previously was developing normally
- Two or more episodes of recurrent head nodding occurring spontaneously or consequent to the sight of food or coldness
- With or without other types of seizures, neurological signs, regression in growth or learning disability.

This case definition was revised during the International Meeting on Nodding Syndrome later in 2012.However, all selected patients fulfilled the revised criteria[19].

Permission for the study was obtained from Makerere University School of Medicine Research and Ethics Committee. However, as we had no study protocol prior to the arrival of the patients, clinical care and assessment followed the hospital's standard procedures for routine non-surgical care for children. Verbal parental consent was obtained for all clinical, laboratory and imaging procedures. As is policy, however, parents gave written consent for photography, as this is considered over and above routine care and for any surgical procedures. Parents were specifically made aware that the objective of the assessments was not cure, but a better

understanding of the disease and that the general findings from the evaluation of the group of patients with nodding syndrome would be made available to the wider scientific community in presentations and publications, with the specific aim of improving the care of people affected by the disorder in the future. To this effect, a submission was then made to the Ethics Committee and permission to use results of the investigations subsequently granted.

Study measurements and Procedures

All had detailed clinical, electrophysiologic, and brain imaging assessments and laboratory testing.

Clinical assessment

The history included an inquiry about the time from pregnancy to the onset and the progressive development of symptoms, physical and functional difficulties. The clinical examination included general, nutritional, neurologic, cognitive and mental state assessments. Wasting was defined as weight for height Z score of -<2 and stunting as height for age Z score of -<2. Sexual maturity was assessed using the Tanner Sexual Maturity staging. Patients were classified as having nodding syndrome only or nodding syndrome plus depending on whether they also had other seizure types[9]. X-rays of the left wrist were taken for bone age and reported using a Greulich and Pyle Atlas by a blinded radiologist[20]. Bone growth was considered delayed if it was 2 years below the chronological age. Cognitive functioning was assessed in detail in four children - median age 14.5 (range 13-15) years - two weeks after initiation of sodium valproate using the Kaufman Assessment Battery for Children 2nd Edition (KABC-2). This test has previously been adapted for use in Uganda[21]. All four had had symptoms for longer than five years.

Laboratory procedures

Ten millilitres of blood was drawn for full blood count, ESR, malaria parasites, electrolytes, liver and renal function tests, and HIV testing. Cerebrospinal fluid was examined for cells, glucose, protein, microscopy and bacteriologic culture. In addition, 10 children had a skin snip examined for *Onchocerca volvulus* as previously described[9].

Neurophysiology and imaging

All had a 30 minute EEG recording with an XLTEK EEG system (Optima Medical Ltd, London, UK) using the 10-20 electrode placement system , which was reviewed by a consultant clinical neurophysiologist(SW) in the UK. Brain MRI in T1, T2 and Flair sequences were obtained

without contrast in 19/22 patients using a 0.5Tesla machine (BASDA Medical Apparatus, Guangzhou) and the images also examined in the UK by a Consultant Neuroradiologist (KC).

Natural history and staging

At the end of the first week after patients and carers had acclimatised to the referral hospital environment, the attending clinician sat with each carer and obtained detailed histories of the progressive development and timing of symptoms and complications of nodding syndrome to characterize the natural history. A standardised proforma with a diagrammatic representation of possible events and a linear timeline was used to obtain these descriptions. Information from each patient was plotted on the timeline and later combined with the data from other patients to identify emerging patterns, from which the proposed stages of the disorder were derived.

Treatment

Patients were started on symptomatic treatment (sodium valproate for seizure control, nutritional and physical therapy, counselling and social support) according to national guidelines developed a month earlier[22]. In this protocol, all received sodium valproate starting at 10mg/kg/day. The dose was titrated in 5-10 mg/kg/day increases according to the level of seizure control. Nutritional rehabilitation included Ready to Use Therapeutic Foods (Plumpy'Nut®, Nutriset, Malaunay) and locally prepared food. Occupational and physiotherapy, family counselling and support were provided as appropriate.

Data analysis

Data was analysed using STATA version 12 (STATA Corp, TX). Results are summarised as frequencies, proportions and medians as appropriate. The clinical features, complications and disability were then used to describe treatment and rehabilitation needs. Clinical stages were identified and brain imaging and EEG correlated with the clinical stages.

RESULTS

General features

Nine patients (40.9%) were male. The age range was 12-18 years. The median age at onset of symptoms was 6 (range 4–10) years and the median duration of symptoms was 8.5(range 2-11) years (**Table 1)**. Sixteen of the 22 families reported more than one case (median 2 (range 0–4)**)**. Prior to hospitalisation, all patients had received antiepileptic drug treatment with phenobarbitone, phenytoin or carbamazepine with no clear documentation of benefit. Treatment had often been intermittent and at sub-therapeutic doses.

Striking features on physical examination included stunting, cognitive impairment (on KABC or performance of basic tasks), lip changes **(Figure 1)** and other physical deformities. Several children had burns and scars from burns. The skin was dry, thin and scaly. Extremities, especially the feet, felt cold with a temperature gradient with the trunk, but a normal capillary refill time. Among those with mild lip changes, the lower lip was enlarged with no visible or palpable localised swellings. In progressively more severe cases, the mucosa was deep purple, with soft papular growths and increasingly large, thick bands of tissue. One child, not exposed to sodium valproate previously, had unexplained alopecia.

Table 1 Characteristics of 22 patients with nodding syndrome

ID	Age (years)	Duration of symptoms in yrs	Seizure based classification	Main Psychiatric morbidity	Other prominent complications	EEG Seizure classification
1	14	11	Head nodding plus other seizures types	Behaviour problems Hallucinations	Severe cognitive impairment Burns Lip deformity Severe stunting, with severe wasting Spasticity and contractures with musculoskeletal deformities	Generalised epileptiform discharges
2	13	5	Head nodding plus other seizures types	Hallucinations Aggressive behaviour	Moderate wasting	Generalised epileptiform discharges
3	15	10	Head nodding plus other seizures types	Behaviour problems Aggression Pychosocial disorder	Severe wasting Speech difficulties	Generalised epileptiform discharges
4	14	9	Head nodding only		Severe cognitive impairment Stunting	Generalised epileptiform discharges
5	16	9	Head nodding plus other seizures types	Aggressive behaviour Wandering Hallucinations	Severe cognitive impairment Speech difficulties Moderate wasting	Right temporal discharges

6	14	5	Head nodding plus other seizures types			Generalised epileptiform discharges
7	14	7	Head nodding plus other seizures types		Severe cognitive impairment Lip deformity Severe wasting	Generalised epileptiform discharges
8	18	10	Head nodding plus other seizures types	Aggressive behaviour Hallucinations	Severe cognitive impairment Speech difficulties	Generalised epileptiform discharges
9	18	8	Head nodding plus other seizures types	Psychotic symptoms Behavioural problems	Severe cognitive impairment Lip deformity Speech difficulties Severe wasting	Left temporal discharges
10	16	11	Head nodding plus other seizures types		Moderate wasting Burns Marked lip deformity	Generalised epileptiform discharges
11	15	9	Head nodding plus other seizures types	Depression	Hearing impairment Stunting Burns Musculoskeletal Deformities Severe cognitive impairment Severe wasting	Generalised epileptiform discharges
12	13	8	Head nodding plus other seizures types	Hallucinations		Generalised epileptiform discharges
13	13	3	Head nodding plus other seizures types		Moderate wasting	Generalised epileptiform discharges
14	14	9	Head nodding plus other seizures types	Hallucinations		Generalised epileptiform discharges
15	12	8	Head nodding plus other seizures types		Severe wasting Stunting Kyphosis, pectus deformity Generalised skin changes	Generalised epileptiform discharges
16	12	2	Head nodding only		Stunting Severe wasting	Generalised epileptiform discharges
17	14	8	Head nodding plus other seizures types	Post- ictal aggression Wandering	Severe cognitive impairment Stunting Lip deformity, Ataxia Speech difficulties Spasticity and contractures with musculoskeletal deformities Moderate wasting	Generalised epileptiform discharges
18	18	6	Head nodding plus other seizures types		Moderate wasting	Generalised epileptiform

						discharges
19	12	4	Head nodding only		Moderate wasting Stunting	Generalised epileptiform discharges
20	15	9	Head nodding only		Stunting	Generalised epileptiform discharges
21	15	9	Head nodding plus other seizures types		Severe cognitive impairment Lip deformity Speech difficulties Stunting Moderate wasting Spasticity with contractures and severe musculoskeletal deformity, wasting/dystrophy	Generalised epileptiform discharges
22	15	9	Head nodding plus other seizures types	Behavioural problems Aggression	Severe cognitive impairment Stunting Burns Episodes of disorientation Speech difficulties	Generalised epileptiform discharges

Growth and sexual maturity

Sixteen of the 22 children were wasted and nine stunted. Increasingly more severe wasting was observed with a longer duration of symptoms. Thus, patients with moderate wasting had symptoms lasting 3-6 years, while severe wasting was more common among those with symptoms lasting longer than 7 years. Ten had sexual maturity assessed; 3/10 children (aged 12, 13, 14 years) scored Tanner Stage 3. All remaining 7 children (ages 12-17 years) were either Tanner Stage 1 or 2. The bone age was delayed by a median 2(range 1-6) years.

Musculoskeletal findings

Almost all had peripheral muscle wasting with progressively flat feet and hands, thin cylindrical digits and increasing generalised wasting. Other physical changes included kyphosis and pectus deformities of the chest. Flexion limb deformities were seen in patients with severe disability (**Figure 2).**

Neurological, cognitive and behavioural features

Seizures

Other than head nodding, a variety of other seizure types were described in 18/22 patients - including absence, complex partial, myoclonic, and tonic-clonic seizures. *Head nodding*

Nodding was precipitated by food in 16/22 children. In 4/22, it was associated with cold weather or a cold breeze, while in 13/22 it developed spontaneously. Nodding episodes came in clusters occurring during both the day and the night and were characterised by repetitive flexion and forward drop of the head. The clusters of head nodding lasted several seconds to minutes. Some children became unresponsive and stared blankly with each cluster of nodding, stopped feeding or drooled saliva.

Initially head nodding was the predominant seizure type but as the disease progressed, generalised tonic-clonic seizures became more prominent. Myoclonic seizures were not often reported, but were observed in several children while in hospital. One such child had a prolonged cluster of nodding with concurrent myoclonic jerks involving both upper limbs, lasting about 10 minutes. In a second child, similar myoclonic jerking was followed by a generalised tonic-clonic seizure. Several children had sudden falls, sustaining facial and head injuries.

Four children experienced paroxysmal events associated with fear, panic and visual hallucinations. We could not obtain clear descriptions of the images seen by two. The third child would shout and run with onset of the hallucinations and the forth reported seeing a person with knives whose intention ‘was to kill her’. None of these events was captured on EEG.

Other neurologic complications

Focal neurological signs were uncommon. There were no obvious cranial nerve palsies. However, six children were lethargic with an apathetic and expressionless face or ‘myopathic facies’. Three of the six drooled saliva while two had very slow speech and repeated epileptiform (spike and wave) discharges on EEG. The deep tendon reflexes were increased in a minority of patients. In the majority, however, the reflexes were either normal or reduced.

Vision, hearing and speech difficulties

No parent reported visual impairment and we did not test visual acuity but hearing impairment was reported in one child. Speech difficulties were reported in 10/22 children. These included immature speech for age and slow, slurred or dysarthric speech. Two children were mute but retained gestural ability and receptive language.

Behaviour and psychiatric features and complications

The earliest psychiatric manifestation was wandering behaviour or running away. Because of concerns about injury or getting lost, some parents tied up the patients to restrain them in the home. Aggression, particularly towards familiar people, was reported in 6/22 cases, manifesting 3-6 years after onset of nodding. In two children, the onset was concurrent with wandering behaviour. Five children had sleep difficulties and at least 8/22 had moderate to severe mood problems with one clinically depressed.

Cognitive function

All 22 children had cognitive difficulties and were out of school. Academic performance declined with symptom onset; as symptoms increased, pupils started getting poorer grades and were eventually withdrawn from school within 2-4 years of disease onset. Three of the 4 children who had cognitive functioning assessed using the KABC-2 responded to the test instructions. The fourth child did not respond at all. All 3 children had severe cognitive impairment (**Table 2**).

Table 2: Cognitive function on the KABC 2nd Edition in 3 children two weeks after initiation of sodium valproate

Cognitive Domain	Patient 1 Male 13 years		Patient 2 Male 15 years		Patient 3 Male 15 years	
	Test Score	Age equivalent in years	Test Score	Age equivalent in years	Test Score	Age equivalent in years
Working memory	8	<5	7	<5	21	=5
Planning	7	<8	1	<5	3	<5
Learning	28	<5	25	<5	54	=5
Visual spatial	0	<5	0	<5	31	<5
Knowledge	11	<5	5	<5	52	<8

Laboratory findings

The mean haemoglobin was 12.4 (range 10.8–14.8) g/dl and the mean red cell volume was 81.4 (range 65.8-89.1) fl. Five children had iron deficiency anaemia. The total white blood cell and platelet counts were normal but 10/22 children had eosinophilia, median eosinophil count 0.4 (range 0.1 – 1.9) x 10^9/L. The ESR was high in 17/22 children with a median of 28.5 (range 5-90) mm in the first hour. Other than mild elevations of gamma GT, the liver and renal function was normal. All tested negative for malaria on admission to Mulago, although one subsequently developed malaria in the third week of hospitalisation. Nine children had osteopenia on x ray but only one had hypocalcaemia and four hypophosphataemia. Creatine kinase levels were normal in all children and all tested HIV negative. Cerebrospinal fluid total protein, cells and glucose were all normal and all bacteriologic cultures had no growth. Three out of 10 patients had *O.volvulus* microfilaria on the skin snip. Microfilaria density was, however, not reported.

EEG

The routine diagnostic EEG was abnormal in all cases. The background activity showed a generalised excess of slow activity mainly in the conventional theta and delta frequency ranges. Generalised inter-ictal epileptiform activity was observed in all but two patients, in whom there were focal temporal discharges (unilateral in one and bilateral in the second). All patients with generalised epileptiform activity had high amplitude spikes or sharp waves, some associated with slow wave activity and often occurring in irregular bursts rather than runs (**Figure 3)**. There was no consistent frequency to this. The discharges had bilateral fronto-temporal or fronto-centro-temporal emphasis, but some were more generalised and increased in frequency in light sleep. There was a clear gradation from mild to more severe background abnormalities and epileptiform activity. No overnight recordings were performed. The EEG findings suggested symptomatic generalised epilepsy in 20 and symptomatic focal epilepsy in the remaining 2.

Brain imaging

Brain MRI without contrast was performed in 19/22 patients. The imaging showed different degrees of cortical and cerebellar atrophy. No focal cerebral cortical or hippocampal changes were observed (**Figure 4)**. Cerebellar disease was evident in the majority of cases, but among patients with especially generalised cortical atrophy, there was a suggestion of more atrophy in the occipital lobes or the parieto-occipital regions than anteriorly.

Disease progression

Five stages with deteriorating seizures, neuro-cognitive and psychiatric disability were identified: a prodrome; development of head nodding and cognitive impairment; other seizure types; multiple complications and severe debilitation (**Panel 1**).

Panel 1: A mum's description of the sequential chronology of symptoms and disease progression in her 18 year old daughter.

"She was growing well until the age of 8 years when symptoms of nodding began. The head nodding is triggered by food. When food is given, she freezes with it in her hand, stares blankly into space with a fixed gaze, and then nods repeatedly for a time which varies with each episode but the maximum time was initially 5 minutes. The symptoms got worse with time and about 6 years later, the nodding symptoms were immediately followed by or associated with big seizures during which the whole body shook. She would drool saliva, foam around the mouth and loses consciousness. After the big seizure, she would sleep and on waking is often weak and sometimes disoriented. On some nights, she reports seeing a figure that holds a knife and wants to kill her. She is distressed by her illness and gets embarrassed on waking if she had a seizure in public. She is very quiet but sometimes aggressive. Overtime, her speech has become sluggish. Although she is 18 years old, she still has childish behaviour which is evident as she speaks. Her father died following a febrile illness. She has six siblings two of who have similar symptoms."

Stage 1 The prodromal period

This poorly defined and short-lived period was reported in four patients. The earliest symptoms included "dizziness" and increasing inattention. The children were excessively sleepy, lethargic and would sometimes stare blankly during meals.

Stage 2 Development of head nodding

Among the four patients reporting prodromal symptoms, head nodding developed within 6 weeks of the prodrome. In the majority, however, the initial feature was an abrupt onset of nodding. Subsequently, parents reported declining cognitive abilities and behaviour difficulties. Disease progression however appeared to arrest in these four.

Stage 3 Development of other seizure types

Apart from the four children with nodding only, 18 children developed other seizure types including absence, complex partial, myoclonic and generalised tonic-clonic seizures. One child developed generalised tonic clonic seizures almost simultaneously with the nodding. In the others, however, additional seizure types developed 1-3 years after initial symptoms. It was around this time that almost all school going children dropped out of school.

Stage 4 Development of multiple complications

Multiple complications developed 4-8 years after the initial symptoms, associated with marked regression in achievement. These consisted of deteriorating behaviour and psychiatric symptoms and a decline in motor, speech and other cognitive functions. Some patients developed physical deformities including kyphosis, limb and pectus deformities (**Figure 2)**. Some sustained severe facial injuries with "drop attacks" and burns. Those who were still independently mobile would wander about or run away and were prone to getting lost. Changes in the architecture of the lower lips (**Figure 1**) also occurred at this time. With disrupted and poor feeding, the children became severely wasted.

Stage 5 Severe disability

These children have little, if any, 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. Some had contractures around the major joints.

Patients with head nodding only had less cortical and cerebellar atrophy on brain MRI compared to those with multiple complications. In addition, there was a clear gradation from milder to more severe epileptiform and background EEG abnormalities in patients with the later clinical stages of the disease.

Response of seizures to sodium valproate

The patients had previously been on mostly low doses of various anti-epileptic drugs including phenytoin, phenbarbitone and carbamazepine. In conformity with proposed national guidelines, all were started on sodium valproate and the other anti-epileptic drugs weaned off. Prior to this, a 24 hour seizure count was obtained and this was repeated 14 days later. Overall, there was a 57% reduction in total seizures including clusters of nodding. The median total daily number of seizures reduced from 5 (range 2–14) on admission to 2 (range 0-8) 14 days after initiation of sodiumvalproate. Concurrent improvements were also seen on the EEG with substantially reduced or absent interictal discharges in 3/5 patients who had repeat recordings on the day of assessment **(Figure 3)**.

DISCUSSION

Recently, there have been media reports of “a mysterious disease” baffling scientists – the nodding syndrome.[7 23 24] There are many uncertainties about this newly recognized disorder: what is the cause, the pathogenesis, disease classification, clinical spectrum and treatment? In this paper, we describe the clinical features and complications of nodding syndrome in Ugandan children, together with the EEG and brain imagingappearances. Our findings suggest that nodding syndrome is a neurologic disorder characterised by a symptomatic generalised epilepsy.

Clinical features and complications

Nodding syndrome in Ugandan children manifests with head nodding, cognitive dysfunction, psychiatric features, and/or multiple seizure types. It may be complicated by stunted growth, pubertal delay, wasting, motor decline and physical deformities. The earliest manifestation is a poorly defined prodrome followed within weeks by head nodding. In the later stages, there is cognitive dysfunction, psychiatric disturbance, and severe muscle wasting and musculoskeletal deformity. Delayed physical growth, bone age and sexual maturity are common in affected children. This may partly be a result of delayed puberty, since most were in Tanner Stage 2. Pubertal delay may be secondary to chronic illness, poor nutrition and/or psychosocial deprivation. If so, improved nutrition, a supportive environment and symptom control should lead to improved growth and the initiation of puberty.

The progressive stages of the disorder appear to reflect the natural progression of an epileptic encephalopathy. In Stage 1, there are brief seizures, while by Stage 3 uncontrolled seizures prevent the child from continuing in school. In Stage 4 a high seizure burden contributes to regression, which together with ensuing poor nutrient intake leaves a severely disabled child by Stage 5, when multiple factors impair functioning.

The clinical features in Ugandan children are as severe as in South Sudanese children,[6] but may be more severe than in Tanzanian patients[9]. Despite similar age of onset and duration of symptoms, only 18% of Ugandan children had the milder nodding only variant, compared to 45% in Tanzania; all our patients had abnormal interictal background EEG compared to 60% in Tanzania. Ugandan children also had more severe cognitive impairment and a much greater burden and variety of seizures. These differences may suggest a variation in the presentation of

the disease by region. Family clustering in all three countries, however, suggests a common exposure factor.

Aetiology and pathogenesis

The aetiology of nodding syndrome and pathogenesis of the complications remain unknown. A variety of viral central nervous system infections have been screened for on PCR but no association has been demonstrated[19]. An association with infestation with *Onchocerca Volvulus* has been reported in some series,[5 9] but has not been evident in other studies.[18 25]. Other aetiologic considerations have included toxic brain injury, inflammatory brain disease, a slow virus infection or prion disease, an atypical mitochondrial disease or other genetic disorder. Repeated severe psychological trauma has also been proposed as a mechanism[26]. Earlier studies by the Ugandan Ministry of Health and the US Centers of Disease Control found a higher proportion of cases with low serum vitamin B6 compared to controls. Although unlikely, the possibility was raised that nodding syndrome could be an atypical form of pyridoxine dependent epilepsy. Studies to explore this hypothesis further are awaited[27].

Children with the syndrome show some features reminiscent of prion protein disease, including motor and cognitive dysfunction, epilepsy, behaviour and psychiatric morbidity. However, other features commonly seen in prion disease - such as extrapyramidal involvement and cortical blindness - have not been reported. The age of onset of symptoms is also much younger and progression much slower[28]. The brain imaging and EEG findings too are not suggestive of prion disease. Nevertheless, brain biopsy or autopsy studies would be important in excluding prion disease.

The brain MRI findings might suggest viral encephalitis, a para-infectious phenomenon (such as an antibody- mediated channelopathy) or even a neurotoxin as possible aetiologies. A genetic disorder or metabolic disease is also possible. Future studies should also consider the recently described auto-immune encephalitides. Among Tanzanian patients, hippocampal gliosis, probably from inflammation, was described in some patients[9]. Although this could partly explain the cognitive difficulties, we did not observe such lesions, even in the sub-group with more severe cognitive impairment.. We consider that an epileptic encephalopathy is more likely. The background EEG in all 22 cases showed a generalized excess of theta and slow activity. Prolonged EEG recording (including during sleep) with detailed neuropsychological testing and functional brain imaging may help with understanding the pathogenesis of cognitive decline.

Study limitations

Our patients may not be a representative sample, as they were not drawn randomly from the community. The study did not investigate aetiology and the proposed staging was derived primarily from parental descriptions rather than prospective observations and so may be influenced by recall bias. We only performed routine diagnostic EEGs, rather than prolonged recordings which are important in investigating associations between seizures and cognitive dysfunction. The resolution of our MRI images is also quite low.

CONCLUSIONS

Nodding syndrome is a neurologic disorder that is complicated by multiple physical and functional disabilities and may be considered as symptomatic generalised epilepsy. Assessment and care should be provided by a multidisciplinary team. Studies of aetiology, pathogenesis, evidence- based treatment and rehabilitation strategies are urgently needed.

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Author contributions

RI, ROO, AKM, HAT, TPW, PB, JN1, SBM, ADM, HN, , EM, JN2, SK, JRA and JKT all participated in patient care and performed the different assessments. ROO, AKM, HAT and SBN were in-charge of daily care, TPW and EM performed the growth and sexual staging assessments, JN1 the psychiatric assessments, HN the nutrition assessment, SW reported the EEG recordings, KC the brain MRI and RI wrote the first draft. All provided a critical review of the manuscript.

Conflict of Interest

The authors report no competing interests.

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Figure legends

Figure 1 Lip changes

The figure shows changes in the lips with increasing distortion. In patients with mild involvement, the lower lip is enlarged but with no visible or palpable swellings. With more severe involvement, there is deep purple discolouration of the mucosa, soft papular growths and increasingly larger and thicker bands of tissue. Other oral abnormalities included lacerations and loss of teeth from injuries.

Figure 2 Muscle wasting, deformities and contractures

Figure 2 shows wasting of the muscles of the foot, knee and foot flexion deformities and contractures, pectus deformity of the chest and kyphosis. Such marked deformities were seen with increasing symptom duration.

Figure 3 EEG recordings

Figure 3 is an EEG recording of a 12 year old girl. She had head nodding and cognitive impairment. During the recording, interictal epileptiform discharges (spikes and sharp waves) were observed in wakefulness (3a) and during light sleep, when more prominent epileptiform discharges were evident. There was no apparent clinical change with these discharges (3b).

Figure 4 Brain MRI

Figure 4 shows T2-weighted brain MRI images in the axial (Fig 4a, 4b) and sagittal (Fig 4c, 4d) plane showing marked cerebellar atrophy and generalised cerebral atrophy.

NODDING SYNDROME IN UGANDAN CHILDREN - CLINICAL FEATURES, BRAIN IMAGING AND COMPLICATIONS; AN OBSERVATIONAL CASE SERIES

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ABSTRACT

Objectives: Nodding syndrome is a devastating neurological disorder of uncertain aetiology affecting children in Africa. There is no diagnostic test and risk factors and symptoms that would allow early diagnosis are poorly documented. This study aimed to describe the clinical, ~~neurophysiologic~~electrophysiologic and brain imaging (MRI) features and complications of nodding syndrome in Ugandan children.

Design: Case series

Participants: 22 children with nodding syndrome brought to Mulago National Referral ~~h~~Hospital for assessment.

Outcome measures: Clinical features, physical and functional disabilities, electro-encephalogram (EEG) and brain MRI findings and a staging system with a progressive development of symptoms and complications.

Results

The median age of symptom onset was 6(range 4-10) years and median duration of symptoms was 8.5(range 2-11) years. Sixteen of 22 families reported multiple affected children. Physical manifestations and complications included stunting, wasting, lip changes and gross physical deformities. The bone age was delayed by 2(range 1-6) years. There was peripheral muscle wasting and progressive~~ly,~~ generalised wasting. Four children had nodding as the only seizure type; 18 in addition had myoclonic, absence and/or generalised tonic-clonic seizures developing 1-3years ~~in during the course~~ after the onset of illness. Psychiatric manifestations included wandering, aggression, depression and disordered perception. Cognitive assessment in 3 children demonstrated profound impairment. The EEG was abnormal in all, suggesting symptomatic ~~generalized~~ generalised epilepsy in the majority. There were different degrees of cortical and cerebellar atrophy on brain MRI but no hippocampal changes. Five stages with worsening physical, EEG and brain imaging features were identified: a prodrome, development of head nodding and cognitive decline, other seizure types, multiple complications, and severe ~~debilitation~~disability.

Conclusions

Nodding syndrome is a neurologic disorder that may be characterised as probably symptomatic generali~~z~~sed epilepsy. Clinical manifestations and complications develop in stages which might be useful in defining treatment and rehabilitation. Studies of risk factors, pathogenesis, management, and ~~long term~~ outcome are urgently needed.

ARTICLE SUMMARY

Article focus

- This paper offers detailed descriptions of the clinical features and complications of nodding syndrome in Ugandan children and the ~~neurophysiologic~~electrophysiologic and brain imaging features.
- It also proposes a clinical staging system for the disease.

Key messages

- Nodding syndrome is an epidemic neurologic disorder affecting children in parts of sub-Saharan Africa that may be characterised as a ~~probably~~ probable symptomatic ~~generalized~~ generalised epilepsy ~~and~~ with features of ~~an~~ epileptic encephalopathy.
- Patients progressively develop both physical and functional deficits including multiple seizure types, cognitive and physical decline, malnutrition, and psychiatric features. Five ~~such~~ clinical stages could be identified.
- The proposed clinical stages are associated with worsening cortical and cerebellar atrophy on brain imaging and more severe epileptiform and background EEG changes. These stages may be useful in guiding treatment and rehabilitation.

Strengths and limitations of this study

- ~~•~~ Although the sample size is small and there is no comparison group, this is one of the few ~~the first study~~ studies so far to have carefully documented ~~a~~ the clinical features ~~range of co-morbidities~~ and complications ~~in~~ of nodding syndrome combined with extensive electro~~neuro~~physiology and brain imaging data, describe the natural history and the first to provide a staging system~~, and combine these with extensive neurophysiology and brain imaging data~~.
- The study patients, however, may not be representative of the population, as they were not randomly drawn from the community.
- The study did not investigate aetiology and the proposed staging was ~~majorly~~ mainly derived from parental descriptions rather than prospective observations and, therefore, suffers from recall bias.
- The resolution of our brain MRI images is quite low.

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BACKGROUND

Nodding syndrome is an emerging and devastating neurological disorder of uncertain aetiology affecting described in African children[1] in sub-Saharan Africa. Current estimates suggest there are about 10,000 affected children. The syndrome It was first reporteddescribed in Tanzania in 1960's[2] and subsequent reports have come from Liberia[3], South Sudan[4-6] and Uganda[7 8]. It The syndrome is characterized by head noddings, now determined to be as atonic seizures[8], often occurring in association with feeding, a cold breeze or cold weather and development of otherscomplicated by other seizure types, malnutrition and cognitive decline[6 9 10].

In Uganda, almost all affected individuals are from the north of the country where there are close to an estimated 3,000 cases. The region has for the past 20 years, had instability from rebel activity[11]. As a result, the population was internally displaced into densely populated camps. It is only in the last 5 years that peace returned and population returned to their homes. This region is crossed by two rivers - the *Aswa* and *Pager* Rivers; with has high malaria transmission and is endemic for *Onchocerca volvulus*. This parasite has variously been associated with the *Nakalanga* syndrome (a tropical syndrome characterised by short stature and malnutrition)[12-15], epilepsy[16 17] and nodding syndrome[5 9]. This association has, however, been indirect as no O. volvulus contamination of cerebrospinal fluid has been documented[18]. The region has also, for the past 20 years, had instability due to rebel activity(Wendo 2003). As a result, the population was internally displaced into densely populated camps. It is only in the last 5 years that peace has returned and people returned to their homes.

There are only limited descriptions of nodding syndrome[4 5 8-10]. Winkler et al provided the most detailed description account of the syndrome to date, describing clinical features in 62 Tanzanian patients and classifying them as either head nodding only or head nodding plus, if they in addition also had other seizure types[9]. Initial symptoms that would allowing early recognition of the disease, theits natural history and potentially modifiable risk factors to identify any modifiable factors are *however only* poorly understooddescribedcharacterized. There is no diagnostic test and the current case definition is based solely on clinical criteria only. The objective of this study was to describe the clinical, neurophysiologic electrophysiologic and brain imaging features and complications of nodding syndrome in Ugandan children and to propose a staging system.

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METHODS

Design and setting

This is a case series of 22 Ugandan children with nodding syndrome. The study was conducted in Mulago, the National Referral ~~h~~Hospital in Uganda and teaching hospital for Makerere University College of Health Sciences in Kampala. This hospital provides tertiary level care for patients in a country in which most public healthcare services are paid for by the state.

Participants

Participants were patients with suspected nodding syndrome brought by the Ministry of Health from Kitgum district near the border with South Sudan, to Mulago Hospital in March 2012 for specialist assessments to better understand the syndrome. Kitgum district is the epicentre of the disease and one of the most affected districts in the country. Of the 25 patients brought to Mulago, one young adult (a 23 year old male found to have a brain tumour) and two adolescents (an 18 year old girl with a cerebellar hypoplasia syndrome and a 16 year old boy with history of cerebral malaria at the age of 4 years and subsequent neurologic sequelae) were excluded. The remaining 22 children had probable nodding syndrome and were included in the study. ~~Then, a~~ A case of probable nodding syndrome was defined as:

- A child older than 2 years or an adolescent who previously was developing normally~~,~~
- ~~Presents with two~~ Two or more episodes of recurrent head nodding occurring spontaneously or consequent to the sight of food or coldness
- With or without other types of seizures, neurological signs, regression in growth or ~~mental retardation~~ learning disability.

This case definition was revised during the International Meeting on Nodding ~~s~~Syndrome later in 2012. ~~All the same~~However, all selected patients ~~still~~ fulfilled the revised criteria[19].

Permission for the study was obtained from Makerere University School of Medicine Research and Ethics Committee. However, as we had no study protocol prior to the arrival of the patients ~~and so~~, clinical~~patient~~ care and assessment~~s~~ followed the hospital's standard procedures for routine non-surgical care for children. ~~Thus, verbal~~ Verbal parental consent was obtained for all clinical, laboratory and imaging procedures. As is policy, however, parents ~~provided~~ gave written consent for photography, as this is considered over and above routine care and for any surgical procedures. Parents were specifically made aware that the objective of the

assessments was not cure, but a better understanding of the disease and that the general findings from the evaluation of the group of patients with nodding syndrome , ~~results of investigations will~~ would be made available to the wider scientific community in presentations and publications, with the specific aim of improving the care of people affected by the disorder in the future. To this effect, a submission was then made to the Ethics Committee and permission to use results of the investigations subsequently granted.

Study measurements and Procedures

All had detailed clinical, ~~neurophysiologic~~electrophysiologic, and brain imaging assessments and laboratory testing.

Clinical assessment

The history included an inquiry ~~of~~ about the time from pregnancy to the onset and the progressive development of symptoms, physical and functional difficulties. The ~~physical~~ clinical examination included ~~the~~ general, nutritional[9], neurologic, cognitive and mental state assessments. Wasting was defined as weight for height Z score of -<2 and stunting as height for age Z score of -<2. Sexual maturity was assessed using the Tanner Sexual Maturity staging. Patients were classified as having nodding syndrome only or nodding syndrome plus depending on whether they~~if they in addition~~ also had ~~complications such as a report of~~ other seizure types ~~, neurologic and clinically evident cognitive decline, physical and functional difficulties~~. X-rays of the left wrist were taken for bone age and reported using a Greulich and Pyle Atlas by a blinded radiologist[20]. Bone growth was considered delayed if it was 2 years below the chronological age. Cognitive functioning was assessed in detail in four children - median age 14.5 (range 13-15) years - two weeks after initiation of sodium valproate using the Kaufman Assessment Battery for Children 2nd Edition (KABC-2). This test has previously been adapted ~~to~~ for use in Uganda[21]. All four had had symptoms for longer than five years.

Laboratory procedures

Ten millilitres of blood was drawn for full blood count, ESR, malaria parasites, electrolytes, liver and renal function tests, and HIV testing. Cerebrospinal fluid was examined for cells, glucose, protein, microscopy and bacteriologic culture. In addition, 10 children had a skin snip examined for *Onchocerca volvulus* as previously described[9].

Neurophysiology and imaging

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All had a 30 minute EEG recording with an XLTE~~C~~K EEG system (Optima Medical Ltd, London, UK) using the 10-20 electrode placement system ~~and the recording~~ , which was ~~examined~~ reviewed by a consultant ~~neurophysiologist electrophysiologist~~ clinical neurophysiologist(SW) in the UK. Brain MRI in T1, T2 and Flair sequences were obtained without contrast in 19/22 patients using a 0.5Tesla machine (BASDA Medical Apparatus, Guangzhou) and the images also examined in the UK by a Consultant Neuro-radiologist (KC).

Natural history and staging

At the end of the first week after patients and carers had acclimatised to the referral hospital environment, the attending clinician sat with each carer and obtained detailed histories of the progressive development and timing of symptoms and complications of nodding syndrome to ~~describe~~ characterize the natural history. A standardised proforma with a diagrammatic representation of possible events and a linear timeline was used to obtain these descriptions. Information from each patient was plotted on the timeline and ~~these~~ later combined with ~~that of~~ the data from other patients to identify emerging patterns, from which the proposed stages of the disorder were ~~then~~ derived.

Treatment

Patients were started on symptomatic treatment (sodium valproate for seizure control, nutritional and physical therapy, counselling and social support) according to national guidelines developed a month earlier[22]. In this ~~management~~ protocol, all received sodium valproate starting at 10mg/kg/day. The dose was titrated in 5-10 mg/kg/day increases ~~with~~ according to the level of seizure control. Nutritional rehabilitation included Ready to Use Therapeutic Foods (Plumpy'Nut®, Nutriset, Malaunay) and locally prepared food. Occupational and physiotherapy, family counselling and support were provided as appropriate.

Data analysis

Data was analysed using STATA version 12 (STATA Corp, TX). Results are summarised as frequencies, proportions and medians as appropriate. The clinical features, complications and disability were then used to describe treatment and rehabilitation needs. Clinical stages were identified and brain imaging and EEG correlated with the clinical stages.

RESULTS

General features

Nine patients (40.9%) were male. The age range was 12-18 years. The median age at onset of symptoms was 6 (range 4–10) years and t. The the median duration of symptoms was 8.5(range 2-11) years (. **Table 1**). Sixteen of the 22 families reported multiple casesmore than one case; (median 2 (range 0–4), **Table 1**). Prior to hospitalisation, all patients had received varying but mostly sub-therapeutic and intermittent antiepileptic drug treatment with phenobarbitone, phenytoin or carbamazepine with no clear documentation of benefit. Treatment had often been intermittent and at sub-therapeutic doses.

Striking features on physical examination included stunting, cognitive impairment (on KABC or performance of basic tasks), lip changes **(Figure 1)** and with or without other physical deformities. Several children had burns and scars from falls into fireburns. The skin was dry, thin and scaly. Extremities, especially the feet, felt cold with a temperature gradient with the trunk, but a normal capillary refill time. There were striking changes of the lower lip **(Figure 1)**. Among those with In mild lip changases, the lower lip was enlarged with no visible or palpable localised swellings. In progressively more severe cases, the mucosa was deep purple, with soft papular growths and increasingly large, thick bands of tissue. One child, not exposed to sodium valproate previously, had unexplained alopecia.

Table 1 Characteristics of 22 patients with nodding syndrome

ID	Age (years)	Duration of symptoms in yrs	Seizure based classification	Main Psychiatric morbidity	Other prominent complications	EEG Seizure classification
1	14	11	Head nodding plus other seizures types	Behaviour problems Hallucinations	Severe cognitive impairment Burns Lip deformity Severe stunting, with severe wasting Motor difficultiesSpasticity and contractures with musculoskeletal deformities and contractures	Generalised epileptiform discharges
2	13	5	Head nodding plus other seizures types	Hallucinations Aggressive behaviour	Moderate wasting	Generalised epileptiform discharges
3	15	10	Head nodding plus other seizures types	Behaviour problems Aggression Pycho-social disorder	Severe wasting Speech difficulties	Generalised epileptiform discharges
4	14	9	Head nodding only		Severe cognitive impairment	Generalised epileptiform

					Stunting	discharges
5	16	9	Head nodding plus other seizures types	Aggressive behaviour Wandering Hallucinations	Severe cognitive impairment Speech difficulties Moderate wasting	Right temporal discharges
6	14	5	Head nodding plus other seizures types			Generalised epileptiform discharges
7	14	7	Head nodding plus other seizures types		Severe cognitive impairment Lip deformity Severe wasting	Generalised epileptiform discharges
8	18	10	Head nodding plus other seizures types	Aggressive behaviour Hallucinations	Severe cognitive impairment Speech difficulties	Generalised epileptiform discharges
9	18	8	Head nodding plus other seizures types	Psychotic symptoms Behavioural problems	Severe cognitive impairment Lip deformity Speech difficulties Severe wasting	Left temporal discharges
10	16	11	Head nodding plus other seizures types		Moderate wasting Burns Marked lip deformity	Generalised epileptiform discharges
11	15	9	Head nodding plus other seizures types	Depression	Hearing impairment Stunting Burns Musculoskeletal Deformities Severe cognitive impairment Severe wasting	Generalised epileptiform discharges
12	13	8	Head nodding plus other seizures types	Hallucinations		Generalised epileptiform discharges
13	13	3	Head nodding plus other seizures types		Moderate wasting	Generalised epileptiform discharges
14	14	9	Head nodding plus other seizures types	Hallucinations		Generalised epileptiform discharges
15	12	8	Head nodding plus other seizures types		Severe wasting Stunting Kyphosis, pectus deformity Generalised skin changes	Generalised epileptiform discharges
16	12	2	Head nodding ~~alone~~only		Stunting Severe wasting	Generalised epileptiform discharges
17	14	8	Head nodding plus other seizures types	Post- ictal A~~a~~ggression Wandering	Severe cognitive impairment Stunting Lip deformity, Ataxia Speech difficulties	Generalised epileptiform discharges

					~~Motor difficulties~~Spasticity and contractures with musculoskeletal deformities Moderate wasting	
18	18	6	Head nodding plus other seizures types		Moderate wasting	Generalised epileptiform discharges
19	12	4	Head nodding only~~alone~~		Moderate wasting Stunting	Generalised epileptiform discharges
20	15	9	Head nodding only~~alone~~		Stunting	Generalised ~~symptomatic~~ epileptiform ~~epilepsy~~discharges
21	15	9	Head nodding plus other seizures types		Severe cognitive impairment Lip deformity Speech difficulties Stunting Moderate wasting ~~Motor disability~~Spasticity with contractures and severe musculoskeletal deformity, wasting/dystrophy	Generalised epileptiform discharges
22	15	9	Head nodding plus other seizures types	Behavioural problems Aggression	Severe cognitive impairment Stunting Burns Episodes of disorientation Speech difficulties	Generalised epileptiform discharges

Growth and sexual maturity

Sixteen of the 22 children were wasted and nine stunted. Increasingly more severe wasting was observed with a longer duration of symptoms. Thus, patients with moderate wasting had symptoms lasting 3-6 years, while severe wasting was more common among those with symptoms lasting longer than 7 years. Ten had sexual maturity assessed; 3/10 children (aged 12, 13, 14 years) scored Tanner Stage 3. All remaining 7 children (ages 12-17 years) were either Tanner Stage 1 or 2. The bone age was delayed by a median 2(range 1-6) years.

Musculoskeletal findings

Almost all had peripheral muscle wasting with progressively flat feet and hands, thin cylindrical digits and increasing~~progressively, more~~ generalised wasting. Other physical changes included kyphosis and pectus deformities of the chest. Flexion limb deformities were seen in patients with severe disability ~~debilitated patients~~ (**Figure 2).**

Neurological, cognitive and behavioural features

Seizures

Other than head nodding, a variety of other seizures types were described in 18/22 patients - including absence, complex partial, myoclonic, and tonic-clonic seizures. were described in 18/22 patients.

a) *Head nodding*

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Nodding was precipitated by food in 16/22 children. In 4/22, it was associated with cold weather or a cold breeze, while in 13/22, it developed spontaneously. Nodding episodes came in clusters occurring during (both the day and the night) and were characterised by repetitive flexion and forward drop of the head. around the neck. The clusters of head nodding It lasted several seconds to minutes. Some children became unresponsive and stared blankly with each cluster of nodding, stopped feeding or drooled saliva.

b)a) *Other seizure types*

Initially head nodding was the predominant seizure type but as the disease progressed, generalised tonic-clonic seizures gained became more prominentce. Myoclonic seizures were not readily often reported, but were observed in several children while in hospital. One such child had a prolonged cluster of nodding with concurrent myoclonic jerks involving both upper limbs, lasting about 10 minutes. In a second child, similar myoclonic jerking was followed by a generalised tonic-clonic seizure. Several children reported had sudden falls, sustaining facial and head injuries.

Four children reported experienced paroxysmal events associated with fear, panic and visual hallucinations. We could not obtain clear descriptions of the images seen by two. The third child would shout and run with onset of the hallucinations and the forth reported seeing a person with knives whose intention 'was to kill her'. None of these events was captured on EEG.

Other neurologic complications

Focal neurological signs were uncommon exception. There were no obvious cranial nerve palsies. However, six children were lethargic with an apathetic and expressionless face or 'myopathic facies'. Three of the six drooled saliva while two had very slow speech and repeated epileptiform (spike and wave) discharges on EEG. The deep tendon reflexes were increased in a minority of patients. In the majority, however, the reflexes were either normal or reduced.

~~Almost all these had peripheral muscle wasting manifesting with flat feet and hands and thin cylindrical fingers and progressively, generalised wasting.~~

Vision, hearing and speech difficulties

No parent reported visual impairment and we did not test visual acuity but hearing impairment was reported in one child. Speech difficulties were reported in 10/22 children. These included immature speech for age and slow, slurred or dysarthric speech. Two children were mute but retained gestural ability and receptive language.

Behaviour and psychiatric features and complications

The earliest psychiatric manifestation was wandering behaviour or running away. Because of concerns about injury or getting lost, some parents tied up the patients to restrain them in the home. Aggression, particularly towards familiar people, was reported in 6/22 cases, manifesting 3-6 years after onset of nodding. In two children, the onset was concurrent with wandering behaviour. Five children had sleep difficulties and at least 8/22 had moderate to severe mood problems with one clinically depressed.

Cognitive function

All 22 children had cognitive difficulties and were out of school. Academic performance declined with symptom onset; ~~previously well performing~~ ~~with increasing~~ as symptoms increased, pupils started getting poorer grades and were eventually withdrawn from school within 2-4 years of disease onset. ~~Cognitive functioning, using the Kaufman Assessment Battery for Children 2nd Edition (KABC-2), was assessed in four children ages 13-15 years two weeks after initiation of sodium valproate. This test has previously been adapted to Uganda(Bangirana, Seggane et al. 2009).~~ Three of the 4 children who had cognitive functioning assessed using the KABC-2 responded to the test instructions. The fourth child did not respond at all. All 3 children had severe cognitive impairment (**Table 2**).

Table 2: Cognitive function on the KABC 2nd Edition in 3 children two weeks after initiation of sodium valproate

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Cognitive Domain	Patient 1 Male 13 years		Patient 2 Male 15 years		Patient 3 Male 15 years	
	Test Score	Age equivalent in years	Test Score	Age equivalent in years	Test Score	Age equivalent in years
Working memory	8	<5	7	<5	21	=5
Planning	7	<8	1	<5	3	<5
Learning	28	<5	25	<5	54	=5
Visual spatial	0	<5	0	<5	31	<5
Knowledge	11	<5	5	<5	52	<8

Laboratory findings

The mean haemoglobin was 12.4 (range 10.8–14.8) g/dl and the mean red cell volume was 81.4 (range 65.8-89.1) fl. Five children had iron deficiency anaemia. The total white blood cell and platelet counts were normal but 10/22 children had eosinophilia, median eosinophil count 0.4 (range 0.1 – 1.9) x 10^9/L. The ESR was high in 17/22 children with a median of 28.5 (range 5-90) mm in the first hour. Other than mild elevations of gamma ~~G~~GT, the liver and renal function was normal. All tested negative for malaria on admission to Mulago, although~~but~~ one ~~eventually~~ subsequently developed malaria in the third week of hospitalisation. Nine children had osteopenia on x ray but only one had hypocalcaemia and four~~,~~ hypophosphataemia. Creatine kinase levels were normal in all children and all tested HIV negative. Cerebrospinal fluid total protein, cells and glucose were all normal and all bacteriologic cultures had no growth. Three out of 10 patients had *O.volvulus* microfilaria on the skin snip. Microfilaria density was, however, not reported.

EEG

The routine diagnostic EEG was abnormal in all cases. The background activity showed a generalised excess of slow activity mainly in the conventional theta and delta frequency ranges. Generalised inter-ictal epileptiform activity was observed in all but two patients, in whom~~,~~ there~~y~~ were focal temporal discharges (unilateral in one and bilateral in the second). All patients with

generalised epileptiform activity had high amplitude spikes or sharp waves, some associated with slow wave activity and often occurring in irregular bursts rather than runs (**Figure 3)**. There was no consistent frequency to this. The discharges had bilateral fronto-temporal or fronto-centro-temporal emphasis, but some were more generalised and increased in frequency in light sleep. There was a clear gradation from mild to more severe background abnormalities and epileptiform activity. No overnight recordings were performed. The EEG findings suggested symptomatic generalised epilepsy in 20 and symptomatic focal epilepsy in the remaining 2.

Brain imaging

Brain MRI without contrast was performed in 19/22 patients. The imaging showed different degrees of cortical and cerebellar atrophy. No focal cerebral cortical or hippocampal changes were observed (**Figure 4)**. Cerebellar disease was evident in the majority of cases, but among patients with especially generalised cortical atrophy, there was a suggestion of more atrophy in the occipital lobes or the parieto-occipital regions than anteriorly.

Disease progression

Five stages with deteriorating seizures, neuro-cognitive and psychiatric disability were identified: a prodrome; development of head nodding and cognitive impairment; other seizure types; multiple complications and, severe debilitation (**Panel 1**).

Panel 1: A mum's description of the sequential chronology of symptoms and disease progression in her 18 year old daughter.

"She was growing well until the age of 8 years when symptoms of nodding began. The head nodding is triggered by food. When food is given, she freezes with it in her hand, stares blankly into space with a fixed gaze, and then nods repeatedly for a time which varies with each episode but the maximum time was initially 5 minutes. The symptoms got worse with time and about 6 years later, the nodding symptoms were immediately followed by or associated with big seizures during which the whole body shook. She would drool saliva, foam around the mouth and loses consciousness. After the big seizure, she would sleep and on waking is often weak and sometimes disoriented. On some nights, she reports seeing a figure that holds a knife and wants to kill her. She is distressed by her illness and gets embarrassed on waking if she had a seizure in public. She is very quiet but sometimes aggressive. Overtime, her speech has become sluggish. Although she is 18 years old, she still has childish behaviour which is evident as she speaks. Her father died following a febrile illness. She has six siblings two of who have similar symptoms."

Stage 1 The prodromal period

This poorly defined and short-lived period was reported in four patients. The earliest symptoms included “dizziness” and increasing inattention. The children were excessively sleepy, lethargic and would sometimes stare blankly during meals.

Stage 2 Development of head nodding

Among the four patients reporting prodromal symptoms, head nodding developed within 6 weeks of the prodrome. In the majority, however, the initial feature was an abrupt onset of nodding. Subsequently, parents reported declining cognitive abilities and behaviour difficulties. Disease progression however appeared to arrest in these four.

Stage 3 Development of other seizure types

~~Other than~~ Apart from the four children with nodding only, 18 children ~~in addition~~ developed other seizure types including absence, complex partial, myoclonic and generalised tonic-clonic seizures. One child developed generalised tonic clonic seizures almost simultaneously with the nodding. In the others, however, additional seizure types ~~these~~ developed 1-3 years after initial symptoms. It was around this time that almost all school going children dropped out of school.

Stage 4 Development of multiple complications

Multiple complications developed 4-8 years after the initial symptoms, associated with marked regression in achievement. These consisted of deteriorating behaviour and psychiatric symptoms and a decline in motor, speech and other cognitive functions. Some patients developed physical deformities including kyphosis, limb and pectus deformities (**Figure 2**). Some sustained severe facial injuries with “drop attacks” and burns. Those who were still independently mobile would wander about or ~~ran~~ run away and were prone to getting lost. Changes in the architecture of the lower lips (**Figure 1**) also occurred at this time. With disrupted and poor feeding, the children became severely wasted.

Stage 5 ~~The s~~S~~evere~~~~ly~~ disability~~ebilitated child~~

These children have little, if any, independent mobility. The general picture ~~wa~~is that of a severely wasted child with apathy and depressive features including a flat affect, poor appetite and limited speech. Some had contractures around the major joints.

Patients with head nodding only had less cortical and cerebellar atrophy on brain MRI compared to those with multiple complications. In addition, there was a clear gradation from milder to more severe epileptiform and background EEG abnormalities in patients with thesuggested later clinical stages of the disease.

Response of seizures to sodium valproate

The patients had previously been on mostly small low doses of different various anti--epileptic drugs including phenytoin, phenbarbitone and carbamazepine. In conformity with proposed national guidelines, all were started on sodium valproate and the other anti--epileptic drugs weaned off. Prior to this, a 24 hour seizure count was obtained and this was repeated 14 days later. Overall, there was a 57% reduction in total seizures including clusters of nodding. The median total daily number of seizures reduced from 5 (range 2–14) on admission to 2 (range 0-8) 14 days after initiation of sodium valpraotevalproate. Concurrent improvements were also seen on the EEG with substantially reduced marked improvements or absent interictal discharges in 3/5 patients who had repeat recordings on the day of assessment **(Figure 3)**.

DISCUSSION

Recently, world media has highlighted there have been media reports of “a mysterious disease” baffling scientists – the nodding syndrome.[7 23 24] There are many uncertainties about this newly recognized disorder: main questions are: what is the cause, the pathogenesis, disease classification, clinical spectrum and treatment? In this paper, we describe the clinical features and, complications of nodding syndrome in Ugandan children, together with the EEG and brain imaging features appearances. Our results findings suggest that nodding syndrome is a neurologic disorder characterised as by a symptomatic generalised epilepsy.

Clinical features and complications

Nodding syndrome in Ugandan children manifests with head nodding, cognitive dysfunction, psychiatric features, and/or multiple other seizure types. It may be complicated by stunted growth, pubertal delay, wasting, motor decline and physical deformities. The earliest manifestations are that of is a poorly defined prodrome followed within weeks by head nodding. In the later stages, there is cognitive dysfunction, psychiatric difficulties disturbance, severe muscle wasting and musculoskeletal deformity. Delayed physical growth, bone age and sexual maturity are common in affected children. This may partly be a result of delayed puberty, since

most were in Tanner Stage 2. Pubertal delay may be secondary to chronic illness, poor nutrition and/or psychosocial deprivation. If so, improved nutrition, a ~~caring~~ supportive environment and symptom control should lead to improved growth and the initiation of puberty.

The progressive ~~development of symptoms and complications~~ stages of the disorder appear~~s~~ to reflect the natural progression of an epileptic encephalopathy. In Stage 1, there are ~~might be~~ brief seizures, while ~~the departure from school in~~ by Stage 3 ~~can be explained by~~ uncontrolled seizures prevent the child from continuing in school. In Stage 4 ~~can be the time when~~ a high seizure ~~load~~ burden contributes to regression, which together with ensuing poor nutrient intake leaves a severely disabled ~~ebilitated~~ child ~~in~~ by Stage 5, when ~~the sum effect of~~ multiple factors ~~on~~ impair functioning.

The clinical features in Ugandan children are as severe as in South Sudanese children,[6] but may be more severe than ~~that reported~~ in Tanzanian patients[9]. Despite similar age of onset and duration of symptoms, only 18% of Ugandan children had the milder nodding only variant, compared to 45% in Tanzania; all our patients had abnormal interictal background EEG compared to 60% in Tanzania. Ugandan children also had ~~severer~~ more severe cognitive impairment and a much ~~higher~~ greater burden and variety of seizures. These differences may suggest a variation in the presentation of the disease by region. Family clustering in all three countries, however, suggests a common exposure factor.

Aetiology and pathogenesis

The aetiology of nodding syndrome and pathogenesis of the complications remain unknown. A variety of viral central nervous system infections have been screened for on PCR but no association has been demonstrated[19]. ~~There is uncertain~~ An association with infestation with *Onchocerca Volvulus* ~~however remains~~ has been reported in some series,[5 9] but ~~. Others have postulated that nodding syndrome is a consequence of treatment of patients with heavy *Onchocerca volvulus* infestation or dual infection with other similar parasites. Ccontrary evidence of any association with onchocerciasis also exists~~ has not been evident in other studies.[18 25]. Other aetiologic considerations have included toxic brain injury, ~~an~~ inflammatory brain disease, a slow virus infection or prion disease, an atypical mitochondrial disease or other genetic disorder. Repeated severe ~~psycho~~ psychological trauma has also been proposed as a mechanism[26]. Earlier studies by the Ugandan Ministry of Health and the US Centers of Disease Control found ~~demonstrated~~ a higher proportion of cases with ~~very~~ low serum ~~levels of~~ vitamin

B6 ~~in cases~~ compared to controls. Although unlikely, ~~the question then was~~ the possibility was raised that ~~whether~~ nodding syndrome could be ~~is~~ an atypical form of pyridoxine dependent epilepsy.~~?~~ Studies to ~~further investigate~~ explore this hypothesis further ~~this~~ are awaited[27].

Children with the syndrome ~~demonstrate~~ show some features reminiscent of prion protein disease, including motor and cognitive dysfunction, epilepsy, behaviour and psychiatric morbidity. However, other features commonly seen in prion disease - such as extrapyramidal involvement and cortical blindness - have not been reported. The age of onset of symptoms is also ~~-~~much younger and progression much slower[28]. The brain imaging and EEG findings too are not suggestive of prion disease.~~supportive~~. Nevertheless, ~~B~~ brain biopsy or autopsy studies would be important in excluding prion disease. ~~Future studies should also include consider the recently described the auto-immune encephalitides.~~

The brain MRI findings ~~may~~ might suggest viral encephalitis, a para-infectious phenomenon (such as an antibody- mediated channelopathy) or ~~an outside chance of~~ even a neurotoxin as possible aetiologies. A genetic disorder or metabolic disease is also possible. Future studies should also consider the recently described auto-immune encephalitides. ~~Some cases however did not exhibit these finding and therefore further evaluation is needed.~~ Among Tanzanian patients, hippocampal gliosis, probably from inflammation, was described in some patients[9]. Although this could partly explain the cognitive difficulties, we did not observe such lesions, even in the sub-group with ~~with the~~ more severe cognitive impairment. ~~in our patients~~. ~~Instead, we~~ We consider that ~~think~~ an epileptic encephalopathy is more likely. The background EEG in all 22 cases showed a generalized excess of theta and slow activity. ~~Interictal epileptiform activity was demonstrated in all but one patient.~~ Prolonged EEG recording (including during sleep) with detailed neuropsychological testing and functional brain imaging may help with understanding the pathogenesis of ~~the~~ cognitive decline.

Study limitations

Our patients may not be a representative sample, as they were not drawn randomly from the community. ~~This~~ The study did not investigate aetiology and the proposed staging was ~~mostly~~ derived primarily from parental descriptions rather than prospective observations and so ~~therefore~~ may be influenced by recall bias.~~suffers from recall.~~ ~~Third, we~~ We only performed routine diagnostic EEGs, rather than prolonged recordings which are important in investigating

associations between seizures and cognitive dysfunction. The resolution of our MRI images is also quite low.

CONCLUSIONS

Nodding syndrome is a neurologic disorder that is complicated by multiple physical and functional disabilities and may be ~~classified~~ considered as a symptomatic generalised epilepsy. Assessment and care should be provided by a multidisciplinary team. Studies of aetiology, pathogenesis, evidence- based treatment and rehabilitation strategies are urgently needed.

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Author contributions

RI, ROO, AKM, HAT, TPW, PB, JN1, SBM, ADM, HN, ~~SW~~, EM, JN2, SK, JRA and JKT all participated in patient care and performed the different assessments. ROO, AKM, HAT and SBN were in-charge of daily care, TPW and EM performed the growth and sexual staging assessments, JN1 the psychiatric assessments, HN the nutrition assessment, SW reported the EEG recordings, KC the brain MRI and RI wrote the first draft. All provided a critical review of the manuscript.

Conflict of Interest

The authors report no competing interests.

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Figure legends

Figure 1 Lip changes

The figure shows changes in the lips with increasing distortion. In patients with mild involvement, the lower lip is enlarged but with no visible or palpable swellings. With more severe involvement, there is deep purple discolouration of the mucosa, soft papular growths and increasingly larger and thicker bands of tissue. Other oral abnormalities included lacerations and loss of teeth from injuries.

Figure 2 ~~Hand and foot m~~Muscle wasting, deformities and contractures

Figure 2 shows wasting of the muscles of the ~~hand and~~ foot, knee and foot flexion deformities and contractures, pectus deformity of the chest and kyphosis. Such marked deformities we~~a~~re seen with increasing symptom duration.

Figure 3 EEG recordings

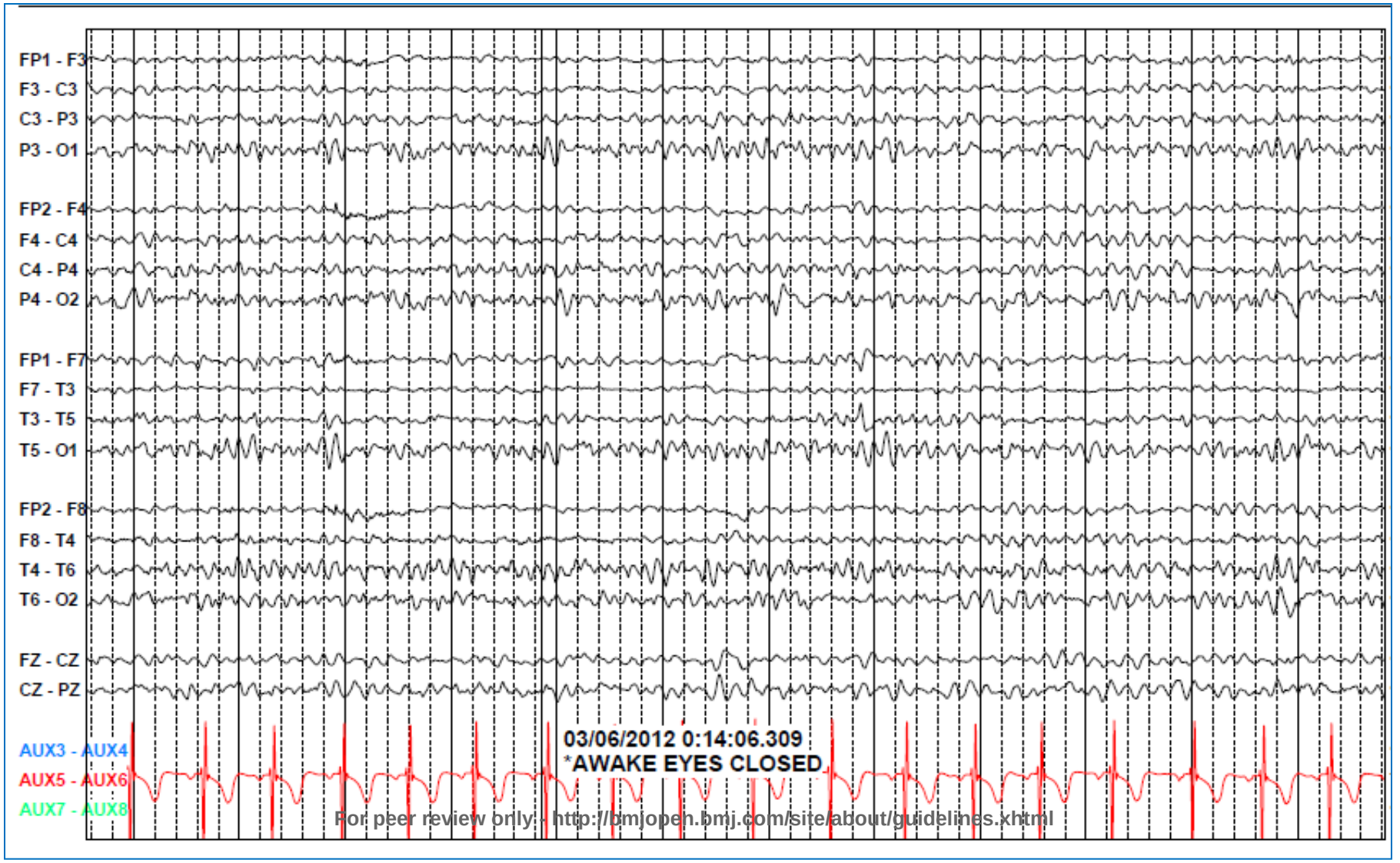
Figure 3 is an EEG recording of a 12 year old girl. She had head nodding and cognitive impairment. During the recording, interictal epileptiform discharges (spikes and sharp waves) were observed in wakefulness (3a) and during light sleep, when ~~increasingly~~ more ~~florid~~ prominent epileptiform discharges were evident.~~observed~~. There was no apparent clinical ~~event with this recording~~ change with these discharges (3b).

Figure 4 Brain MRI

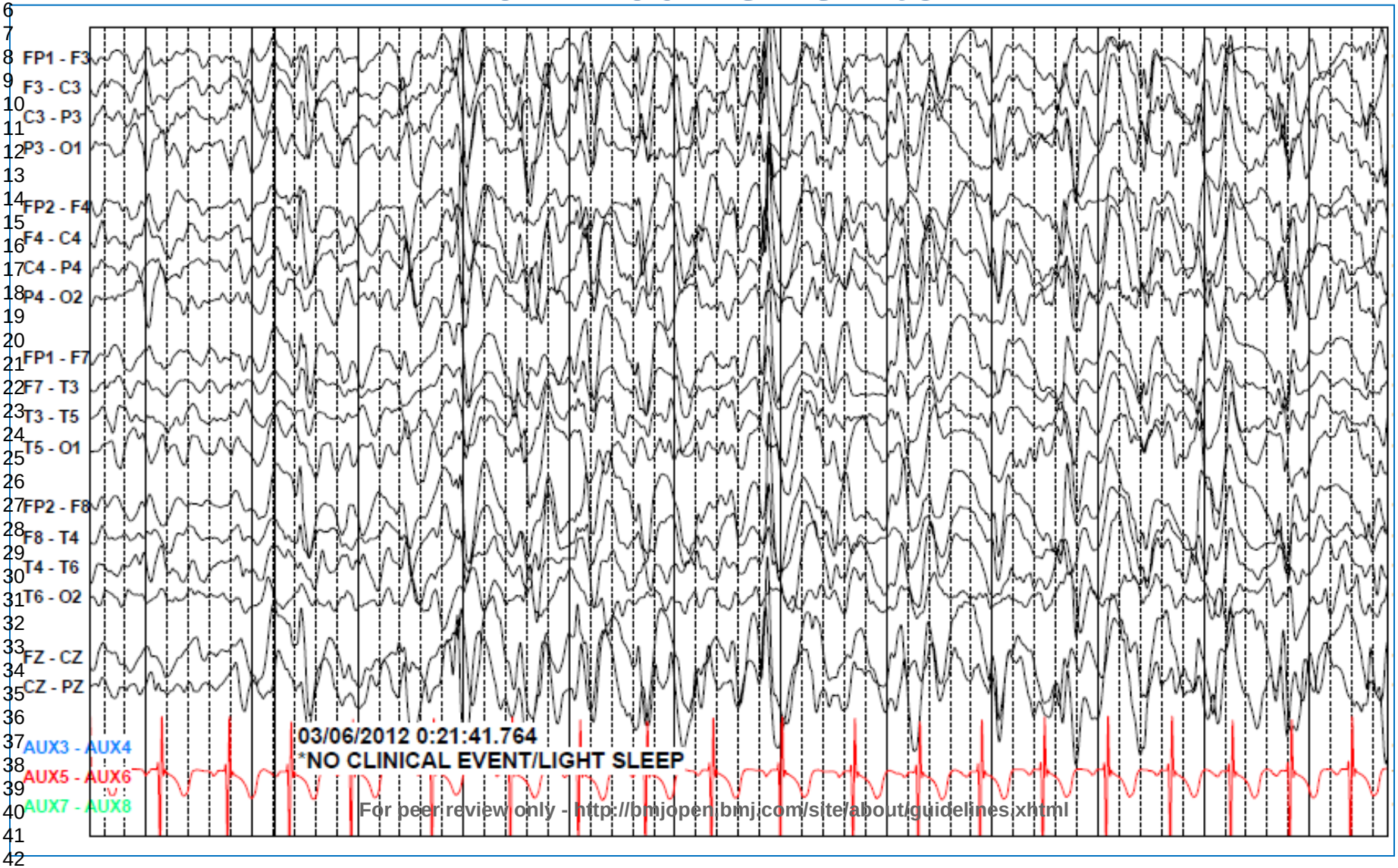
Figure 4 shows T2-weighted brain MRI images in the axial (Fig 4a, 4b) and sagittal (Fig 4c, 4d) plane showing marked cerebellar atrophy and generalised cerebral atrophy.

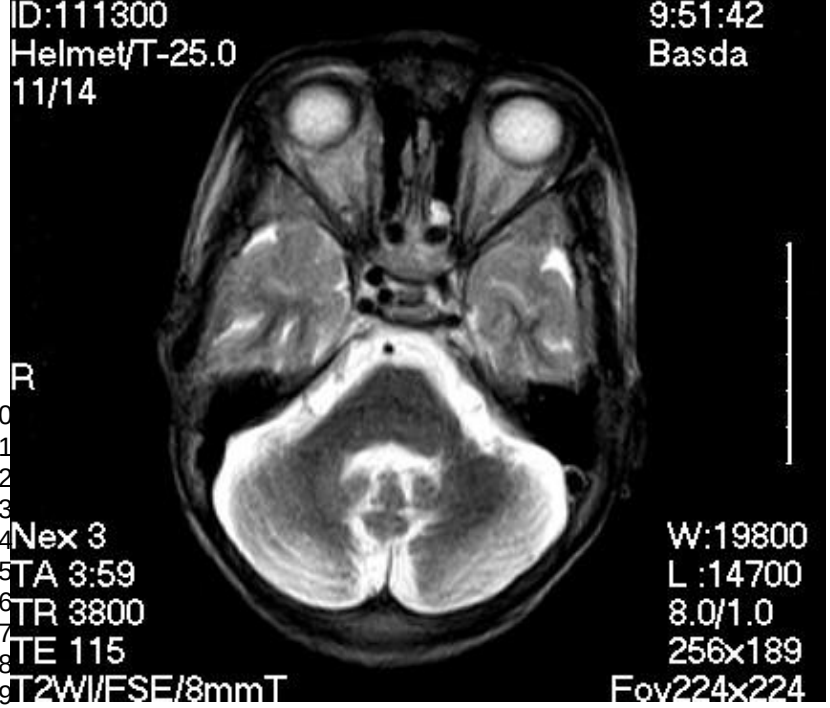
~~Figure 4 shows T1 and T2 brain MRI images of a 15 year old boy. He had head nodding, myoclonic and absence seizures but no tonic clonic seizures. There is cortical brain atrophy with widening of adjacent sulci, but no focal lesions or obvious abnormalities in the hippocampi.~~

EEG at onset of recording - awake

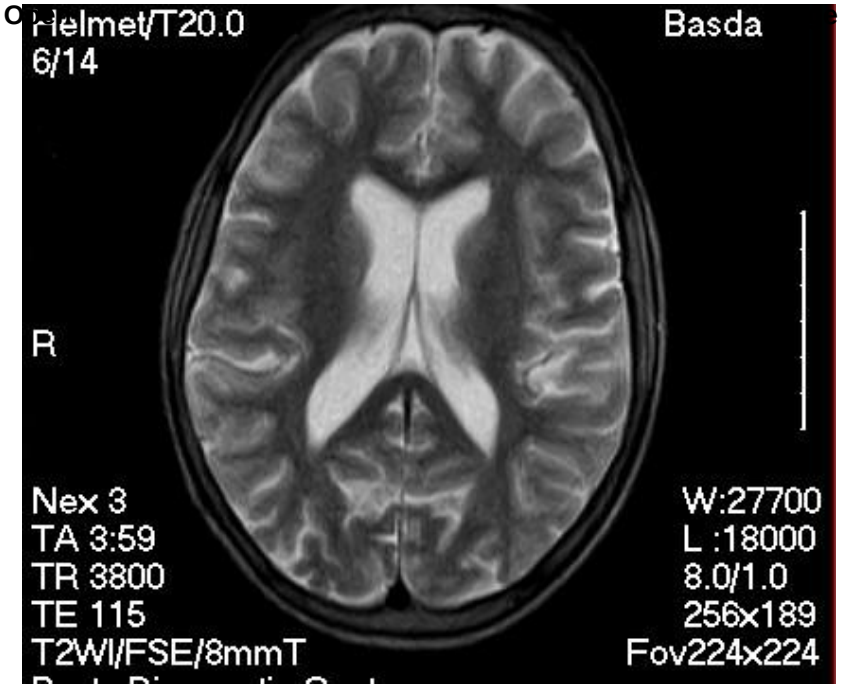


Florid discharges in light sleep, no clinical events

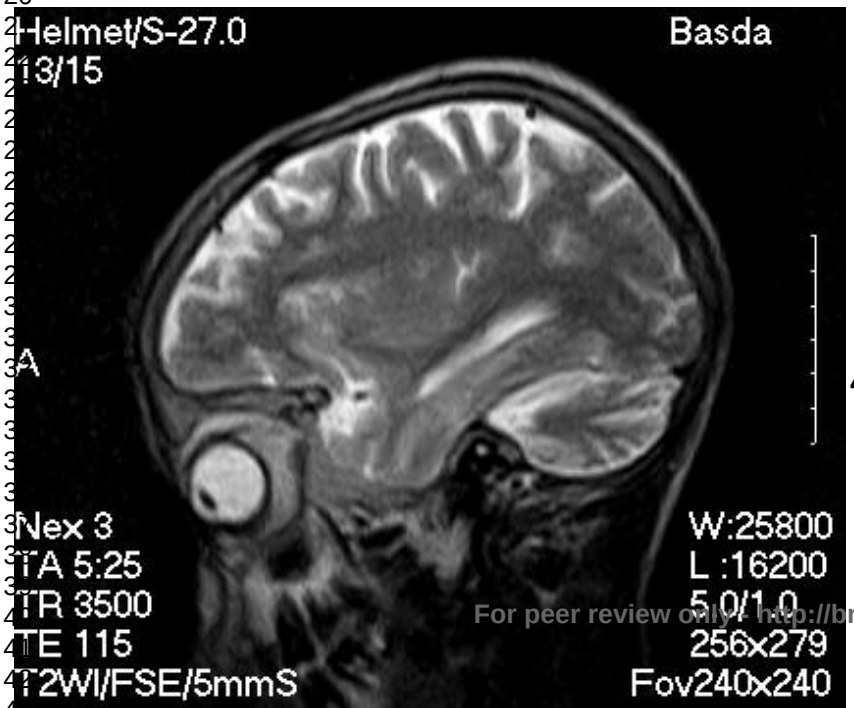




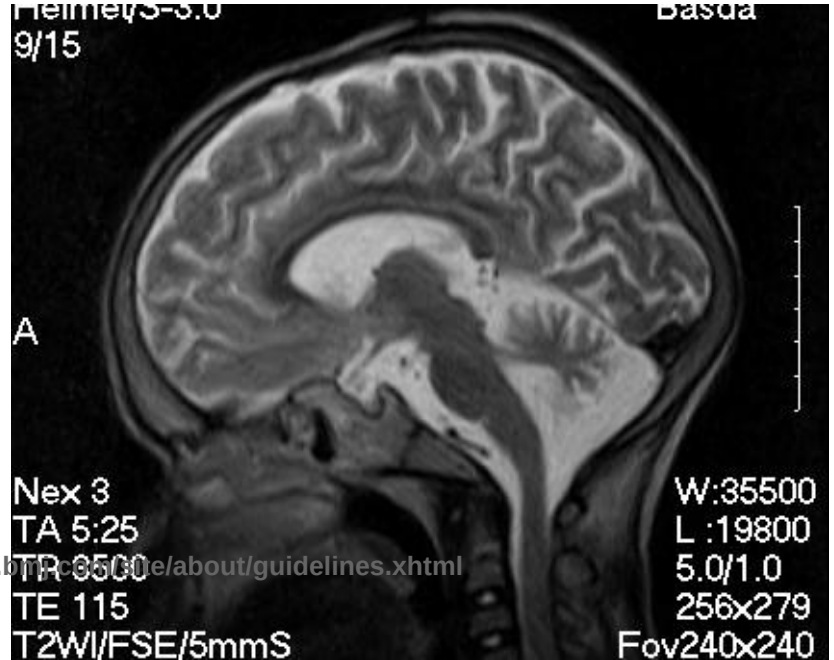
4a



4b



4c



4d

R Idro et al, Nodding Syndrome in Ugandan Children

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	N/A
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	N/A

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4-5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	12-13
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	-
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	7-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-13
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Nodding Syndrome in Ugandan Children - Clinical features, Brain imaging and Complications; an observational case series

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NODDING SYNDROME IN UGANDAN CHILDREN - CLINICAL FEATURES, BRAIN IMAGING AND COMPLICATIONS; AN OBSERVATIONAL CASE SERIES

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ABSTRACT

Objectives: Nodding syndrome is a devastating neurological disorder of uncertain aetiology affecting children in Africa. There is no diagnostic test and risk factors and symptoms that would allow early diagnosis are poorly documented. This study aimed to describe the clinical, electrophysiologic and brain imaging (MRI) features and complications of nodding syndrome in Ugandan children.

Design: Case series

Participants: 22 children with nodding syndrome brought to Mulago National Referral Hospital for assessment.

Outcome measures: Clinical features, physical and functional disabilities, electro-encephalogram (EEG) and brain MRI findings and a staging system with a progressive development of symptoms and complications.

Results

The median age of symptom onset was 6(range 4-10) years and median duration of symptoms was 8.5(range 2-11) years. Sixteen of 22 families reported multiple affected children. Physical manifestations and complications included stunting, wasting, lip changes and gross physical deformities. The bone age was delayed by 2(range 1-6) years. There was peripheral muscle wasting and progressive generalised wasting. Four children had nodding as the only seizure type; 18 in addition had myoclonic, absence and/or generalised tonic-clonic seizures developing 1-3years after the onset of illness. Psychiatric manifestations included wandering, aggression, depression and disordered perception. Cognitive assessment in 3 children demonstrated profound impairment. The EEG was abnormal in all, suggesting symptomatic generalised epilepsy in the majority. There were different degrees of cortical and cerebellar atrophy on brain MRI but no hippocampal changes. Five stages with worsening physical, EEG and brain imaging features were identified: a prodrome, development of head nodding and cognitive decline, other seizure types, multiple complications, and severe disability.

Conclusions

Nodding syndrome is a neurologic disorder that may be characterised as probably symptomatic generalised epilepsy. Clinical manifestations and complications develop in stages which might be useful in defining treatment and rehabilitation. Studies of risk factors, pathogenesis, management, and outcome are urgently needed.

ARTICLE SUMMARY

Article focus

- This paper offers detailed descriptions of the clinical features and complications of nodding syndrome in Ugandan children and the electrophysiologic and brain imaging features.
- It also proposes a clinical staging system for the disease.

Key messages

- Nodding syndrome is an epidemic neurologic disorder affecting children in parts of sub-Saharan Africa that may be characterised as a probable symptomatic generalised epilepsy with features of epileptic encephalopathy.
- Patients progressively develop both physical and functional deficits including multiple seizure types, cognitive and physical decline, malnutrition, and psychiatric features. Five clinical stages could be identified.
- The proposed clinical stages are associated with worsening cortical and cerebellar atrophy on brain imaging and more severe epileptiform and background EEG changes. These stages may be useful in guiding treatment and rehabilitation.

Strengths and limitations of this study

- Although the sample size is small and there is no comparison group, this is one of the few studies so far to have carefully documented the clinical features and complications of nodding syndrome combined with extensive electrophysiology and brain imaging data, describe the natural history and the first to provide a staging system.The study patients, however, may not be representative of the population, as they were not randomly drawn from the community.
- The study did not investigate aetiology and the proposed staging was mainly derived from parental descriptions rather than prospective observations and, therefore, suffers from recall bias.
- The resolution of our brain MRI images is quite low.

BACKGROUND

Nodding syndrome is a devastating neurological disorder of uncertain aetiology described in African children[1]. It was first described in Tanzania in 1960s[2] and subsequent reports have come from Liberia[3], South Sudan[4-6] and Uganda[7 8]. The syndrome is characterized by head nodding determined to be atonic seizures[8] often occurring in association with feeding, a cold breeze or cold weather and complicated by other seizure types, malnutrition and cognitive decline[6 9 10].

In Uganda, almost all affected individuals are from the north of the country where there are an estimated 3,000 cases. The region has for the past 20 years, had instability from rebel activity[11]. As a result, the population was internally displaced into densely populated camps. It is only in the last 5 years that peace returned and population returned to their homes. This region is crossed by two rivers - the *Aswa* and *Pager* Rivers, has high malaria transmission and is endemic for *Onchocerca volvulus*. This parasite has variously been associated with the *Nakalanga* syndrome (a tropical syndrome characterised by short stature and malnutrition)[12-15], epilepsy[16 17] and nodding syndrome[5 9]. This association has, however, been indirect as no O. volvulus contamination of cerebrospinal fluid has been documented[18].

There are only limited descriptions of nodding syndrome[4 5 8-10]. Winkler et al provided the most detailed account of the syndrome to date, describing clinical features in 62 Tanzanian patients and classifying them as either head nodding only or head nodding plus, if they also had other seizure types[9]. Initial symptoms allowing early recognition of the disease, its natural history and potentially modifiable risk factors are poorly characterized. There is no diagnostic test and the current case definition is based solely on clinical criteria. The objective of this study was to describe the clinical, electrophysiologic and brain imaging features and complications of nodding syndrome in Ugandan children and to propose a staging system.

METHODS

Design and setting

This is a case series of 22 Ugandan children with nodding syndrome. The study was conducted in Mulago, the National Referral Hospital in Uganda and teaching hospital for Makerere University College of Health Sciences in Kampala. This hospital provides tertiary level care for patients in a country in which most public healthcare services are paid for by the state.

Participants

Participants were patients with suspected nodding syndrome brought by the Ministry of Health from Kitgum district near the border with South Sudan, to Mulago Hospital in March 2012 for specialist assessments to better understand the syndrome. Kitgum district is the epicentre of the disease and one of the most affected districts in the country. Of the 25 patients brought to Mulago, one young adult (a 23 year old male found to have a brain tumour) and two adolescents (an 18 year old girl with a cerebellar hypoplasia syndrome and a 16 year old boy with history of cerebral malaria at the age of 4 years and subsequent neurologic sequelae) were excluded. The remaining 22 children had probable nodding syndrome and were included in the study. A case of probable nodding syndrome was defined as:

- A child older than 2 years or an adolescent who previously was developing normally
- Two or more episodes of recurrent head nodding occurring spontaneously or consequent to the sight of food or coldness
- With or without other types of seizures, neurological signs, regression in growth or learning disability.

This case definition was revised during the International Meeting on Nodding Syndrome later in 2012.However, all selected patients fulfilled the revised criteria[19].

Permission for the study was obtained from Makerere University School of Medicine Research and Ethics Committee. However, as we had no study protocol prior to the arrival of the patients, clinical care and assessment followed the hospital's standard procedures for routine non-surgical care for children. Verbal parental consent was obtained for all clinical, laboratory and imaging procedures. As is policy, however, parents gave written consent for photography, as this is considered over and above routine care and for any surgical procedures. Parents were specifically made aware that the objective of the assessments was not cure, but a better

understanding of the disease and that the general findings from the evaluation of the group of patients with nodding syndrome would be made available to the wider scientific community in presentations and publications, with the specific aim of improving the care of people affected by the disorder in the future. To this effect, a submission was then made to the Ethics Committee and permission to use results of the investigations subsequently granted.

Study measurements and Procedures

All had detailed clinical, electrophysiologic, and brain imaging assessments and laboratory testing.

Clinical assessment

The history included an inquiry about the time from pregnancy to the onset and the progressive development of symptoms, physical and functional difficulties. The clinical examination included general, nutritional, neurologic, cognitive and mental state assessments. Wasting was defined as weight for height Z score of -<2 and stunting as height for age Z score of -<2. Sexual maturity was assessed using the Tanner Sexual Maturity staging. Patients were classified as having nodding syndrome only or nodding syndrome plus depending on whether they also had other seizure types[9]. X-rays of the left wrist were taken for bone age and reported using a Greulich and Pyle Atlas by a blinded radiologist[20]. Bone growth was considered delayed if it was 2 years below the chronological age. Cognitive functioning was assessed in detail in four children - median age 14.5 (range 13-15) years - two weeks after initiation of sodium valproate using the Kaufman Assessment Battery for Children 2nd Edition (KABC-2). This test has previously been adapted for use in Uganda[21]. All four had had symptoms for longer than five years.

Laboratory procedures

Ten millilitres of blood was drawn for full blood count, ESR, malaria parasites, electrolytes, liver and renal function tests, and HIV testing. Cerebrospinal fluid was examined for cells, glucose, protein, microscopy and bacteriologic culture. In addition, 10 children had a skin snip examined for *Onchocerca volvulus* as previously described[9].

Neurophysiology and imaging

All had a 30 minute EEG recording with an XLTEK EEG system (Optima Medical Ltd, London, UK) using the 10-20 electrode placement system , which was reviewed by a consultant clinical neurophysiologist(SW) in the UK. Brain MRI in T1, T2 and Flair sequences were obtained

without contrast in 19/22 patients using a 0.5Tesla machine (BASDA Medical Apparatus, Guangzhou) and the images also examined in the UK by a Consultant Neuroradiologist (KC).

Natural history and staging

At the end of the first week after patients and carers had acclimatised to the referral hospital environment, the attending clinician sat with each carer and obtained detailed histories of the progressive development and timing of symptoms and complications of nodding syndrome to characterize the natural history. A standardised proforma with a diagrammatic representation of possible events and a linear timeline was used to obtain these descriptions. Information from each patient was plotted on the timeline and later combined with the data from other patients to identify emerging patterns, from which the proposed stages of the disorder were derived.

Treatment

Patients were started on symptomatic treatment (sodium valproate for seizure control, nutritional and physical therapy, counselling and social support) according to national guidelines developed a month earlier[22]. In this protocol, all received sodium valproate starting at 10mg/kg/day. The dose was titrated in 5-10 mg/kg/day increases according to the level of seizure control. Nutritional rehabilitation included Ready to Use Therapeutic Foods (Plumpy'Nut®, Nutriset, Malaunay) and locally prepared food. Occupational and physiotherapy, family counselling and support were provided as appropriate.

Data analysis

Data was analysed using STATA version 12 (STATA Corp, TX). Results are summarised as frequencies, proportions and medians as appropriate. The clinical features, complications and disability were then used to describe treatment and rehabilitation needs. Clinical stages were identified and brain imaging and EEG correlated with the clinical stages.

RESULTS

General features

Nine patients (40.9%) were male. The age range was 12-18 years. The median age at onset of symptoms was 6 (range 4–10) years and the median duration of symptoms was 8.5(range 2-11) years (**Table 1)**. Sixteen of the 22 families reported more than one case (median 2 (range 0–4)**)**. Prior to hospitalisation, all patients had received antiepileptic drug treatment with phenobarbitone, phenytoin or carbamazepine with no clear documentation of benefit. Treatment had often been intermittent and at sub-therapeutic doses.

Striking features on physical examination included stunting, cognitive impairment (on KABC or performance of basic tasks), lip changes and other physical deformities. Several children had burns and scars from burns. The skin was dry, thin and scaly. Extremities, especially the feet, felt cold with a temperature gradient with the trunk, but a normal capillary refill time. Among those with mild lip changes, the lower lip was enlarged with no visible or palpable localised swellings. In progressively more severe cases, the mucosa was deep purple, with soft papular growths and increasingly large, thick bands of tissue. One child, not exposed to sodium valproate previously, had unexplained alopecia.

Table 1 Characteristics of 22 patients with nodding syndrome

ID	Age (years)	Duration of symptoms in yrs	Seizure based classification	Main Psychiatric morbidity	Other prominent complications	EEG Seizure classification
1	14	11	Head nodding plus other seizures types	Behaviour problems Hallucinations	Severe cognitive impairment Burns Lip deformity Severe stunting, with severe wasting Spasticity and contractures with musculoskeletal deformities	Generalised epileptiform discharges
2	13	5	Head nodding plus other seizures types	Hallucinations Aggressive behaviour	Moderate wasting	Generalised epileptiform discharges
3	15	10	Head nodding plus other seizures types	Behaviour problems Aggression Pychosocial disorder	Severe wasting Speech difficulties	Generalised epileptiform discharges
4	14	9	Head nodding only		Severe cognitive impairment Stunting	Generalised epileptiform discharges
5	16	9	Head nodding plus other seizures types	Aggressive behaviour Wandering Hallucinations	Severe cognitive impairment Speech difficulties Moderate wasting	Right temporal discharges

6	14	5	Head nodding plus other seizures types			Generalised epileptiform discharges
7	14	7	Head nodding plus other seizures types		Severe cognitive impairment Lip deformity Severe wasting	Generalised epileptiform discharges
8	18	10	Head nodding plus other seizures types	Aggressive behaviour Hallucinations	Severe cognitive impairment Speech difficulties	Generalised epileptiform discharges
9	18	8	Head nodding plus other seizures types	Psychotic symptoms Behavioural problems	Severe cognitive impairment Lip deformity Speech difficulties Severe wasting	Left temporal discharges
10	16	11	Head nodding plus other seizures types		Moderate wasting Burns Marked lip deformity	Generalised epileptiform discharges
11	15	9	Head nodding plus other seizures types	Depression	Hearing impairment Stunting Burns Musculoskeletal Deformities Severe cognitive impairment Severe wasting	Generalised epileptiform discharges
12	13	8	Head nodding plus other seizures types	Hallucinations		Generalised epileptiform discharges
13	13	3	Head nodding plus other seizures types		Moderate wasting	Generalised epileptiform discharges
14	14	9	Head nodding plus other seizures types	Hallucinations		Generalised epileptiform discharges
15	12	8	Head nodding plus other seizures types		Severe wasting Stunting Kyphosis, pectus deformity Generalised skin changes	Generalised epileptiform discharges
16	12	2	Head nodding only		Stunting Severe wasting	Generalised epileptiform discharges
17	14	8	Head nodding plus other seizures types	Post- ictal aggression Wandering	Severe cognitive impairment Stunting Lip deformity, Ataxia Speech difficulties Spasticity and contractures with musculoskeletal deformities Moderate wasting	Generalised epileptiform discharges
18	18	6	Head nodding plus other seizures types		Moderate wasting	Generalised epileptiform

						discharges
19	12	4	Head nodding only		Moderate wasting Stunting	Generalised epileptiform discharges
20	15	9	Head nodding only		Stunting	Generalised epileptiform discharges
21	15	9	Head nodding plus other seizures types		Severe cognitive impairment Lip deformity Speech difficulties Stunting Moderate wasting Spasticity with contractures and severe musculoskeletal deformity, wasting/dystrophy	Generalised epileptiform discharges
22	15	9	Head nodding plus other seizures types	Behavioural problems Aggression	Severe cognitive impairment Stunting Burns Episodes of disorientation Speech difficulties	Generalised epileptiform discharges

Growth and sexual maturity

Sixteen of the 22 children were wasted and nine stunted. Increasingly more severe wasting was observed with a longer duration of symptoms. Thus, patients with moderate wasting had symptoms lasting 3-6 years, while severe wasting was more common among those with symptoms lasting longer than 7 years. Ten had sexual maturity assessed; 3/10 children (aged 12, 13, 14 years) scored Tanner Stage 3. All remaining 7 children (ages 12-17 years) were either Tanner Stage 1 or 2. The bone age was delayed by a median 2(range 1-6) years.

Musculoskeletal findings

Almost all had peripheral muscle wasting with progressively flat feet and hands, thin cylindrical digits and increasing generalised wasting. Other physical changes included kyphosis and pectus deformities of the chest. Flexion limb deformities were seen in patients with severe disability.

Neurological, cognitive and behavioural features

Seizures

Other than head nodding, a variety of other seizure types were described in 18/22 patients - including absence, complex partial, myoclonic, and tonic-clonic seizures.

Head nodding

Nodding was precipitated by food in 16/22 children. In 4/22, it was associated with cold weather or a cold breeze, while in 13/22 it developed spontaneously. Nodding episodes came in clusters occurring during both the day and the night and were characterised by repetitive flexion and forward drop of the head. The clusters of head nodding lasted several seconds to minutes. Some children became unresponsive and stared blankly with each cluster of nodding, stopped feeding or drooled saliva.

Initially head nodding was the predominant seizure type but as the disease progressed, generalised tonic-clonic seizures became more prominent. Myoclonic seizures were not often reported, but were observed in several children while in hospital. One such child had a prolonged cluster of nodding with concurrent myoclonic jerks involving both upper limbs, lasting about 10 minutes. In a second child, similar myoclonic jerking was followed by a generalised tonic-clonic seizure. Several children had sudden falls, sustaining facial and head injuries.

Four children experienced paroxysmal events associated with fear, panic and visual hallucinations. We could not obtain clear descriptions of the images seen by two. The third child would shout and run with onset of the hallucinations and the forth reported seeing a person with knives whose intention ‘was to kill her’. None of these events was captured on EEG.

Other neurologic complications

Focal neurological signs were uncommon. There were no obvious cranial nerve palsies. However, six children were lethargic with an apathetic and expressionless face or ‘myopathic facies’. Three of the six drooled saliva while two had very slow speech and repeated epileptiform (spike and wave) discharges on EEG. The deep tendon reflexes were increased in a minority of patients. In the majority, however, the reflexes were either normal or reduced.

Vision, hearing and speech difficulties

No parent reported visual impairment and we did not test visual acuity but hearing impairment was reported in one child. Speech difficulties were reported in 10/22 children. These included immature speech for age and slow, slurred or dysarthric speech. Two children were mute but retained gestural ability and receptive language.

Behaviour and psychiatric features and complications

The earliest psychiatric manifestation was wandering behaviour or running away. Because of concerns about injury or getting lost, some parents tied up the patients to restrain them in the home. Aggression, particularly towards familiar people, was reported in 6/22 cases, manifesting 3-6 years after onset of nodding. In two children, the onset was concurrent with wandering behaviour. Five children had sleep difficulties and at least 8/22 had moderate to severe mood problems with one clinically depressed.

Cognitive function

All 22 children had cognitive difficulties and were out of school. Academic performance declined with symptom onset; as symptoms increased, pupils started getting poorer grades and were eventually withdrawn from school within 2-4 years of disease onset. Three of the 4 children who had cognitive functioning assessed using the KABC-2 responded to the test instructions. The fourth child did not respond at all. All 3 children had severe cognitive impairment (**Table 2**).

Table 2: Cognitive function on the KABC 2nd Edition in 3 children two weeks after initiation of sodium valproate

Cognitive Domain	Patient 1 Male 13 years		Patient 2 Male 15 years		Patient 3 Male 15 years	
	Test Score	Age equivalent in years	Test Score	Age equivalent in years	Test Score	Age equivalent in years
Working memory	8	<5	7	<5	21	=5
Planning	7	<8	1	<5	3	<5
Learning	28	<5	25	<5	54	=5
Visual spatial	0	<5	0	<5	31	<5
Knowledge	11	<5	5	<5	52	<8

Laboratory findings

The mean haemoglobin was 12.4 (range 10.8–14.8) g/dl and the mean red cell volume was 81.4 (range 65.8-89.1) fl. Five children had iron deficiency anaemia. The total white blood cell and platelet counts were normal but 10/22 children had eosinophilia, median eosinophil count 0.4 (range 0.1 – 1.9) x 10^9/L. The ESR was high in 17/22 children with a median of 28.5 (range 5-90) mm in the first hour. Other than mild elevations of gamma GT, the liver and renal function was normal. All tested negative for malaria on admission to Mulago, although one subsequently developed malaria in the third week of hospitalisation. Nine children had osteopenia on x ray but only one had hypocalcaemia and four hypophosphataemia. Creatine kinase levels were normal in all children and all tested HIV negative. Cerebrospinal fluid total protein, cells and glucose were all normal and all bacteriologic cultures had no growth. Three out of 10 patients had *O.volvulus* microfilaria on the skin snip. Microfilaria density was, however, not reported.

EEG

The routine diagnostic EEG was abnormal in all cases. The background activity showed a generalised excess of slow activity mainly in the conventional theta and delta frequency ranges. Generalised inter-ictal epileptiform activity was observed in all but two patients, in whom there were focal temporal discharges (unilateral in one and bilateral in the second). All patients with generalised epileptiform activity had high amplitude spikes or sharp waves, some associated with slow wave activity and often occurring in irregular bursts rather than runs (**Figure 1)**. There was no consistent frequency to this. The discharges had bilateral fronto-temporal or fronto-centro-temporal emphasis, but some were more generalised and increased in frequency in light sleep. There was a clear gradation from mild to more severe background abnormalities and epileptiform activity. No overnight recordings were performed. The EEG findings suggested symptomatic generalised epilepsy in 20 and symptomatic focal epilepsy in the remaining 2.

Brain imaging

Brain MRI without contrast was performed in 19/22 patients. The imaging showed different degrees of cortical and cerebellar atrophy. No focal cerebral cortical or hippocampal changes were observed (**Figure 2)**. Cerebellar disease was evident in the majority of cases, but among patients with especially generalised cortical atrophy, there was a suggestion of more atrophy in the occipital lobes or the parieto-occipital regions than anteriorly.

Disease progression

Five stages with deteriorating seizures, neuro-cognitive and psychiatric disability were identified: a prodrome; development of head nodding and cognitive impairment; other seizure types; multiple complications and severe debilitation (**Panel 1**).

Panel 1: A mum's description of the sequential chronology of symptoms and disease progression in her 18 year old daughter.

"She was growing well until the age of 8 years when symptoms of nodding began. The head nodding is triggered by food. When food is given, she freezes with it in her hand, stares blankly into space with a fixed gaze, and then nods repeatedly for a time which varies with each episode but the maximum time was initially 5 minutes. The symptoms got worse with time and about 6 years later, the nodding symptoms were immediately followed by or associated with big seizures during which the whole body shook. She would drool saliva, foam around the mouth and loses consciousness. After the big seizure, she would sleep and on waking is often weak and sometimes disoriented. On some nights, she reports seeing a figure that holds a knife and wants to kill her. She is distressed by her illness and gets embarrassed on waking if she had a seizure in public. She is very quiet but sometimes aggressive. Overtime, her speech has become sluggish. Although she is 18 years old, she still has childish behaviour which is evident as she speaks. Her father died following a febrile illness. She has six siblings two of who have similar symptoms."

Stage 1 The prodromal period

This poorly defined and short-lived period was reported in four patients. The earliest symptoms included "dizziness" and increasing inattention. The children were excessively sleepy, lethargic and would sometimes stare blankly during meals.

Stage 2 Development of head nodding

Among the four patients reporting prodromal symptoms, head nodding developed within 6 weeks of the prodrome. In the majority, however, the initial feature was an abrupt onset of nodding. Subsequently, parents reported declining cognitive abilities and behaviour difficulties. Disease progression however appeared to arrest in these four.

Stage 3 Development of other seizure types

Apart from the four children with nodding only, 18 children developed other seizure types including absence, complex partial, myoclonic and generalised tonic-clonic seizures. One child developed generalised tonic clonic seizures almost simultaneously with the nodding. In the others, however, additional seizure types developed 1-3 years after initial symptoms. It was around this time that almost all school going children dropped out of school.

Stage 4 Development of multiple complications

Multiple complications developed 4-8 years after the initial symptoms, associated with marked regression in achievement. These consisted of deteriorating behaviour and psychiatric symptoms and a decline in motor, speech and other cognitive functions. Some patients developed physical deformities including kyphosis, limb and pectus deformities. Some sustained severe facial injuries with “drop attacks” and burns. Those who were still independently mobile would wander about or run away and were prone to getting lost. Changes in the architecture of the lower lips also occurred at this time. With disrupted and poor feeding, the children became severely wasted.

Stage 5 Severe disability

These children have little, if any, 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. Some had contractures around the major joints.

Patients with head nodding only had less cortical and cerebellar atrophy on brain MRI compared to those with multiple complications. In addition, there was a clear gradation from milder to more severe epileptiform and background EEG abnormalities in patients with the later clinical stages of the disease.

Response of seizures to sodium valproate

The patients had previously been on mostly low doses of various anti-epileptic drugs including phenytoin, phenbarbitone and carbamazepine. In conformity with proposed national guidelines, all were started on sodium valproate and the other anti-epileptic drugs weaned off. Prior to this, a 24 hour seizure count was obtained and this was repeated 14 days later. Overall, there was a 57% reduction in total seizures including clusters of nodding. The median total daily number of seizures reduced from 5 (range 2–14) on admission to 2 (range 0-8) 14 days after initiation of sodiumvalproate. Concurrent improvements were also seen on the EEG with substantially reduced or absent interictal discharges in 3/5 patients who had repeat recordings on the day of assessment **(Figure 1)**.

DISCUSSION

Recently, there have been media reports of “a mysterious disease” baffling scientists – the nodding syndrome.[7 23 24] There are many uncertainties about this newly recognized disorder: what is the cause, the pathogenesis, disease classification, clinical spectrum and treatment? In this paper, we describe the clinical features and complications of nodding syndrome in Ugandan children, together with the EEG and brain imagingappearances. Our findings suggest that nodding syndrome is a neurologic disorder characterised by a symptomatic generalised epilepsy.

Clinical features and complications

Nodding syndrome in Ugandan children manifests with head nodding, cognitive dysfunction, psychiatric features, and/or multiple seizure types. It may be complicated by stunted growth, pubertal delay, wasting, motor decline and physical deformities. The earliest manifestation is a poorly defined prodrome followed within weeks by head nodding. In the later stages, there is cognitive dysfunction, psychiatric disturbance, and severe muscle wasting and musculoskeletal deformity. Delayed physical growth, bone age and sexual maturity are common in affected children. This may partly be a result of delayed puberty, since most were in Tanner Stage 2. Pubertal delay may be secondary to chronic illness, poor nutrition and/or psychosocial deprivation. If so, improved nutrition, a supportive environment and symptom control should lead to improved growth and the initiation of puberty.

The progressive stages of the disorder appear to reflect the natural progression of an epileptic encephalopathy. In Stage 1, there are brief seizures, while by Stage 3 uncontrolled seizures prevent the child from continuing in school. In Stage 4 a high seizure burden contributes to regression, which together with ensuing poor nutrient intake leaves a severely disabled child by Stage 5, when multiple factors impair functioning.

The clinical features in Ugandan children are as severe as in South Sudanese children,[6] but may be more severe than in Tanzanian patients[9]. Despite similar age of onset and duration of symptoms, only 18% of Ugandan children had the milder nodding only variant, compared to 45% in Tanzania; all our patients had abnormal interictal background EEG compared to 60% in Tanzania. Ugandan children also had more severe cognitive impairment and a much greater burden and variety of seizures. These differences may suggest a variation in the presentation of

the disease by region. Family clustering in all three countries, however, suggests a common exposure factor.

Aetiology and pathogenesis

The aetiology of nodding syndrome and pathogenesis of the complications remain unknown. A variety of viral central nervous system infections have been screened for on PCR but no association has been demonstrated[19]. An association with infestation with *Onchocerca Volvulus* has been reported in some series,[5 9] but has not been evident in other studies[18 25]. Other aetiologic considerations have included toxic brain injury, inflammatory brain disease, a slow virus infection or prion disease, an atypical mitochondrial disease or other genetic disorder. Repeated severe psychological trauma has also been proposed as a mechanism[26]. Earlier studies by the Ugandan Ministry of Health and the US Centers of Disease Control found a higher proportion of cases with low serum vitamin B6 compared to controls. Although unlikely, the possibility was raised that nodding syndrome could be an atypical form of pyridoxine dependent epilepsy. Studies to explore this hypothesis further are awaited[27].

Children with the syndrome show some features reminiscent of prion protein disease, including motor and cognitive dysfunction, epilepsy, behaviour and psychiatric morbidity. However, other features commonly seen in prion disease - such as extrapyramidal involvement and cortical blindness - have not been reported. The age of onset of symptoms is also much younger and progression much slower[28]. The brain imaging and EEG findings too are not suggestive of prion disease. Nevertheless, brain biopsy or autopsy studies would be important in excluding prion disease.

The brain MRI findings might suggest viral encephalitis, a para-infectious phenomenon (such as an antibody- mediated channelopathy) or even a neurotoxin as possible aetiologies. A genetic disorder or metabolic disease is also possible. Future studies should also consider the recently described auto-immune encephalitides. Among Tanzanian patients, hippocampal sclerosis, probably from inflammation, was described in some patients[9]. Although this could partly explain the cognitive difficulties, we did not observe such lesions, even in the sub-group with more severe cognitive impairment. We consider that an epileptic encephalopathy is more likely. The background EEG in all 22 cases showed a generalized excess of theta and slow activity. Prolonged EEG recording (including during sleep) with detailed neuropsychological testing and functional brain imaging may help with understanding the pathogenesis of cognitive decline.

Study limitations

Our patients may not be a representative sample, as they were not drawn randomly from the community. The study did not investigate aetiology and the proposed staging was derived primarily from parental descriptions rather than prospective observations and so may be influenced by recall bias. We only performed routine diagnostic EEGs, rather than prolonged recordings which are important in investigating associations between seizures and cognitive dysfunction. The resolution of our MRI images is also quite low.

CONCLUSIONS

Nodding syndrome is a neurologic disorder that is complicated by multiple physical and functional disabilities and may be considered as symptomatic generalised epilepsy. Assessment and care should be provided by a multidisciplinary team. Studies of aetiology, pathogenesis, evidence- based treatment and rehabilitation strategies are urgently needed.

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Author contributions

RI, ROO, AKM, HAT, TPW, PB, JN1, SBM, ADM, HN, , EM, JN2, SK, JRA and JKT all participated in patient care and performed the different assessments. ROO, AKM, HAT and SBN were in-charge of daily care, TPW and EM performed the growth and sexual staging assessments, JN1 the psychiatric assessments, HN the nutrition assessment, SW reported the EEG recordings, KC the brain MRI and RI wrote the first draft. All provided a critical review of the manuscript.

Conflict of Interest

The authors report no competing interests.

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Figure legends

Figure 1 EEG recordings

Figure 1 is an EEG recording of a 12 year old girl. She had head nodding and cognitive impairment. During the recording, interictal epileptiform discharges (spikes and sharp waves) were observed in wakefulness (1a) and during light sleep, when more prominent epileptiform discharges were evident. There was no apparent clinical change with these discharges (1b).

Figure 2 Brain MRI

Figure 2 shows T2-weighted brain MRI images in the axial (Fig 2a, 2b) and sagittal (Fig 2c, 2d) plane showing marked cerebellar atrophy and generalised cerebral atrophy.

NODDING SYNDROME IN UGANDAN CHILDREN - CLINICAL FEATURES, BRAIN IMAGING AND COMPLICATIONS; AN OBSERVATIONAL CASE SERIES

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ABSTRACT

Objectives: Nodding syndrome is a devastating neurological disorder of uncertain aetiology affecting children in Africa. There is no diagnostic test and risk factors and symptoms that would allow early diagnosis are poorly documented. This study aimed to describe the clinical, electrophysiologic and brain imaging (MRI) features and complications of nodding syndrome in Ugandan children.

Design: Case series

Participants: 22 children with nodding syndrome brought to Mulago National Referral Hospital for assessment.

Outcome measures: Clinical features, physical and functional disabilities, electro-encephalogram (EEG) and brain MRI findings and a staging system with a progressive development of symptoms and complications.

Results

The median age of symptom onset was 6(range 4-10) years and median duration of symptoms was 8.5(range 2-11) years. Sixteen of 22 families reported multiple affected children. Physical manifestations and complications included stunting, wasting, lip changes and gross physical deformities. The bone age was delayed by 2(range 1-6) years. There was peripheral muscle wasting and progressive generalised wasting. Four children had nodding as the only seizure type; 18 in addition had myoclonic, absence and/or generalised tonic-clonic seizures developing 1-3years after the onset of illness. Psychiatric manifestations included wandering, aggression, depression and disordered perception. Cognitive assessment in 3 children demonstrated profound impairment. The EEG was abnormal in all, suggesting symptomatic generalised epilepsy in the majority. There were different degrees of cortical and cerebellar atrophy on brain MRI but no hippocampal changes. Five stages with worsening physical, EEG and brain imaging features were identified: a prodrome, development of head nodding and cognitive decline, other seizure types, multiple complications, and severe disability.

Conclusions

Nodding syndrome is a neurologic disorder that may be characterised as probably symptomatic generalised epilepsy. Clinical manifestations and complications develop in stages which might be useful in defining treatment and rehabilitation. Studies of risk factors, pathogenesis, management, and outcome are urgently needed.

ARTICLE SUMMARY

Article focus

- This paper offers detailed descriptions of the clinical features and complications of nodding syndrome in Ugandan children and the electrophysiologic and brain imaging features.
- It also proposes a clinical staging system for the disease.

Key messages

- Nodding syndrome is an epidemic neurologic disorder affecting children in parts of sub-Saharan Africa that may be characterised as a probable symptomatic generalised epilepsy with features of epileptic encephalopathy.
- Patients progressively develop both physical and functional deficits including multiple seizure types, cognitive and physical decline, malnutrition, and psychiatric features. Five clinical stages could be identified.
- The proposed clinical stages are associated with worsening cortical and cerebellar atrophy on brain imaging and more severe epileptiform and background EEG changes. These stages may be useful in guiding treatment and rehabilitation.

Strengths and limitations of this study

- Although the sample size is small and there is no comparison group, this is one of the few studies so far to have carefully documented the clinical features and complications of nodding syndrome combined with extensive electrophysiology and brain imaging data, describe the natural history and the first to provide a staging system.The study patients, however, may not be representative of the population, as they were not randomly drawn from the community.
- The study did not investigate aetiology and the proposed staging was mainly derived from parental descriptions rather than prospective observations and, therefore, suffers from recall bias.
- The resolution of our brain MRI images is quite low.

BACKGROUND

Nodding syndrome is a devastating neurological disorder of uncertain aetiology described in African children[1]. It was first described in Tanzania in 1960s[2] and subsequent reports have come from Liberia[3], South Sudan[4-6] and Uganda[7 8]. The syndrome is characterized by head nodding determined to be atonic seizures[8] often occurring in association with feeding, a cold breeze or cold weather and complicated by other seizure types, malnutrition and cognitive decline[6 9 10].

In Uganda, almost all affected individuals are from the north of the country where there are an estimated 3,000 cases. The region has for the past 20 years, had instability from rebel activity[11]. As a result, the population was internally displaced into densely populated camps. It is only in the last 5 years that peace returned and population returned to their homes. This region is crossed by two rivers - the *Aswa* and *Pager* Rivers, has high malaria transmission and is endemic for *Onchocerca volvulus*. This parasite has variously been associated with the *Nakalanga* syndrome (a tropical syndrome characterised by short stature and malnutrition)[12-15], epilepsy[16 17] and nodding syndrome[5 9]. This association has, however, been indirect as no O. volvulus contamination of cerebrospinal fluid has been documented[18].

There are only limited descriptions of nodding syndrome[4 5 8-10]. Winkler et al provided the most detailed account of the syndrome to date, describing clinical features in 62 Tanzanian patients and classifying them as either head nodding only or head nodding plus, if they also had other seizure types[9]. Initial symptoms allowing early recognition of the disease, its natural history and potentially modifiable risk factors are poorly characterized. There is no diagnostic test and the current case definition is based solely on clinical criteria. The objective of this study was to describe the clinical, electrophysiologic and brain imaging features and complications of nodding syndrome in Ugandan children and to propose a staging system.

METHODS

Design and setting

This is a case series of 22 Ugandan children with nodding syndrome. The study was conducted in Mulago, the National Referral Hospital in Uganda and teaching hospital for Makerere University College of Health Sciences in Kampala. This hospital provides tertiary level care for patients in a country in which most public healthcare services are paid for by the state.

Participants

Participants were patients with suspected nodding syndrome brought by the Ministry of Health from Kitgum district near the border with South Sudan, to Mulago Hospital in March 2012 for specialist assessments to better understand the syndrome. Kitgum district is the epicentre of the disease and one of the most affected districts in the country. Of the 25 patients brought to Mulago, one young adult (a 23 year old male found to have a brain tumour) and two adolescents (an 18 year old girl with a cerebellar hypoplasia syndrome and a 16 year old boy with history of cerebral malaria at the age of 4 years and subsequent neurologic sequelae) were excluded. The remaining 22 children had probable nodding syndrome and were included in the study. A case of probable nodding syndrome was defined as:

- A child older than 2 years or an adolescent who previously was developing normally
- Two or more episodes of recurrent head nodding occurring spontaneously or consequent to the sight of food or coldness
- With or without other types of seizures, neurological signs, regression in growth or learning disability.

This case definition was revised during the International Meeting on Nodding Syndrome later in 2012.However, all selected patients fulfilled the revised criteria[19].

Permission for the study was obtained from Makerere University School of Medicine Research and Ethics Committee. However, as we had no study protocol prior to the arrival of the patients, clinical care and assessment followed the hospital's standard procedures for routine non-surgical care for children. Verbal parental consent was obtained for all clinical, laboratory and imaging procedures. As is policy, however, parents gave written consent for photography, as this is considered over and above routine care and for any surgical procedures. Parents were specifically made aware that the objective of the assessments was not cure, but a better

understanding of the disease and that the general findings from the evaluation of the group of patients with nodding syndrome would be made available to the wider scientific community in presentations and publications, with the specific aim of improving the care of people affected by the disorder in the future. To this effect, a submission was then made to the Ethics Committee and permission to use results of the investigations subsequently granted.

Study measurements and Procedures

All had detailed clinical, electrophysiologic, and brain imaging assessments and laboratory testing.

Clinical assessment

The history included an inquiry about the time from pregnancy to the onset and the progressive development of symptoms, physical and functional difficulties. The clinical examination included general, nutritional, neurologic, cognitive and mental state assessments. Wasting was defined as weight for height Z score of -<2 and stunting as height for age Z score of -<2. Sexual maturity was assessed using the Tanner Sexual Maturity staging. Patients were classified as having nodding syndrome only or nodding syndrome plus depending on whether they also had other seizure types[9]. X-rays of the left wrist were taken for bone age and reported using a Greulich and Pyle Atlas by a blinded radiologist[20]. Bone growth was considered delayed if it was 2 years below the chronological age. Cognitive functioning was assessed in detail in four children - median age 14.5 (range 13-15) years - two weeks after initiation of sodium valproate using the Kaufman Assessment Battery for Children 2nd Edition (KABC-2). This test has previously been adapted for use in Uganda[21]. All four had had symptoms for longer than five years.

Laboratory procedures

Ten millilitres of blood was drawn for full blood count, ESR, malaria parasites, electrolytes, liver and renal function tests, and HIV testing. Cerebrospinal fluid was examined for cells, glucose, protein, microscopy and bacteriologic culture. In addition, 10 children had a skin snip examined for *Onchocerca volvulus* as previously described[9].

Neurophysiology and imaging

All had a 30 minute EEG recording with an XLTEK EEG system (Optima Medical Ltd, London, UK) using the 10-20 electrode placement system , which was reviewed by a consultant clinical neurophysiologist(SW) in the UK. Brain MRI in T1, T2 and Flair sequences were obtained

without contrast in 19/22 patients using a 0.5Tesla machine (BASDA Medical Apparatus, Guangzhou) and the images also examined in the UK by a Consultant Neuroradiologist (KC).

Natural history and staging

At the end of the first week after patients and carers had acclimatised to the referral hospital environment, the attending clinician sat with each carer and obtained detailed histories of the progressive development and timing of symptoms and complications of nodding syndrome to characterize the natural history. A standardised proforma with a diagrammatic representation of possible events and a linear timeline was used to obtain these descriptions. Information from each patient was plotted on the timeline and later combined with the data from other patients to identify emerging patterns, from which the proposed stages of the disorder were derived.

Treatment

Patients were started on symptomatic treatment (sodium valproate for seizure control, nutritional and physical therapy, counselling and social support) according to national guidelines developed a month earlier[22]. In this protocol, all received sodium valproate starting at 10mg/kg/day. The dose was titrated in 5-10 mg/kg/day increases according to the level of seizure control. Nutritional rehabilitation included Ready to Use Therapeutic Foods (Plumpy'Nut®, Nutriset, Malaunay) and locally prepared food. Occupational and physiotherapy, family counselling and support were provided as appropriate.

Data analysis

Data was analysed using STATA version 12 (STATA Corp, TX). Results are summarised as frequencies, proportions and medians as appropriate. The clinical features, complications and disability were then used to describe treatment and rehabilitation needs. Clinical stages were identified and brain imaging and EEG correlated with the clinical stages.

RESULTS

General features

Nine patients (40.9%) were male. The age range was 12-18 years. The median age at onset of symptoms was 6 (range 4–10) years and the median duration of symptoms was 8.5(range 2-11) years (**Table 1)**. Sixteen of the 22 families reported more than one case (median 2 (range 0–4)**)**. Prior to hospitalisation, all patients had received antiepileptic drug treatment with phenobarbitone, phenytoin or carbamazepine with no clear documentation of benefit. Treatment had often been intermittent and at sub-therapeutic doses.

Striking features on physical examination included stunting, cognitive impairment (on KABC or performance of basic tasks), lip changes ~~**(Figure 1)**~~ and other physical deformities. Several children had burns and scars from burns. The skin was dry, thin and scaly. Extremities, especially the feet, felt cold with a temperature gradient with the trunk, but a normal capillary refill time. Among those with mild lip changes, the lower lip was enlarged with no visible or palpable localised swellings. In progressively more severe cases, the mucosa was deep purple, with soft papular growths and increasingly large, thick bands of tissue. One child, not exposed to sodium valproate previously, had unexplained alopecia.

Table 1 Characteristics of 22 patients with nodding syndrome

ID	Age (years)	Duration of symptoms in yrs	Seizure based classification	Main Psychiatric morbidity	Other prominent complications	EEG Seizure classification
1	14	11	Head nodding plus other seizures types	Behaviour problems Hallucinations	Severe cognitive impairment Burns Lip deformity Severe stunting, with severe wasting Spasticity and contractures with musculoskeletal deformities	Generalised epileptiform discharges
2	13	5	Head nodding plus other seizures types	Hallucinations Aggressive behaviour	Moderate wasting	Generalised epileptiform discharges
3	15	10	Head nodding plus other seizures types	Behaviour problems Aggression Pychosocial disorder	Severe wasting Speech difficulties	Generalised epileptiform discharges
4	14	9	Head nodding only		Severe cognitive impairment Stunting	Generalised epileptiform discharges
5	16	9	Head nodding plus other seizures types	Aggressive behaviour Wandering Hallucinations	Severe cognitive impairment Speech difficulties Moderate wasting	Right temporal discharges

6	14	5	Head nodding plus other seizures types			Generalised epileptiform discharges
7	14	7	Head nodding plus other seizures types		Severe cognitive impairment Lip deformity Severe wasting	Generalised epileptiform discharges
8	18	10	Head nodding plus other seizures types	Aggressive behaviour Hallucinations	Severe cognitive impairment Speech difficulties	Generalised epileptiform discharges
9	18	8	Head nodding plus other seizures types	Psychotic symptoms Behavioural problems	Severe cognitive impairment Lip deformity Speech difficulties Severe wasting	Left temporal discharges
10	16	11	Head nodding plus other seizures types		Moderate wasting Burns Marked lip deformity	Generalised epileptiform discharges
11	15	9	Head nodding plus other seizures types	Depression	Hearing impairment Stunting Burns Musculoskeletal Deformities Severe cognitive impairment Severe wasting	Generalised epileptiform discharges
12	13	8	Head nodding plus other seizures types	Hallucinations		Generalised epileptiform discharges
13	13	3	Head nodding plus other seizures types		Moderate wasting	Generalised epileptiform discharges
14	14	9	Head nodding plus other seizures types	Hallucinations		Generalised epileptiform discharges
15	12	8	Head nodding plus other seizures types		Severe wasting Stunting Kyphosis, pectus deformity Generalised skin changes	Generalised epileptiform discharges
16	12	2	Head nodding only		Stunting Severe wasting	Generalised epileptiform discharges
17	14	8	Head nodding plus other seizures types	Post- ictal aggression Wandering	Severe cognitive impairment Stunting Lip deformity, Ataxia Speech difficulties Spasticity and contractures with musculoskeletal deformities Moderate wasting	Generalised epileptiform discharges
18	18	6	Head nodding plus other seizures types		Moderate wasting	Generalised epileptiform

						discharges
19	12	4	Head nodding only		Moderate wasting Stunting	Generalised epileptiform discharges
20	15	9	Head nodding only		Stunting	Generalised epileptiform discharges
21	15	9	Head nodding plus other seizures types		Severe cognitive impairment Lip deformity Speech difficulties Stunting Moderate wasting Spasticity with contractures and severe musculoskeletal deformity, wasting/dystrophy	Generalised epileptiform discharges
22	15	9	Head nodding plus other seizures types	Behavioural problems Aggression	Severe cognitive impairment Stunting Burns Episodes of disorientation Speech difficulties	Generalised epileptiform discharges

Growth and sexual maturity

Sixteen of the 22 children were wasted and nine stunted. Increasingly more severe wasting was observed with a longer duration of symptoms. Thus, patients with moderate wasting had symptoms lasting 3-6 years, while severe wasting was more common among those with symptoms lasting longer than 7 years. Ten had sexual maturity assessed; 3/10 children (aged 12, 13, 14 years) scored Tanner Stage 3. All remaining 7 children (ages 12-17 years) were either Tanner Stage 1 or 2. The bone age was delayed by a median 2(range 1-6) years.

Musculoskeletal findings

Almost all had peripheral muscle wasting with progressively flat feet and hands, thin cylindrical digits and increasing generalised wasting. Other physical changes included kyphosis and pectus deformities of the chest. Flexion limb deformities were seen in patients with severe disability ~~(**Figure 2)**~~**.**

Neurological, cognitive and behavioural features

Seizures

Other than head nodding, a variety of other seizure types were described in 18/22 patients - including absence, complex partial, myoclonic, and tonic-clonic seizures.

Head nodding

Nodding was precipitated by food in 16/22 children. In 4/22, it was associated with cold weather or a cold breeze, while in 13/22 it developed spontaneously. Nodding episodes came in clusters occurring during both the day and the night and were characterised by repetitive flexion and forward drop of the head. The clusters of head nodding lasted several seconds to minutes. Some children became unresponsive and stared blankly with each cluster of nodding, stopped feeding or drooled saliva.

Initially head nodding was the predominant seizure type but as the disease progressed, generalised tonic-clonic seizures became more prominent. Myoclonic seizures were not often reported, but were observed in several children while in hospital. One such child had a prolonged cluster of nodding with concurrent myoclonic jerks involving both upper limbs, lasting about 10 minutes. In a second child, similar myoclonic jerking was followed by a generalised tonic-clonic seizure. Several children had sudden falls, sustaining facial and head injuries.

Four children experienced paroxysmal events associated with fear, panic and visual hallucinations. We could not obtain clear descriptions of the images seen by two. The third child would shout and run with onset of the hallucinations and the forth reported seeing a person with knives whose intention ‘was to kill her’. None of these events was captured on EEG.

Other neurologic complications

Focal neurological signs were uncommon. There were no obvious cranial nerve palsies. However, six children were lethargic with an apathetic and expressionless face or ‘myopathic facies’. Three of the six drooled saliva while two had very slow speech and repeated epileptiform (spike and wave) discharges on EEG. The deep tendon reflexes were increased in a minority of patients. In the majority, however, the reflexes were either normal or reduced.

Vision, hearing and speech difficulties

No parent reported visual impairment and we did not test visual acuity but hearing impairment was reported in one child. Speech difficulties were reported in 10/22 children. These included immature speech for age and slow, slurred or dysarthric speech. Two children were mute but retained gestural ability and receptive language.

Behaviour and psychiatric features and complications

The earliest psychiatric manifestation was wandering behaviour or running away. Because of concerns about injury or getting lost, some parents tied up the patients to restrain them in the home. Aggression, particularly towards familiar people, was reported in 6/22 cases, manifesting 3-6 years after onset of nodding. In two children, the onset was concurrent with wandering behaviour. Five children had sleep difficulties and at least 8/22 had moderate to severe mood problems with one clinically depressed.

Cognitive function

All 22 children had cognitive difficulties and were out of school. Academic performance declined with symptom onset; as symptoms increased, pupils started getting poorer grades and were eventually withdrawn from school within 2-4 years of disease onset. Three of the 4 children who had cognitive functioning assessed using the KABC-2 responded to the test instructions. The fourth child did not respond at all. All 3 children had severe cognitive impairment (**Table 2**).

Table 2: Cognitive function on the KABC 2nd Edition in 3 children two weeks after initiation of sodium valproate

Cognitive Domain	Patient 1 Male 13 years		Patient 2 Male 15 years		Patient 3 Male 15 years	
	Test Score	Age equivalent in years	Test Score	Age equivalent in years	Test Score	Age equivalent in years
Working memory	8	<5	7	<5	21	=5
Planning	7	<8	1	<5	3	<5
Learning	28	<5	25	<5	54	=5
Visual spatial	0	<5	0	<5	31	<5
Knowledge	11	<5	5	<5	52	<8

Laboratory findings

The mean haemoglobin was 12.4 (range 10.8–14.8) g/dl and the mean red cell volume was 81.4 (range 65.8-89.1) fl. Five children had iron deficiency anaemia. The total white blood cell and platelet counts were normal but 10/22 children had eosinophilia, median eosinophil count 0.4 (range 0.1 – 1.9) x 10^9/L. The ESR was high in 17/22 children with a median of 28.5 (range 5-90) mm in the first hour. Other than mild elevations of gamma GT, the liver and renal function was normal. All tested negative for malaria on admission to Mulago, although one subsequently developed malaria in the third week of hospitalisation. Nine children had osteopenia on x ray but only one had hypocalcaemia and four hypophosphataemia. Creatine kinase levels were normal in all children and all tested HIV negative. Cerebrospinal fluid total protein, cells and glucose were all normal and all bacteriologic cultures had no growth. Three out of 10 patients had *O.volvulus* microfilaria on the skin snip. Microfilaria density was, however, not reported.

EEG

The routine diagnostic EEG was abnormal in all cases. The background activity showed a generalised excess of slow activity mainly in the conventional theta and delta frequency ranges. Generalised inter-ictal epileptiform activity was observed in all but two patients, in whom there were focal temporal discharges (unilateral in one and bilateral in the second). All patients with generalised epileptiform activity had high amplitude spikes or sharp waves, some associated with slow wave activity and often occurring in irregular bursts rather than runs (**Figure ~~3~~1**). There was no consistent frequency to this. The discharges had bilateral fronto-temporal or fronto-centro-temporal emphasis, but some were more generalised and increased in frequency in light sleep. There was a clear gradation from mild to more severe background abnormalities and epileptiform activity. No overnight recordings were performed. The EEG findings suggested symptomatic generalised epilepsy in 20 and symptomatic focal epilepsy in the remaining 2.

Brain imaging

Brain MRI without contrast was performed in 19/22 patients. The imaging showed different degrees of cortical and cerebellar atrophy. No focal cerebral cortical or hippocampal changes were observed (**Figure 42**). Cerebellar disease was evident in the majority of cases, but among patients with especially generalised cortical atrophy, there was a suggestion of more atrophy in the occipital lobes or the parieto-occipital regions than anteriorly.

Disease progression

Five stages with deteriorating seizures, neuro-cognitive and psychiatric disability were identified: a prodrome; development of head nodding and cognitive impairment; other seizure types; multiple complications and severe debilitation (**Panel 1**).

Panel 1: A mum's description of the sequential chronology of symptoms and disease progression in her 18 year old daughter.

"She was growing well until the age of 8 years when symptoms of nodding began. The head nodding is triggered by food. When food is given, she freezes with it in her hand, stares blankly into space with a fixed gaze, and then nods repeatedly for a time which varies with each episode but the maximum time was initially 5 minutes. The symptoms got worse with time and about 6 years later, the nodding symptoms were immediately followed by or associated with big seizures during which the whole body shook. She would drool saliva, foam around the mouth and loses consciousness. After the big seizure, she would sleep and on waking is often weak and sometimes disoriented. On some nights, she reports seeing a figure that holds a knife and wants to kill her. She is distressed by her illness and gets embarrassed on waking if she had a seizure in public. She is very quiet but sometimes aggressive. Overtime, her speech has become sluggish. Although she is 18 years old, she still has childish behaviour which is evident as she speaks. Her father died following a febrile illness. She has six siblings two of who have similar symptoms."

Stage 1 The prodromal period

This poorly defined and short-lived period was reported in four patients. The earliest symptoms included "dizziness" and increasing inattention. The children were excessively sleepy, lethargic and would sometimes stare blankly during meals.

Stage 2 Development of head nodding

Among the four patients reporting prodromal symptoms, head nodding developed within 6 weeks of the prodrome. In the majority, however, the initial feature was an abrupt onset of nodding. Subsequently, parents reported declining cognitive abilities and behaviour difficulties. Disease progression however appeared to arrest in these four.

Stage 3 Development of other seizure types

Apart from the four children with nodding only, 18 children developed other seizure types including absence, complex partial, myoclonic and generalised tonic-clonic seizures. One child developed generalised tonic clonic seizures almost simultaneously with the nodding. In the others, however, additional seizure types developed 1-3 years after initial symptoms. It was around this time that almost all school going children dropped out of school.

Stage 4 Development of multiple complications

Multiple complications developed 4-8 years after the initial symptoms, associated with marked regression in achievement. These consisted of deteriorating behaviour and psychiatric symptoms and a decline in motor, speech and other cognitive functions. Some patients developed physical deformities including kyphosis, limb and pectus deformities ~~(**Figure 2**)~~. Some sustained severe facial injuries with "drop attacks" and burns. Those who were still independently mobile would wander about or run away and were prone to getting lost. Changes in the architecture of the lower lips ~~(**Figure 1**)~~ also occurred at this time. With disrupted and poor feeding, the children became severely wasted.

Stage 5 Severe disability

These children have little, if any, 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. Some had contractures around the major joints.

Patients with head nodding only had less cortical and cerebellar atrophy on brain MRI compared to those with multiple complications. In addition, there was a clear gradation from milder to more severe epileptiform and background EEG abnormalities in patients with the later clinical stages of the disease.

Response of seizures to sodium valproate

The patients had previously been on mostly low doses of various anti-epileptic drugs including phenytoin, phenbarbitone and carbamazepine. In conformity with proposed national guidelines, all were started on sodium valproate and the other anti-epileptic drugs weaned off. Prior to this, a 24 hour seizure count was obtained and this was repeated 14 days later. Overall, there was a 57% reduction in total seizures including clusters of nodding. The median total daily number of seizures reduced from 5 (range 2–14) on admission to 2 (range 0-8) 14 days after initiation of sodiumvalproate. Concurrent improvements were also seen on the EEG with substantially reduced or absent interictal discharges in 3/5 patients who had repeat recordings on the day of assessment **(Figure ~~3~~1)**.

DISCUSSION

Recently, there have been media reports of “a mysterious disease” baffling scientists – the nodding syndrome.[7 23 24] There are many uncertainties about this newly recognized disorder: what is the cause, the pathogenesis, disease classification, clinical spectrum and treatment? In this paper, we describe the clinical features and complications of nodding syndrome in Ugandan children, together with the EEG and brain imagingappearances. Our findings suggest that nodding syndrome is a neurologic disorder characterised by a symptomatic generalised epilepsy.

Clinical features and complications

Nodding syndrome in Ugandan children manifests with head nodding, cognitive dysfunction, psychiatric features, and/or multiple seizure types. It may be complicated by stunted growth, pubertal delay, wasting, motor decline and physical deformities. The earliest manifestation is a poorly defined prodrome followed within weeks by head nodding. In the later stages, there is cognitive dysfunction, psychiatric disturbance, and severe muscle wasting and musculoskeletal deformity. Delayed physical growth, bone age and sexual maturity are common in affected children. This may partly be a result of delayed puberty, since most were in Tanner Stage 2. Pubertal delay may be secondary to chronic illness, poor nutrition and/or psychosocial deprivation. If so, improved nutrition, a supportive environment and symptom control should lead to improved growth and the initiation of puberty.

The progressive stages of the disorder appear to reflect the natural progression of an epileptic encephalopathy. In Stage 1, there are brief seizures, while by Stage 3 uncontrolled seizures prevent the child from continuing in school. In Stage 4 a high seizure burden contributes to regression, which together with ensuing poor nutrient intake leaves a severely disabled child by Stage 5, when multiple factors impair functioning.

The clinical features in Ugandan children are as severe as in South Sudanese children,[6] but may be more severe than in Tanzanian patients[9]. Despite similar age of onset and duration of symptoms, only 18% of Ugandan children had the milder nodding only variant, compared to 45% in Tanzania; all our patients had abnormal interictal background EEG compared to 60% in Tanzania. Ugandan children also had more severe cognitive impairment and a much greater burden and variety of seizures. These differences may suggest a variation in the presentation of

the disease by region. Family clustering in all three countries, however, suggests a common exposure factor.

Aetiology and pathogenesis

The aetiology of nodding syndrome and pathogenesis of the complications remain unknown. A variety of viral central nervous system infections have been screened for on PCR but no association has been demonstrated[19]. An association with infestation with *Onchocerca Volvulus* has been reported in some series,[5 9] but has not been evident in other studies.[18 25]. Other aetiologic considerations have included toxic brain injury, inflammatory brain disease, a slow virus infection or prion disease, an atypical mitochondrial disease or other genetic disorder. Repeated severe psychological trauma has also been proposed as a mechanism[26]. Earlier studies by the Ugandan Ministry of Health and the US Centers of Disease Control found a higher proportion of cases with low serum vitamin B6 compared to controls. Although unlikely, the possibility was raised that nodding syndrome could be an atypical form of pyridoxine dependent epilepsy. Studies to explore this hypothesis further are awaited[27].

Children with the syndrome show some features reminiscent of prion protein disease, including motor and cognitive dysfunction, epilepsy, behaviour and psychiatric morbidity. However, other features commonly seen in prion disease - such as extrapyramidal involvement and cortical blindness - have not been reported. The age of onset of symptoms is also much younger and progression much slower[28]. The brain imaging and EEG findings too are not suggestive of prion disease. Nevertheless, brain biopsy or autopsy studies would be important in excluding prion disease.

The brain MRI findings might suggest viral encephalitis, a para-infectious phenomenon (such as an antibody- mediated channelopathy) or even a neurotoxin as possible aetiologies. A genetic disorder or metabolic disease is also possible. Future studies should also consider the recently described auto-immune encephalitides. Among Tanzanian patients, hippocampal ~~gliosis~~sclerosis, probably from inflammation, was described in some patients[9]. Although this could partly explain the cognitive difficulties, we did not observe such lesions, even in the sub-group with more severe cognitive impairment. We consider that an epileptic encephalopathy is more likely. The background EEG in all 22 cases showed a generalized excess of theta and slow activity. Prolonged EEG recording (including during sleep) with detailed

neuropsychological testing and functional brain imaging may help with understanding the pathogenesis of cognitive decline.

Study limitations

Our patients may not be a representative sample, as they were not drawn randomly from the community. The study did not investigate aetiology and the proposed staging was derived primarily from parental descriptions rather than prospective observations and so may be influenced by recall bias. We only performed routine diagnostic EEGs, rather than prolonged recordings which are important in investigating associations between seizures and cognitive dysfunction. The resolution of our MRI images is also quite low.

CONCLUSIONS

Nodding syndrome is a neurologic disorder that is complicated by multiple physical and functional disabilities and may be considered as symptomatic generalised epilepsy. Assessment and care should be provided by a multidisciplinary team. Studies of aetiology, pathogenesis, evidence- based treatment and rehabilitation strategies are urgently needed.

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Author contributions

RI, ROO, AKM, HAT, TPW, PB, JN1, SBM, ADM, HN, , EM, JN2, SK, JRA and JKT all participated in patient care and performed the different assessments. ROO, AKM, HAT and SBN were in-charge of daily care, TPW and EM performed the growth and sexual staging assessments, JN1 the psychiatric assessments, HN the nutrition assessment, SW reported the EEG recordings, KC the brain MRI and RI wrote the first draft. All provided a critical review of the manuscript.

Conflict of Interest

The authors report no competing interests.

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Figure legends

Figure 1 ~~Lip changes~~

~~The figure shows changes in the lips with increasing distortion. In patients with mild involvement, the lower lip is enlarged but with no visible or palpable swellings. With more severe involvement, there is deep purple discolouration of the mucosa, soft papular growths and increasingly larger and thicker bands of tissue. Other oral abnormalities included lacerations and loss of teeth from injuries.~~

~~Figure 2 Muscle wasting, deformities and contractures~~

~~Figure 2 shows wasting of the muscles of the foot, knee and foot flexion deformities and contractures, pectus deformity of the chest and kyphosis. Such marked deformities were seen with increasing symptom duration.~~

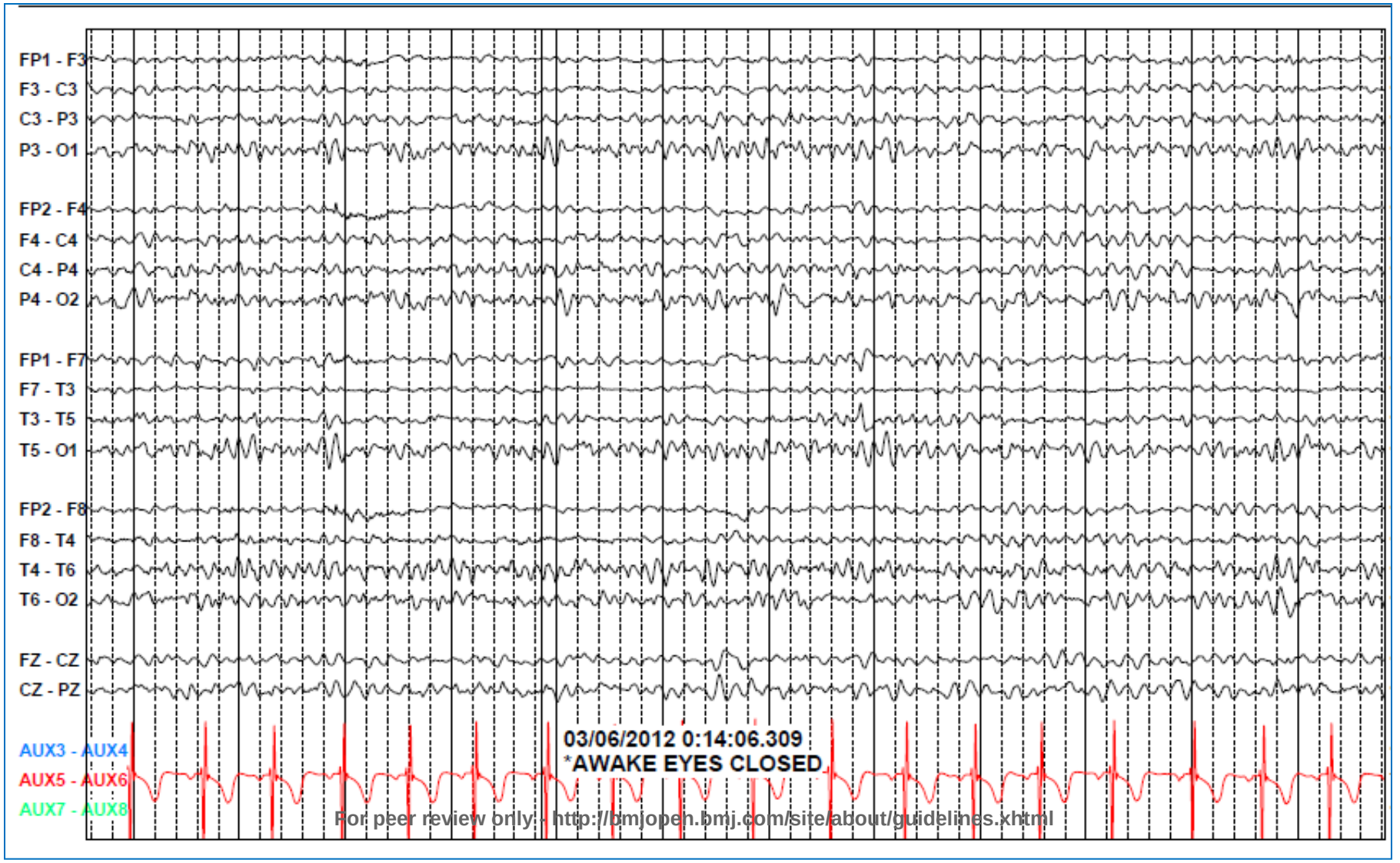
~~Figure 3~~ EEG recordings

Figure ~~3~~ 1 is an EEG recording of a 12 year old girl. She had head nodding and cognitive impairment. During the recording, interictal epileptiform discharges (spikes and sharp waves) were observed in wakefulness (1~~3~~a) and during light sleep, when more prominent epileptiform discharges were evident. There was no apparent clinical change with these discharges (~~3b~~1b).

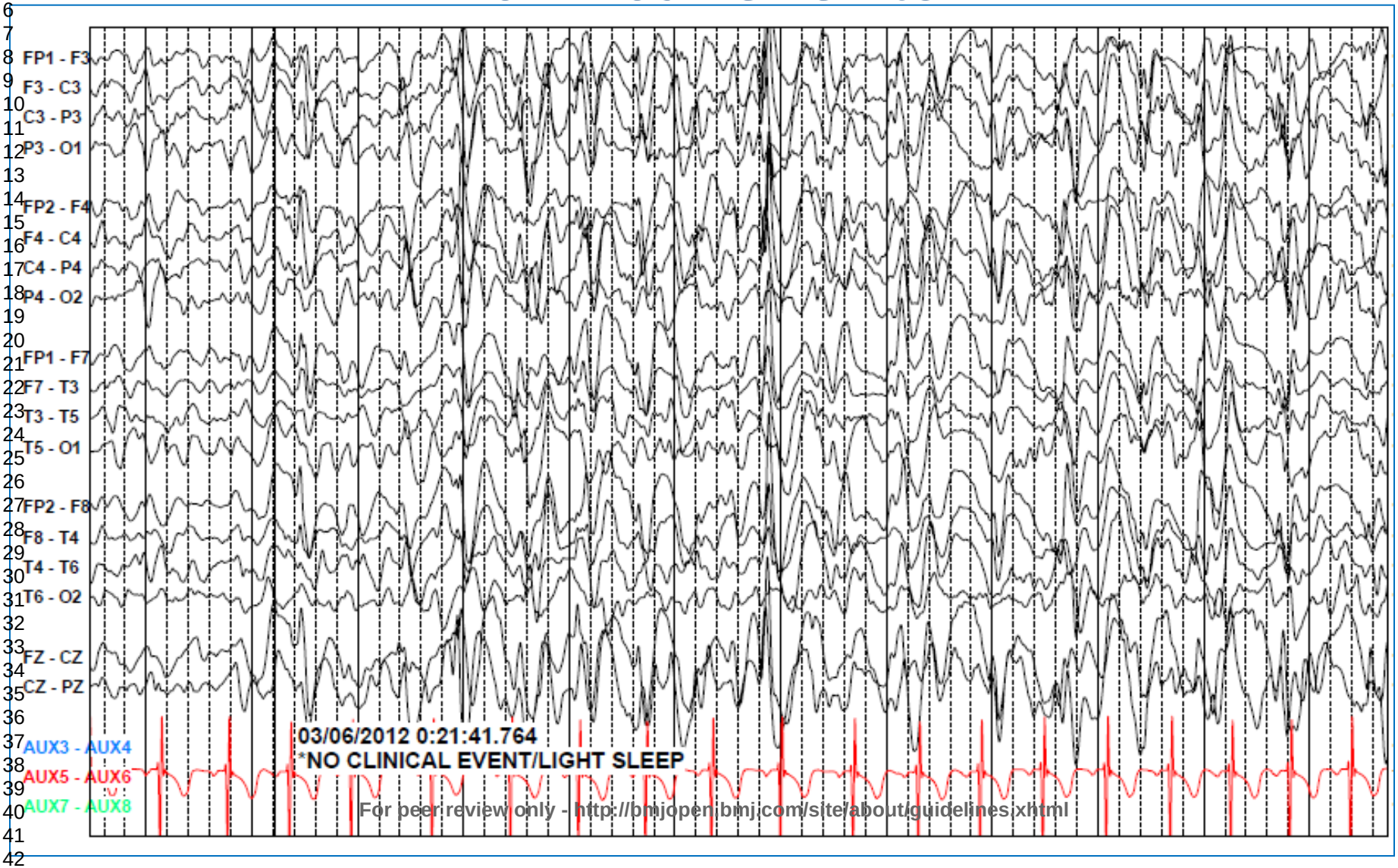
Figure ~~4~~2 Brain MRI

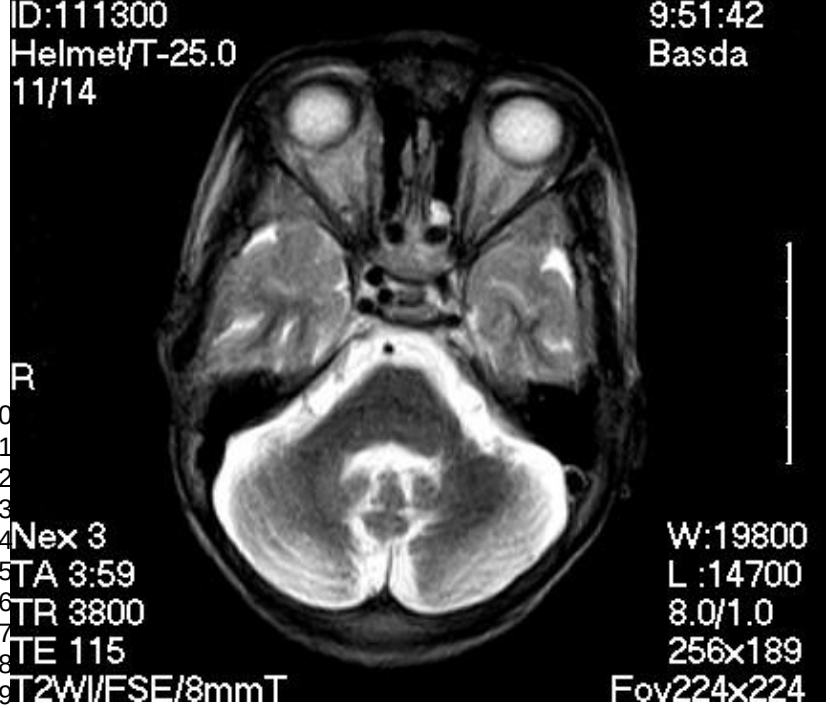
Figure ~~4~~ 2 shows T2-weighted brain MRI images in the axial (Fig ~~4a~~2a, ~~4b~~2b) and sagittal (Fig ~~4c~~2c, ~~4d~~2d) plane showing marked cerebellar atrophy and generalised cerebral atrophy.

EEG at onset of recording - awake

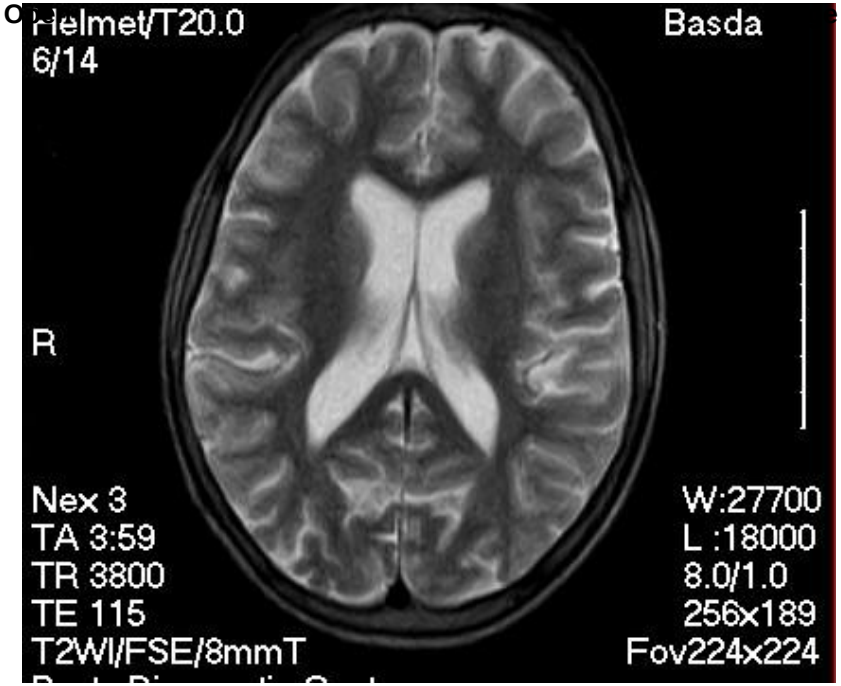


Florid discharges in light sleep, no clinical events

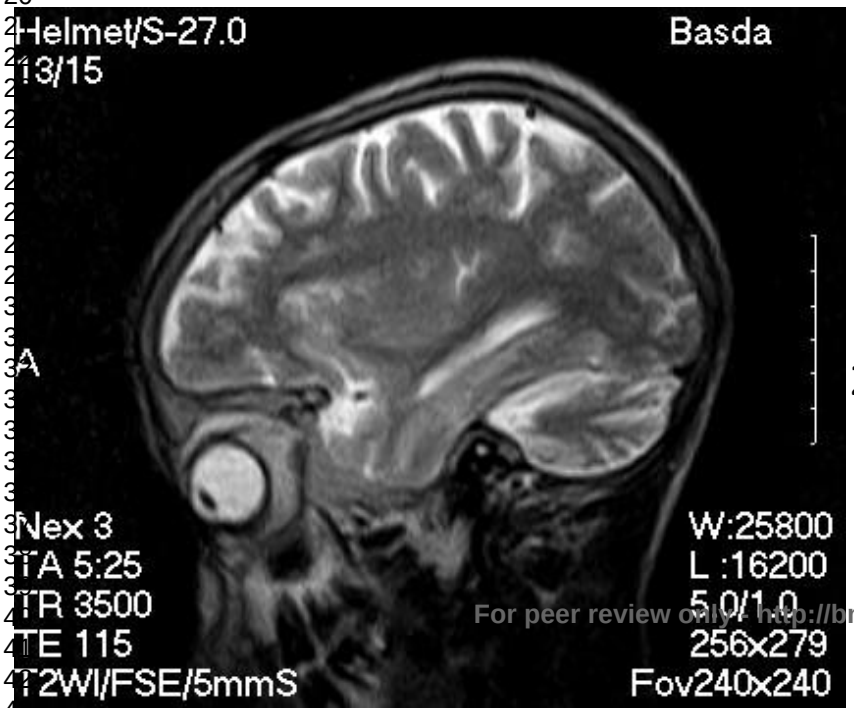




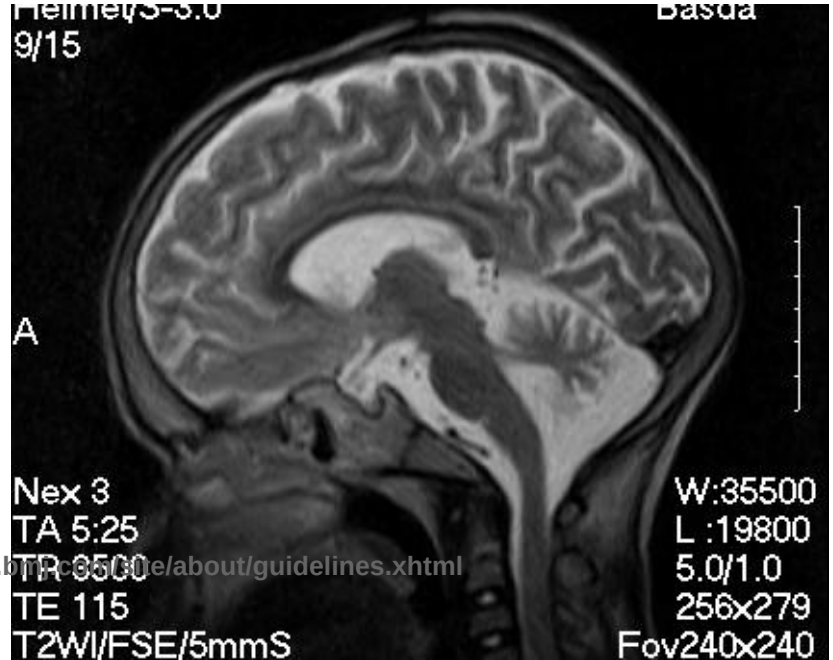
2a



2b



2c



2d

R Idro et al, Nodding Syndrome in Ugandan Children

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	N/A
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	N/A

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4-5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	12-13
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	-
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	7-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-13
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.