Nodding syndrome
– a new infectious(?) disease entity in Eastern Africa

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Learning objectives

- Provide an overview of nodding syndrome
  - History
  - Clinical manifestations
  - Summary of studies aetiology
  - Preliminary studies on outcomes

- Invite suggestions on a way forward

Nodding Syndrome; a mystery?

BMJ

BMJ 2012;344:e349 doi: 10.1136/bmj.e349 (Published 13 January 2012)

NEWS

Ugandan authorities deal with a mysterious ailment that leaves people nodding continuously

Henry Wasswa

Kampala

Ugandan health authorities have launched strategies to deal with a strange disease that has left dozens of people dead in the north of the country and 3000 others, mostly children, nodding continuously.

The ailment, which was first detected in 2009, has mostly affected people in the three districts of Kitgum, Lamwo, and Pader but has also spread in recent weeks to two other districts of Agago and Amuru. Those affected become severely weak, have trembling hands, go into cognitive decline, and

Lawrence Ojom, the director for Kitgum Hospital in the Acholi region of northern Uganda, told the *BMJ* that "there are many patients being brought for treatment but there are many more in the community."

The WHO says that the disease was first detected in neighbouring Tanzania in the 1960s and later in Southern Sudan.

Appropriate nutritional support is required to stem the disease, which is not contagious, said Dr Fisseha.

The health ministry, which launched an investigation into the

CMAJ NEWS

Nodding disease confounds clinicians

Mary Odong sits on the floor of a clinic in northern Uganda as her foot starts to twitch. Her body goes rigid and she drops to the mat, spasming several times and whimpering. She begins to cry and bob her head like a pendulum gone amok.

The 15-year-old girl is suffering from "nodding disease," or nodding syndrome, as some call it, a disabling and often fatal condition characterized by nodding seizures. It typically afflicts children between the ages of 5 and 15. The seizures often begin when a child eats or feels cold. The ensuing pathology is harsh: mental retardation, a damaged hippocampus, stunted growth.

There is no cure, and treatment is largely confined to symptomatic relief in the form of anticonvulsants. The cause of nodding disease remains a mystery. It was first identified in isolated, mountainous communities in Tanzania in the 1960s.

By the middle part of the 2000s, it was increasingly found in Uganda and South Sudan, particularly along the Yei River, leading many to surmise a link to the parasitic worm *Onchocerca volvulus*, which causes river blindness (www.cmaj.ca/lookup/doi/10.1503/cmaj.090821).

But the worm is commonly found in areas with no incidence of disease, and the evidence doesn't appear to firmly support a causal link between the two. Nor does the evidence support another postulate, such as whether the disease is caused by consuming chemically contaminated monkey meat or by a vitamin deficiency.

It's a riddle, says Dr. Scott Dowdell, director of the United States Centers for Disease Control's Division of Global Disease Detection and Emergency Response, who was dispatched to Uganda in 2009 with a team of epidemiologists to root out the cause of the disease.

"It's quite clear now that this is going to take a while to figure out and that we need to be in this for the long haul, because the answers are not so simple or straight forward," says Dowdell.

The team has ruled out more than 30 different hypotheses, including one that nodding disease — which now afflicts 3000 children in Uganda, according to the country's ministry of health — was the product of chemical weapons used in the war between the Ugandan government and the rebel Lord's Resistance Army.

Virus testing in 18 families has revealed nothing, but Dowdell remains hopeful that a link can still be found to a parasite from the Onchocercidae family. Recent skin snips taken from patients in Uganda and South Sudan have revealed high rates of infection with microfilaria from that family of parasites, he says, adding that infection with microfilaria "is a lot more common in the nodding syndrome patients than the controls. That has been a consistent finding in the studies that we have done."

NEWS

Nodding syndrome leaves baffled scientists shaking their heads

ouise Jilek-Aall was a young Norwegian hysician working in the Mahenge mountains f Tanzania in the 1960s, when she noticed hat an unusual number of people there uffered from a debilitating convulsive isorder preceded by a peculiar symptom: in hildhood, their heads would bob back and orth for minutes at a time. The head nodding sually stopped before the general seizures set n. But when the epilepsy started, the children ere typically weaker and of lesser intelligence han other children of the same age, often ith neurological symptoms not seen in eople with general epilepsy. The disease was unexplainable to me," recalls Jilek-Aall, now professor emerita at the University of British Columbia in Vancouver.

For years, the disease remained an isolated ddity. But over the past decade, physicians egan observing this 'nodding syndrome' in everal African countries, where it continues o perplex researchers to this day. "Nobody has et been able to find an explanation," says Jilek-aall, "and we are not sure that we are always escribing the same phenomenon."

The latest attempt to find an explanation taken from children with and without nodding syndrome for signs of the infection.

Reporting in the 27 January issue of the *Morbidity and Mortality Weekly Report* (61, 52–54, 2012), the researchers found that 22 of 25 children with nodding syndrome in one South Sudanese community had the parasitic infection compared to 11 of 25 healthy controls. But the CDC team failed to find any such difference in the second village they visited, with around half of all individuals there infected with the worm whether or not they suffered from nodding syndrome.

"It is still a significant finding that there is some association with onchocerciasis and tells us this is one direction we should continue to pursue," says Sudhir Bunga, the CDC epidemiologist who led the latest study. However, Bunga is quick to point out that the observed association does not necessarily imply a causative relationship. "We do not know whether the infection with onchocerciasis occurred before or after the onset of nodding syndrome," he says. "The skin snip only tells us that they are currently positive."

The findings are largely consistent with

50, 2008–2015, 2008). Last autumn, the CDC also sent scientists to Uganda to investigate more than 1,000 cases of nodding syndrome there. Although the results have yet to be published, agency insiders say the association with the river blindness parasite is similar to that reported from the first South Sudanese community, with a positive association between the worm and the syndrome.

As *Nature Medicine* went to press, data from other candidate drivers of disease—including vitamin deficiencies, genetic markers and worm-specific antibodies—were still being analyzed from the Sudanese and Ugandan cohorts but had not been reported publically. "We have managed to rule out some potential associations," Bunga says of his team's unpublished findings. "But at the same time we still have multiple routes of investigation to pursue."

Heading off nodding

Even without definitive evidence of nodding syndrome's root cause, the CDC intends to move ahead with interventional drug trials. "We plan to assess the effectiveness of standard

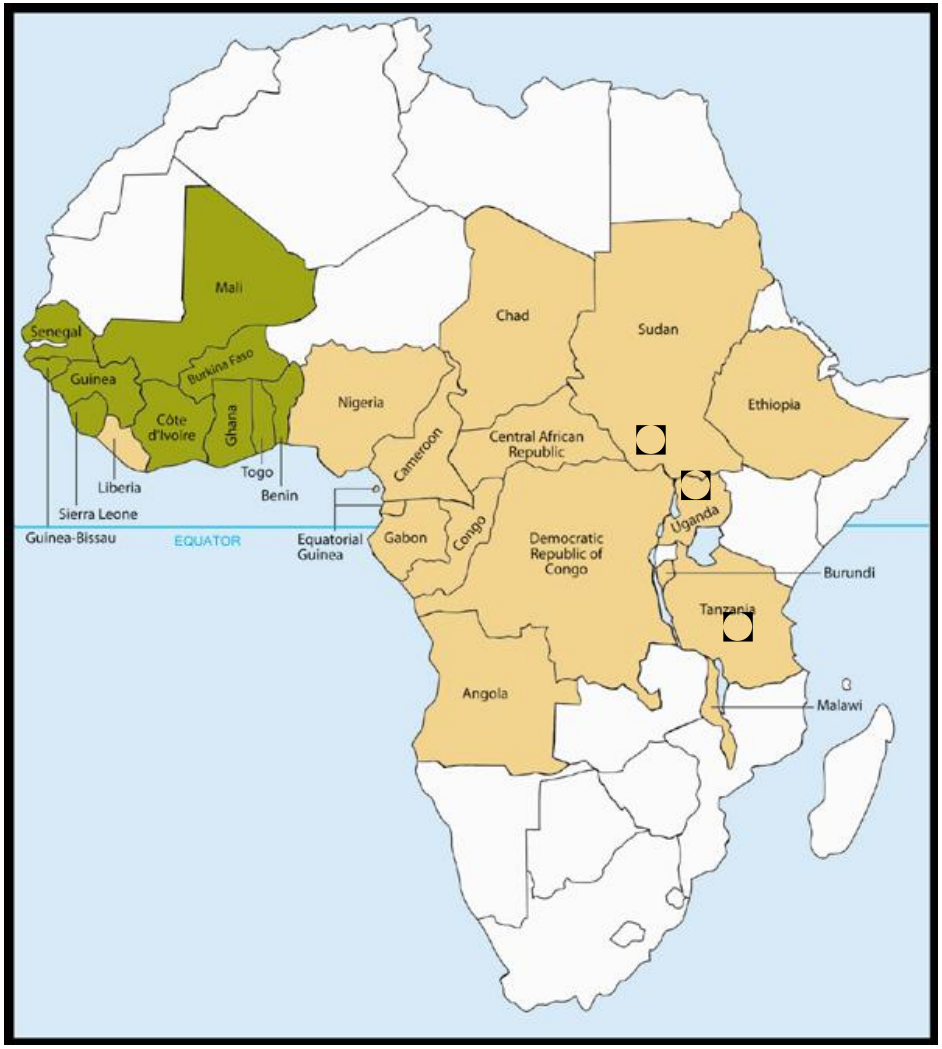
Historical perspectives

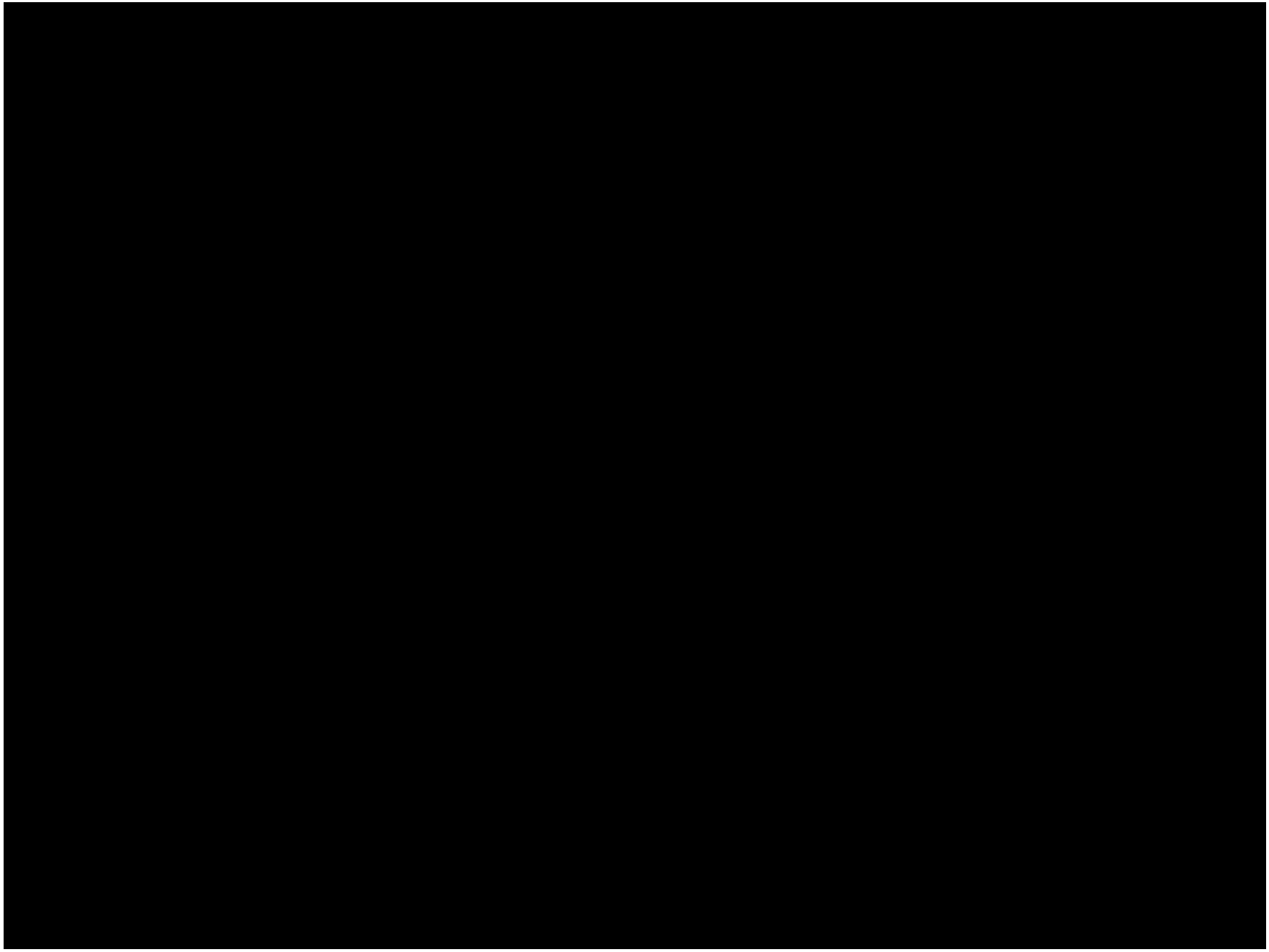
- First described by Dr Aall L Jilek – in 1960's
  - Repetitive involuntary head nodding among Wapogoro tribe – Mahenge, Tanganyika - Aall-Jilek et al 1962, 1965.
  - Descriptions by WHO teams in South Sudan 2001/2
  - More detailed descriptions by Winkler et al 2008, 2010

Photo by Prof Andrea Winkler

Countries known to have cases

- Tanzania (Southern)
- Uganda (Northern)
- South Sudan (Western)
- Non-contiguous areas
  - Endemic for Onchocerciasis





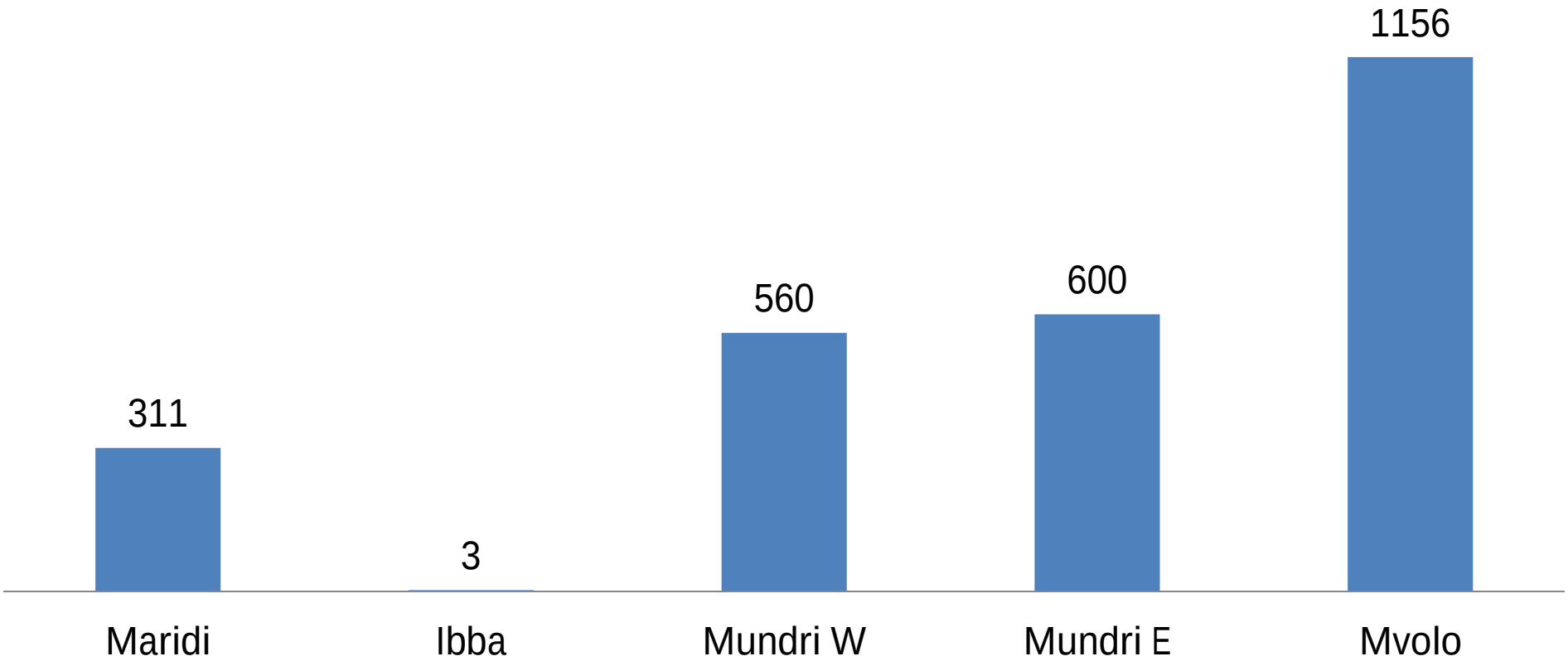
What is the burden?

- Exact number unknown
- Estimates 5000 – 8000 cases

What is the burden of Nodding Syndrome in Uganda?

District	Patients with suspected nodding syndrome in phase 1 community survey	Suspected nodding syndrome patients receiving treatment centres	Patients with other epilepsies receiving treatment at the same centres
Amuru	-	61	62
Gulu	-	333	515
Kitgum	1,086	1,321	2,034
Lamwo	489	349	122
Lira	-	13	344
Pader	1,982	1,210	1,252
Oyam	-	8	860
Total	3,545**	3,295	5,189

Distribution by County in Western Equatoria State - 2011



Slide Courtesy of Dr Lul Riek

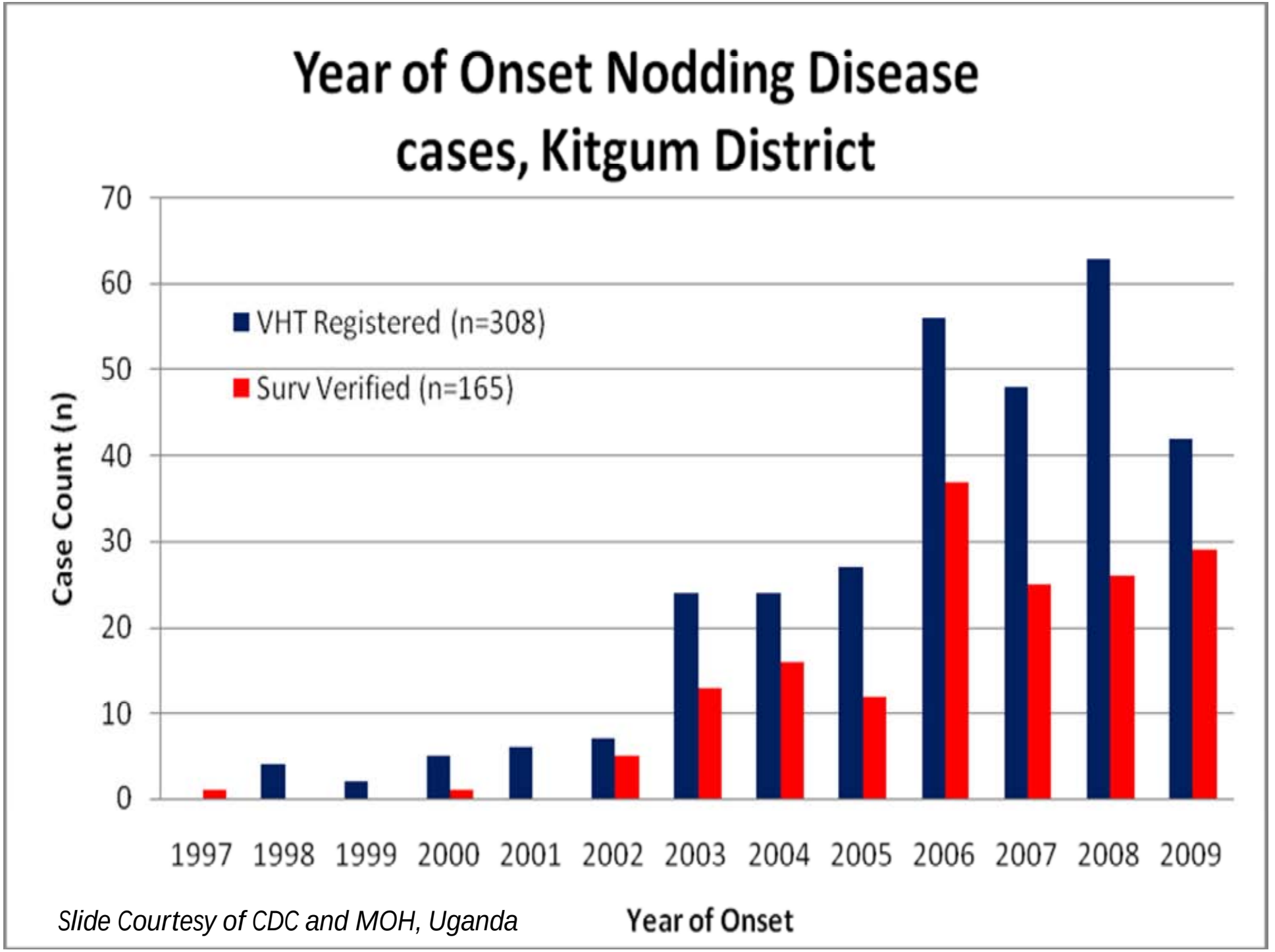
Clinical descriptions

- Winkler et al. The head nodding syndrome; clinical classification and possible causes. *Epilepsia* 2008;49(12):2008-15.

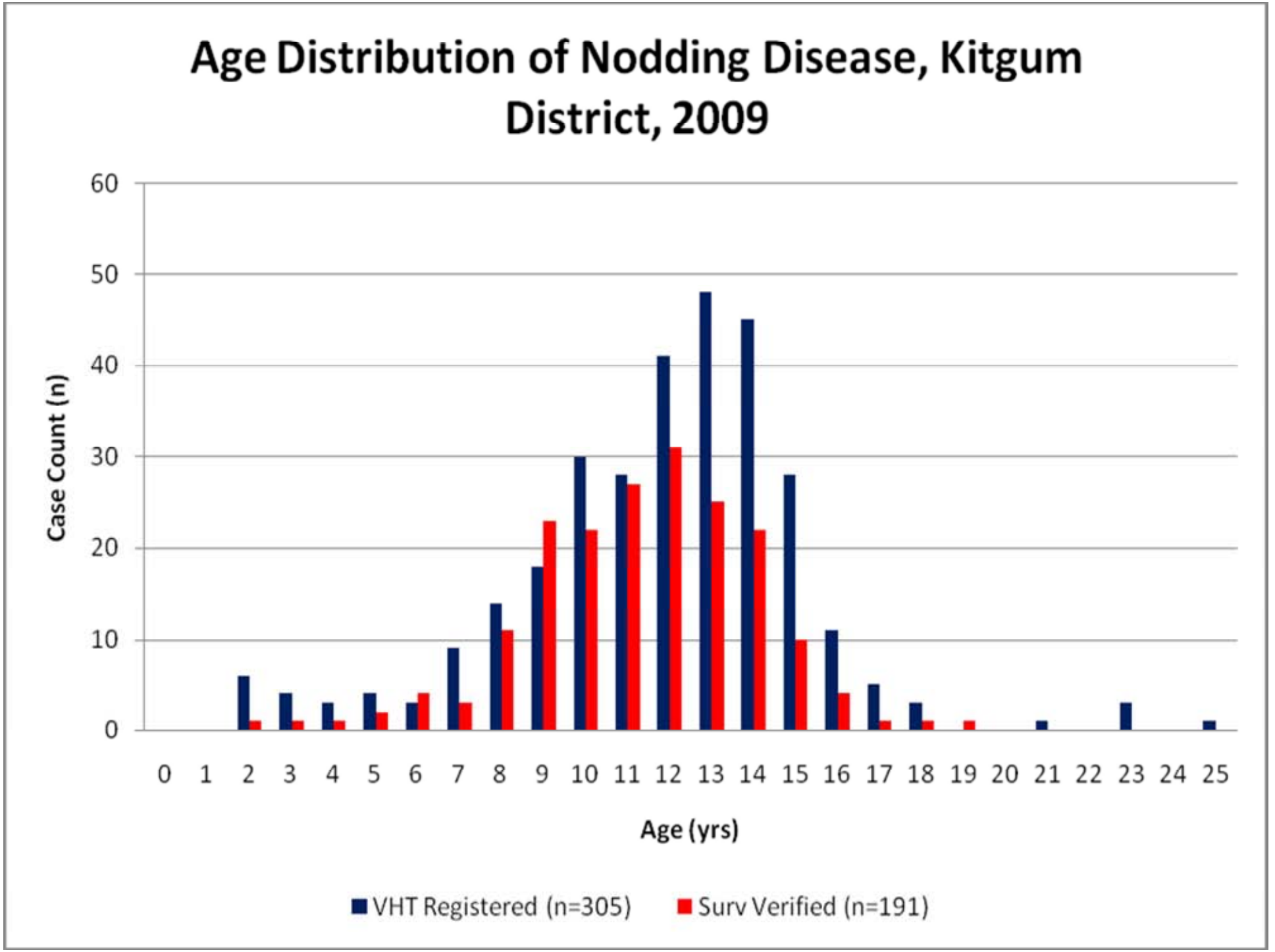
- Nyangura et al. Investigation into the nodding syndrome in Witto Payam, Western Equatoria State. *South Sudan Med J* 2011; 4(1):3-6.

- Sejvar et al. Clinical, neurological, & electrophysiological features of nodding syndrome in Kitgum, Uganda. *Lancet Neurol* 2013; 12: 166-174.

- Idro et al. Nodding syndrome in Ugandan children – Clinical features, brain imaging and complications. *BMJ Open* 2013; 3:e002540



Slide Courtesy of CDC and MOH, Uganda


Age Distribution of Nodding Disease, Kitgum District, 2009
Case Count (n)
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
Age (yrs)
VHT Registered (n=305)
Surv Verified (n=191)

What are the main features of Nodding Syndrome?

- Early manifestations
  - Not well described
  - Initial period of increasing inattention, dizzy spells, withdrawal
  - Head nodding
    - While eating or on sight of food; cool weather/breeze or unprovoked
    - Increasing frequency and clusters

Subsequent features and complications

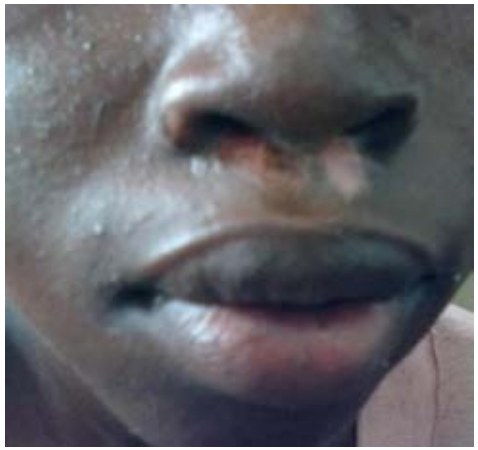
- Development of other seizures 1-3 yrs after onset of symptoms
  - Mostly GTCs
  - Focal, myoclonic, atypical absences
- Cognitive decline
  - Many drop out of school 1-2 yrs later
  - Drooling, Speech difficulties
- Psychiatric manifestations
- Malnutrition
- Growth failure/stunting and delayed sexual development
- Musculoskeletal abnormalities
  - Muscular wasting, contractures
  - Deformities of the chest, back, hands, legs(knees) and feet/ankles, lip changes

Physical growth, sexual development and stunting

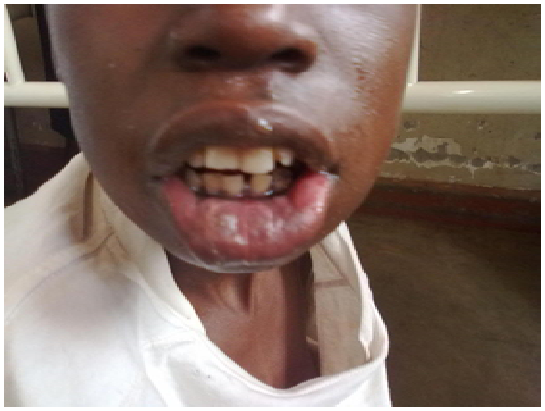
Biological siblings: - 13 yr old boy with nodding syndrome and severe stunting together with his 16 yr and 17yr old siblings; increase in height in that order

Photo Courtesy of Dr Hanifa Namusoke

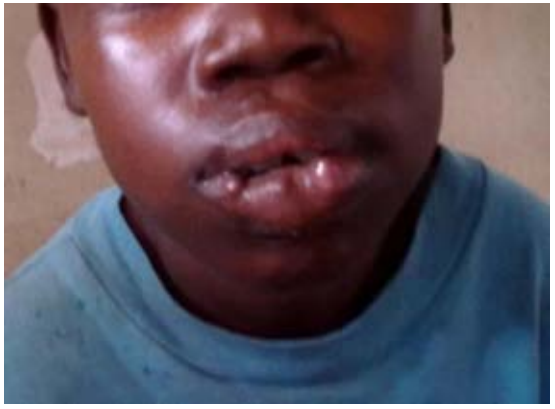
Lip Changes



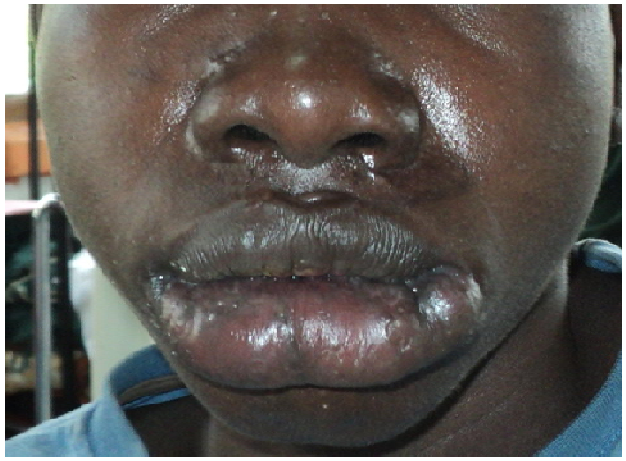
Lip Changes stage 1



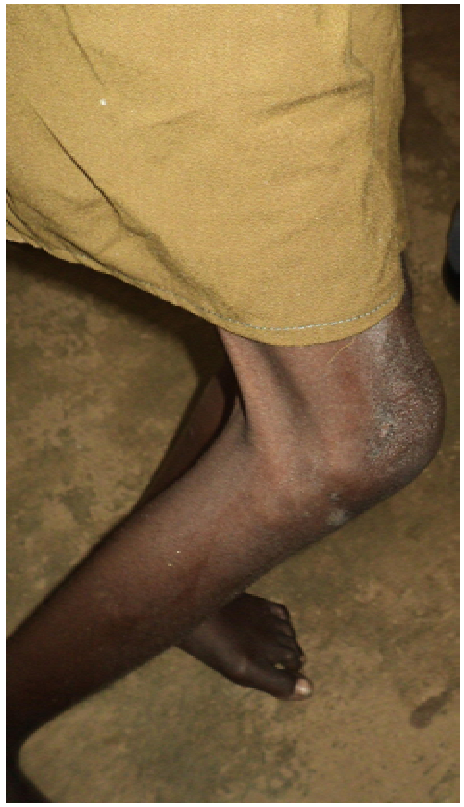
Lip Changes stage 2



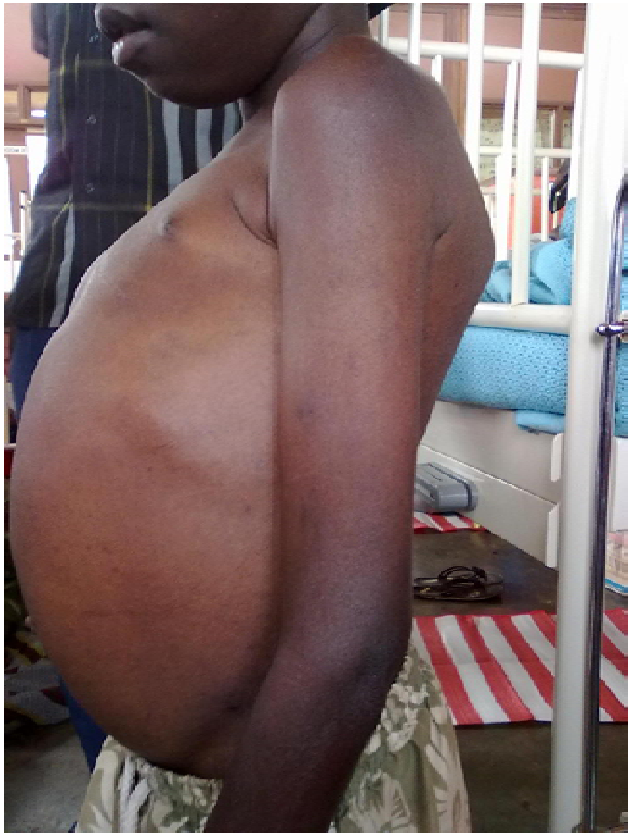
Lip Changes stage 3



Lip Changes stage 4



Flexion deformities and contractures around the knee joint and the foot.

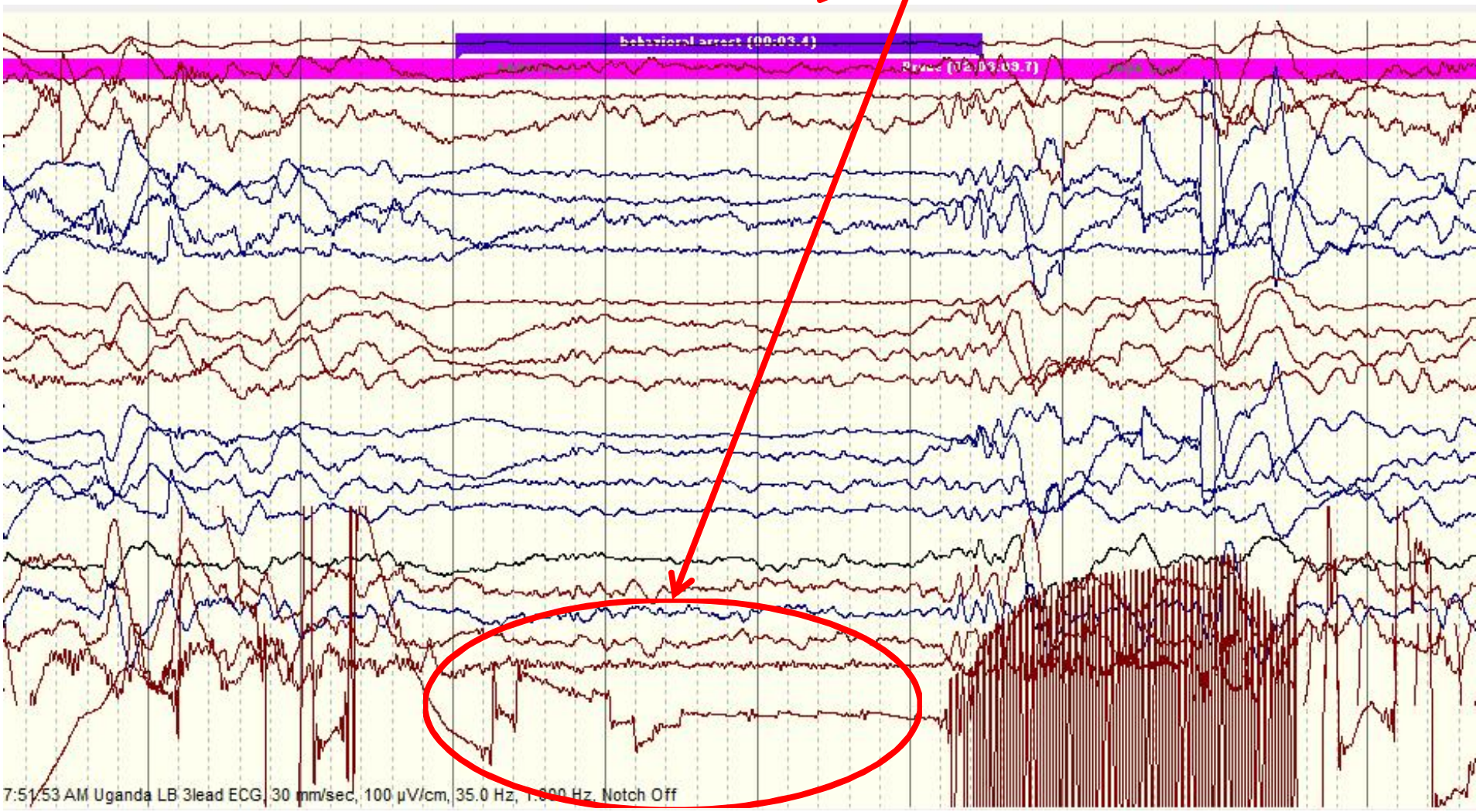


Kyphosis and pectus deformity of the chest

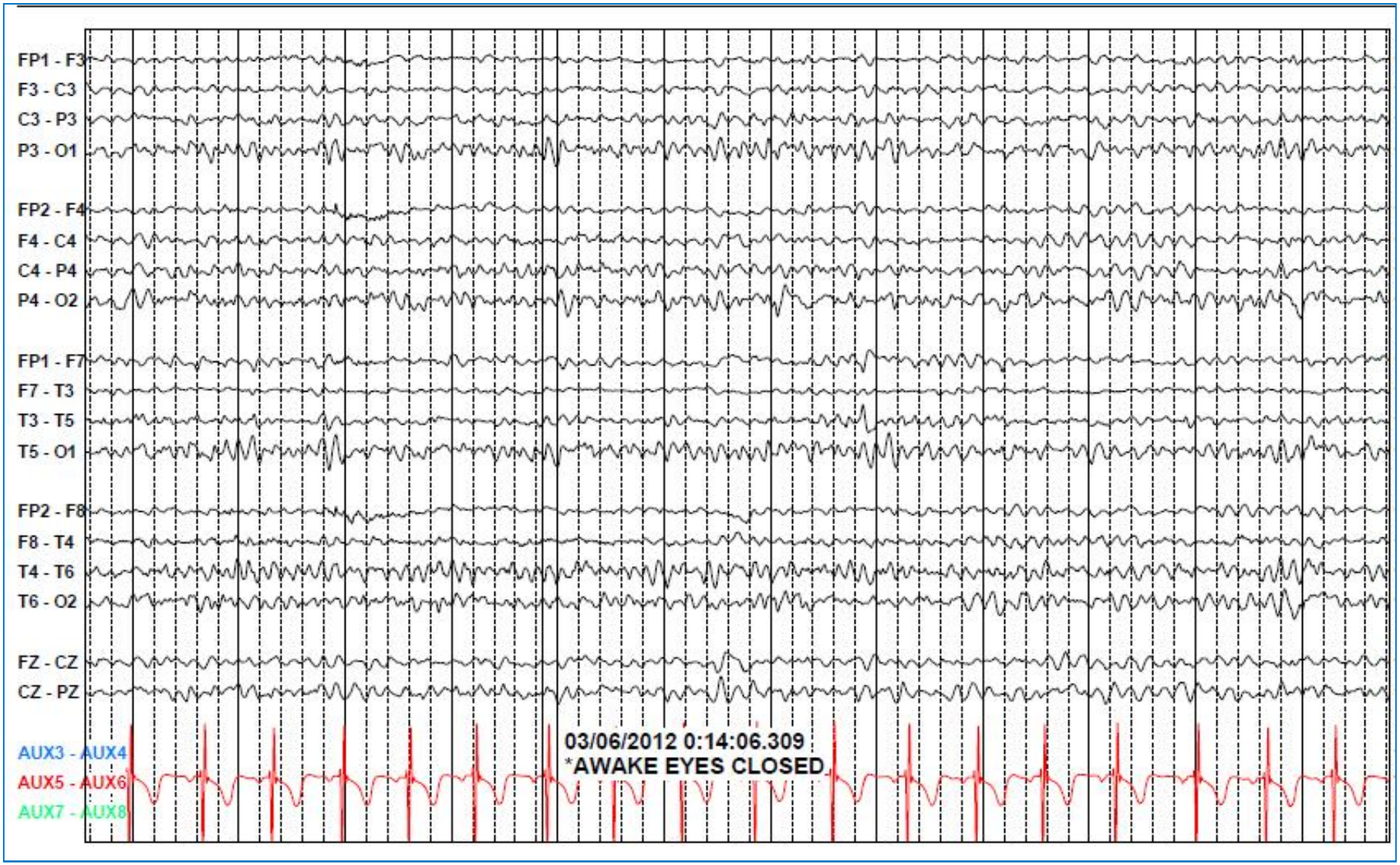
Electrodecrement (brain waves flatten)

Atonia (Loss of muscle tone in neck)

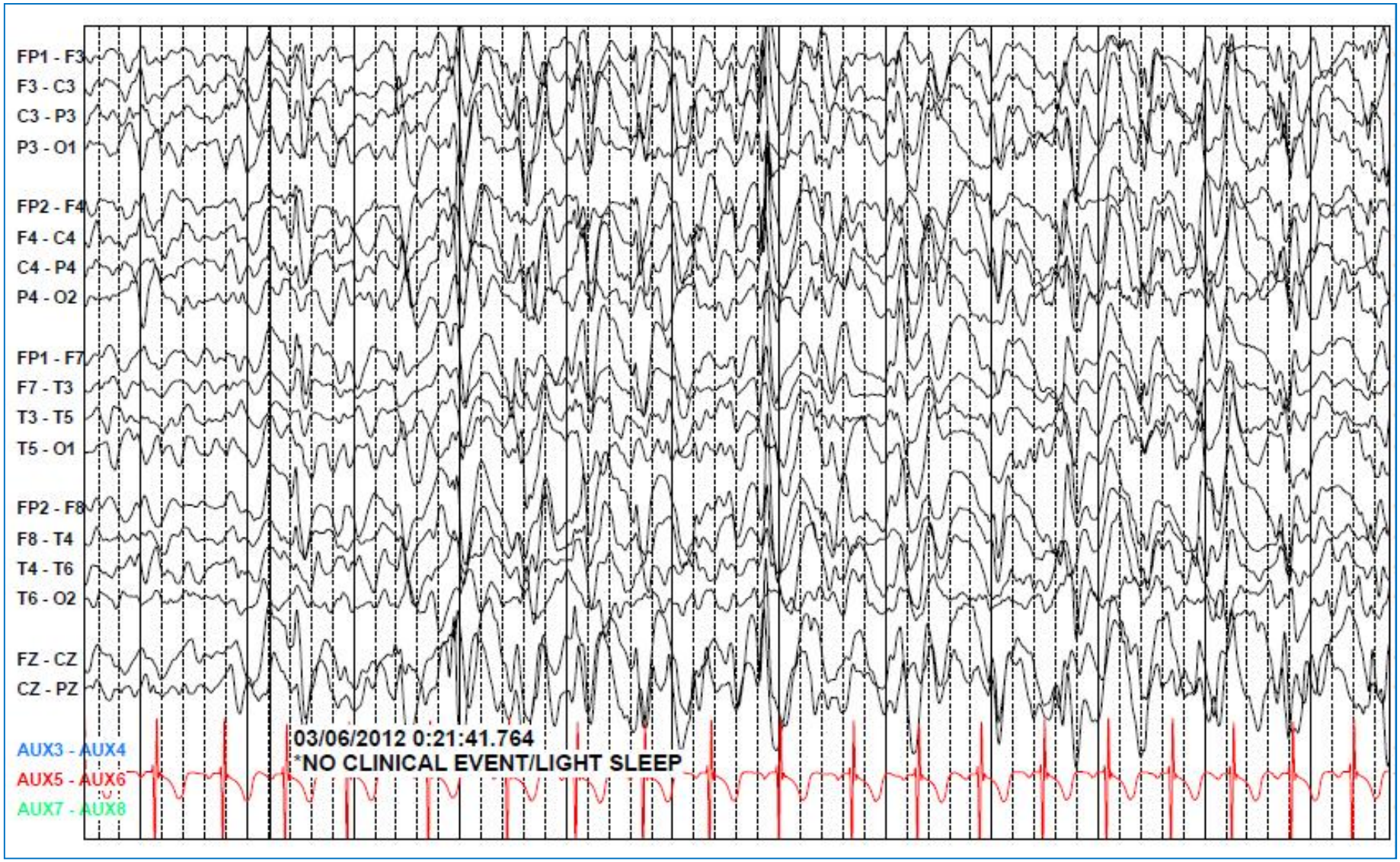
Head nodding happens during Atonic Seizure

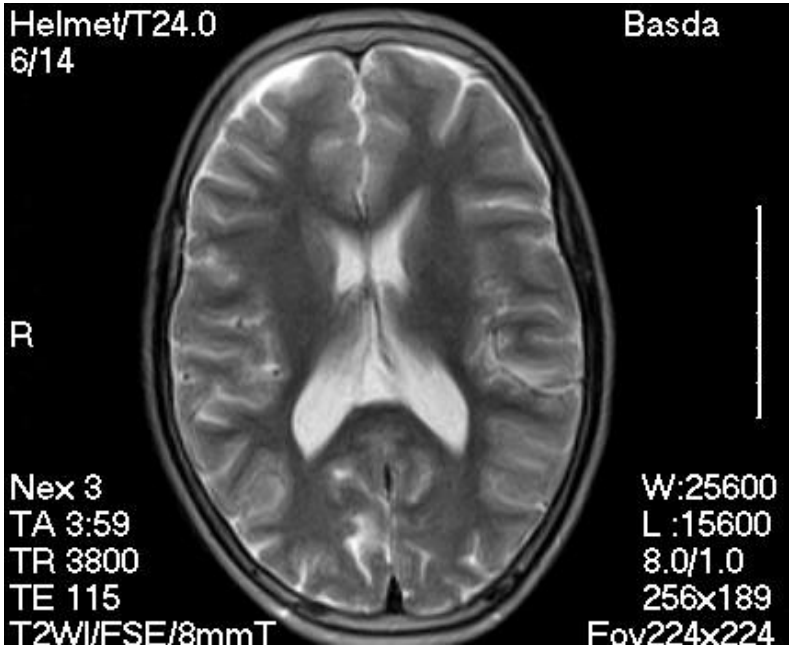


EEG at onset of recording - awake

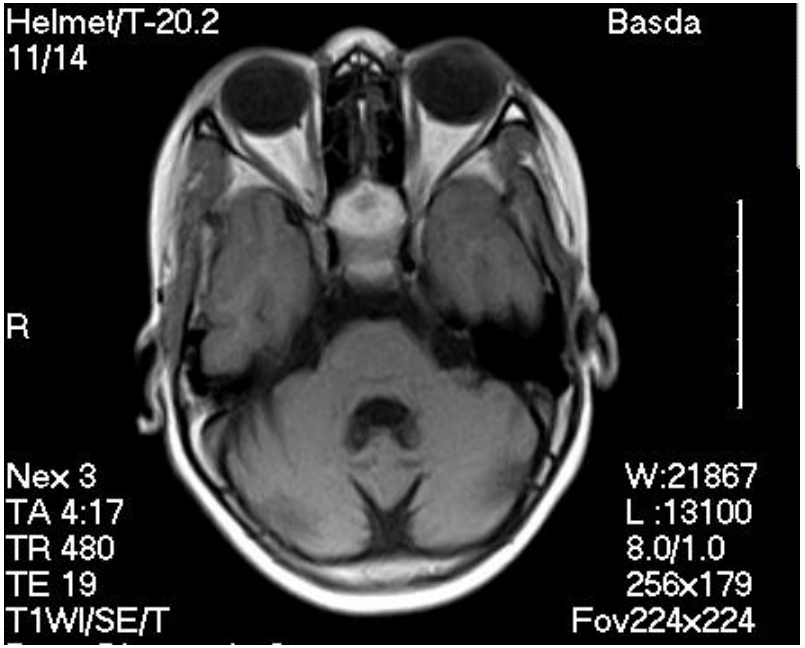


EEG recording in light sleep, no clinical events

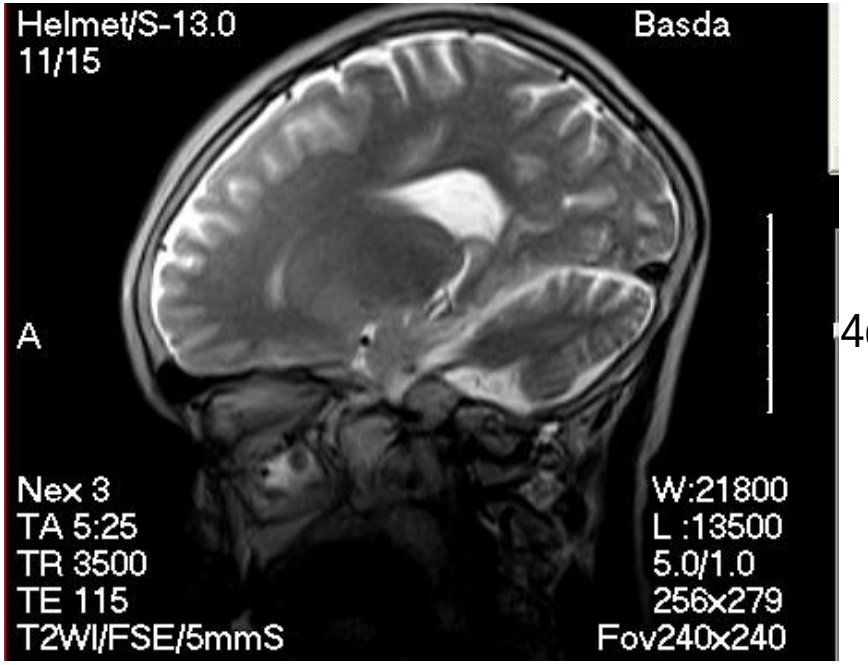



Helmet/T24.0
6/14
Basda
R
Nex 3
TA 3:59
TR 3800
TE 115
T2WI/FSE/8mmT
W:25600
L :15600
8.0/1.0
256x189
Fov224x224

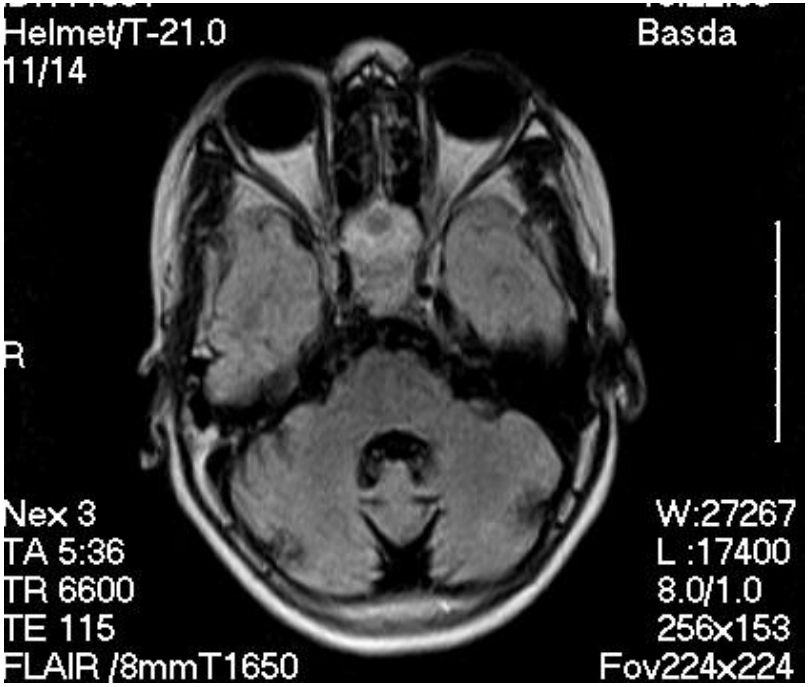
4a


Helmet/T-20.2
11/14
Basda
R
Nex 3
TA 4:17
TR 480
TE 19
T1WI/SE/T
W:21867
L :13100
8.0/1.0
256x179
Fov224x224

4b


Helmet/S-13.0
11/15
Basda
A
Nex 3
TA 5:25
TR 3500
TE 115
T2WI/FSE/5mmS
W:21800
L :13500
5.0/1.0
256x279
Fov240x240

4c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11/14
Basda
R
Nex 3
TA 5:36
TR 6600
TE 115
FLAIR /8mmT1650
W:27267
L :17400
8.0/1.0
256x153
Fov224x224

4d

Proposed clinical staging/ Natural history

- Stage 1 - Prodromal period
  - Reports of “dizziness”, inattention, excessive sleep, lethargy, blank stares
- Stage 2 - Development of head nodding
  - Associated with onset of cognitive decline and behavior problems
- Stage 3 - Development of other seizure types
- Stage 4 - Development of multiple complications
  - Developed 4-8 years after initial symptoms
  - Associated with marked functional regression
- Stage 5 - Severely debilitated child

Joint WHO, CDC, UKAID and Uganda MOH

Decided on

- A name – NS
- A criteria for diagnosis
  - Suspected NS
  - Probable NS
  - Confirmed NS

WHO Case definitions – Jul 2012

- Suspected case
  - Reported head nodding* on 2 more occasions in a previously normal person
- Probable case
  - Suspect case of head nodding, with
  - Both Major Criteria
    - Age of onset of nodding between 3-18 y
    - Frequency of nodding 5-20/minute
  - Plus at least one of the following Minor Criteria
    - Other neurological abnormalities
    - Clustering in space or time with similar cases
    - Triggering by food, cold weather
    - Stunting or wasting
    - Delayed sexual or physical development
    - Psychiatric symptoms
- Confirmed case
  - Probable and
  - Documented nodding episode
    - By a trained health care worker or
    - Videotaped nodding episode, or
    - Video/EEG/EMG

Behaviour and psychiatric features

- Wandering behaviour or running away.
  - Some tied with ropes at home to restrain them.
  - Aggressive behaviour - in 6/22(27%) - 4-6 years after onset of nodding.
  - Ictal event in one
- Emotional problems - 12/22 (55%)
- Mood problems – 8 (36%)
  - Clinical depression
  - Insomnia in 5.
- Psychotic symptoms + disorganised behaviour in 1

Cognitive function in 3 children with nodding syndrome on the KABC 2nd Ed

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

Possible Etiologies & Risk Factors Studied

- Infections
- Environment
- Certain foods
- Nutritional deficiencies
- Genetics

Nodding Syndrome and *Onchocerca volvulus* skin-snip results in 3 case-control studies, South Sudan

Tumwine et al 2012

Environmental toxins and nodding syndrome

Environmental

Domestic water source

Exposure to ill animals

Swimming in river/pond

Infectious Disease

History of

- Malaria, pneumonia, diarrhea, tape worm

Food

Consumption of

- Spoiled foods, plant seeds, bush meat/brain, insects, cassava, river fish, supplements

History of malnutrition

Medical

Use of traditional medicines (except roots)

History of head injury

Slide Courtesy of Drs Scott and Sejvar, CDC

Infectious agents and nodding syndrome; Preliminary results

Test	Results
Infectious	
Trypanosomiasis serology (gambiense)	All negative
Hepatitis E serology (IgM/G)	(-) 52% cases, 58% controls
Malaria blood smears	(-) 93% cases, 92% controls
Measles PCR on CSF	Negative
Pathogen Discovery	
Pan-Viral nucleic acid & random primer assay (serum, CSF)	Negative

Slide Courtesy of Drs Scott and Sejvar, CDC

Association with parasites

	Investigator and Country	Cases	Controls	
Malaria	Foltz, Uganda	98%	95%	
Trypanosomiasis	Foltz, Uganda	-	-	36 tested
Trypanosomiasis	Tumwine, South Sudan	-	-	69 tested
Cysticercosis	Foltz, Uganda	-	-	None on 5 MRI
Prion disease	Idro, Uganda	-		19 EEG &MRI
	Sejvar, Uganda			EEG and MRI
	Winkler, Tanzania			EEG and MRI
Onchocerciasis	Tumwine, South Sudan, 2002	93%	44%	Skin snip microfilaria
	Foltz, Uganda	95%	49%	Antibody based
Mansonella	Tumwine, South Sudan	52%	31%	No Loa Loa or lymphatic filariasis

Mycotoxins as a possible cause of NS?

- Possible role of food contamination of cereals in IPD camps
  - Sorghum, is prone to spoilage by *Fusarium verticillioides which elaborates fumonisin B1,*
    - *Blocks sphingolipid synthesis and causes leukoencephalomalacia in horses and hippocampal lesions in laboratory species*
  - *Aspergillus ochraceus and Penicillium verrusosum that elaborate ochratoxin A,*
    - *a mitochondrial toxin with renal and neurotoxic potential*
  - *Ochratoxin & other mycotoxins Aspergillus (aflatoxin B1) and Fusarium spp. (trichothecenes) inhibit RNA and/or protein synthesis - growth and development.*
  - *Other grass-related tremorgenic mycotoxins*
    - *induce tremulousness in cattle by perturbing neurotransmitter function*

Toxicology or deficiency?

- Toxins
  - Mercury
  - Arsenic
  - Copper
  - Lead
  - Thiocynates
  - Homocysteine
- Deficiencies
  - Vitamin B12/Cobalamin, vitamin A, folate
  - Vitamin B6
  - Zinc, selenium,

Micronutrients and Nodding syndrome

Test	Results*
Nutrition	
Serum B6	Low in 73% cases, 64% friend controls
Serum B12	Low in 8% cases, 8% friend controls
RBC Folate	Low in 9% cases, 0% friend controls
Serum Vitamin A	Low in 40% cases, 33% friend controls
Urine Homocysteine	All normal
Urine Thiocyanates	All normal
Toxicology	
Serum Copper	All normal
Urine Mercury	All normal
Serum Selenium	Low in all
Serum Zinc	Low in 47% cases, 67% friend controls

* Preliminary results.

Low values for nutrition results: PLP <20 nmol/L, B12 <200 pg/mL, folate <317 nmol/L, vitamin A <20 ?g/dL.

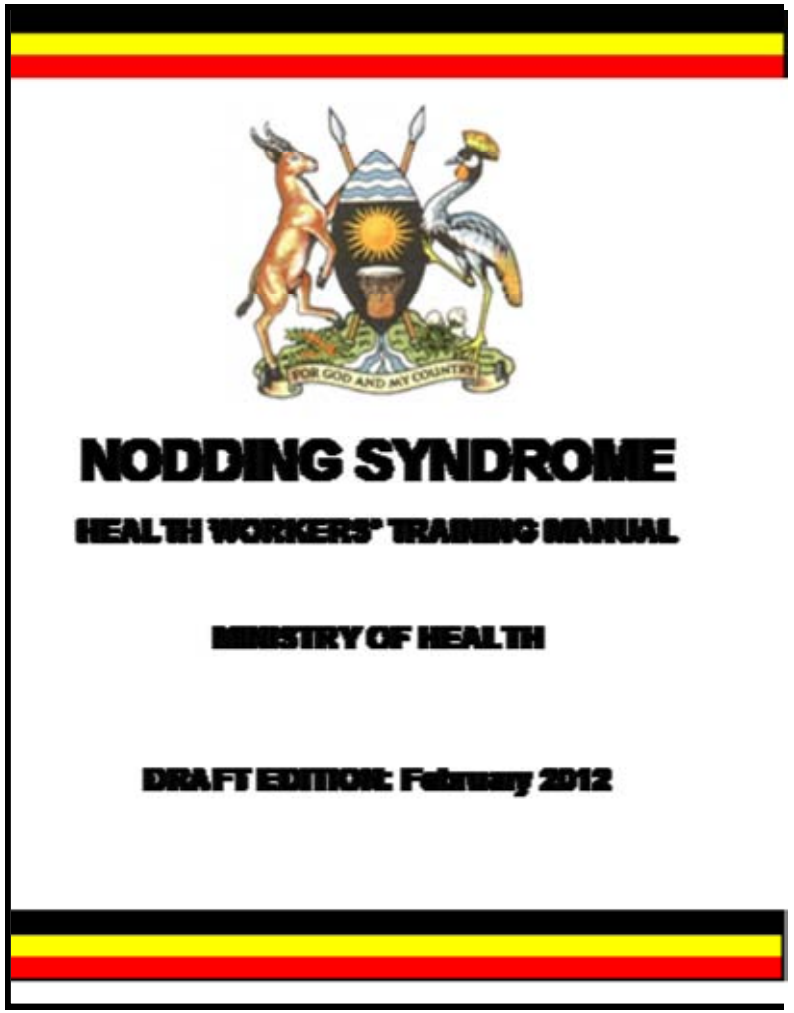
Normal toxicology reference ranges: copper 60-249 ?g/dL, selenium 113-130 ?g/L, zinc 70-120 ?g/dL, mercury 0.42-3.19 ?g/L.

Other causes?

- Genetic mutations? (Exon sequencing in two patients – Uganda and Sudan)
- Neuro-inflammation?
- Others?????

Principles of Management of Nodding Syndrome in Uganda

- Treatment guidelines developed by a multidisciplinary team of clinicians, nurses, and therapists
- 162 specially trained health workers provide care in 7 treatment centres based on the national guidelines
- The goal of treatment is to relieve symptoms, prevent disability and offer rehabilitation to improve function.
  - In the absence of a known cause, care is symptomatic.
    - Initial management focuses on the most urgent needs
- Important needs are seizure control, behavior and psychiatric difficulties, nursing care, nutritional and subsequently, physical and cognitive rehabilitation.



Nutritional management; challenges

- Ready to use therapeutic feeds - severe malnutrition
- Supplemental feeding – in hospital and in the community
- Monitoring with anthropometry
- Challenges with feeding

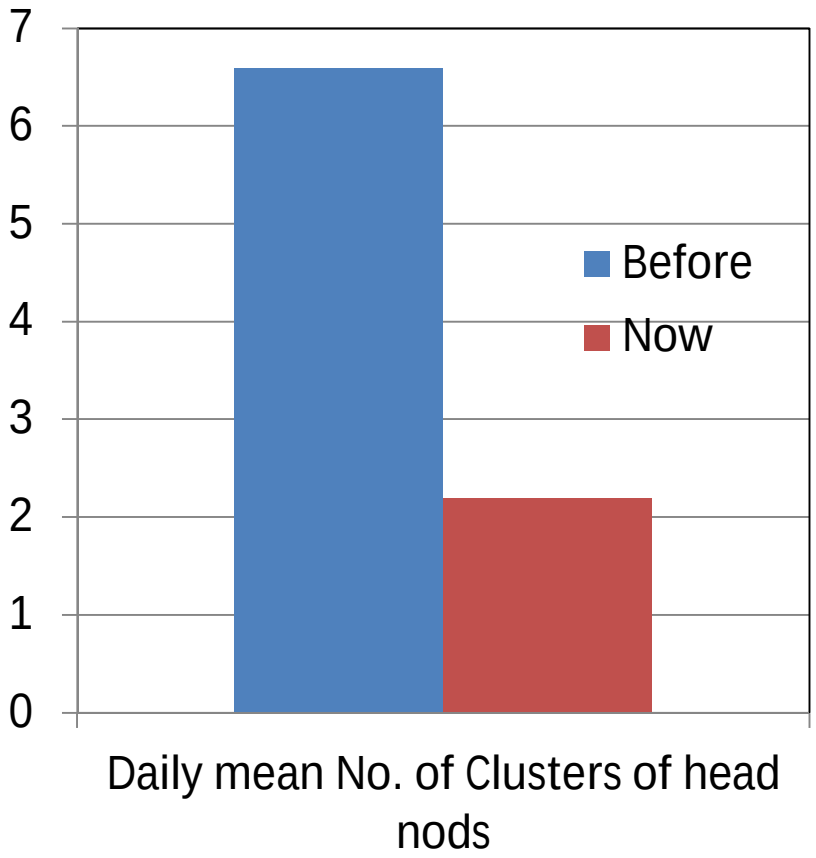
Handicapped due to accidents suffered when fits occur e.g. lost limbs

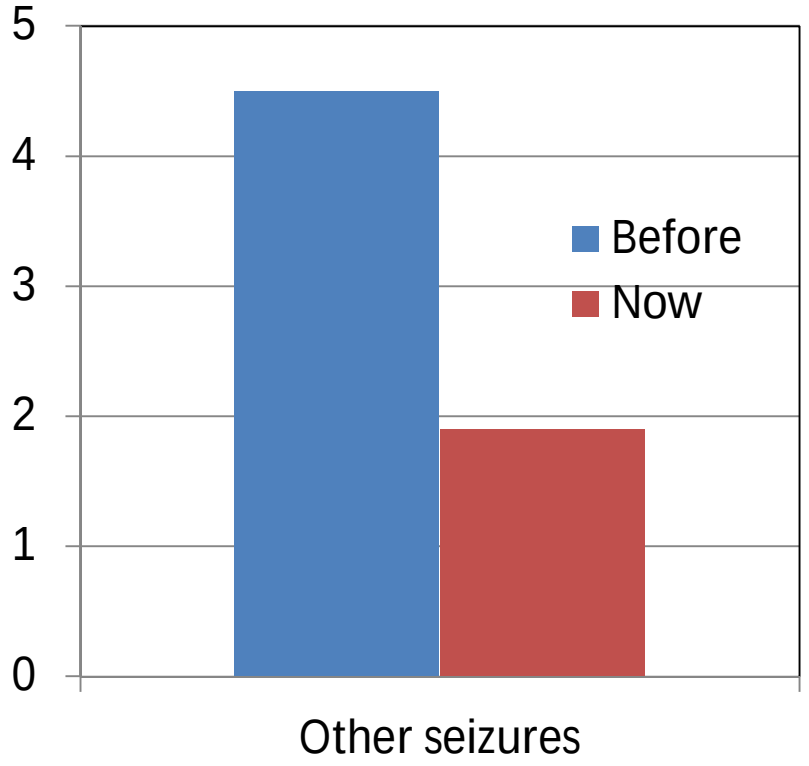
Audit of the nodding syndrome outcomes

Outcomes of Nodding syndrome 12 months after intervention; Preliminary observations

	Nodding syndrome, N=302			Other convulsive epilepsies, N=300		
	Before	After	P value	Before	After	P value
Daily mean No. of clusters of head nods	6	2.2	<0.001	-	-	-
Daily mean No. of other seizure types	4.5	1.9	<0.001	4.4	1.8	<0.001
Attending school	97 (32.1%)	124 (41.6%)	<0.001	83 (27.7%)	153 (51.0%)	<0.001
Percentage weight gain, kg %	-	12.8		-	15.6	

Reduction in the daily mean No. of clusters of head nods and other seizures with treatment





Conclusions

- Nodding syndrome is an epidemic neurologic disorder manifesting as a symptomatic generalized epilepsy syndrome with encephalopathy
- It is associated with multiple physical and functional disabilities.
- Children improve with symptomatic care.
- Studies of aetiology and pathogenesis, evidence based treatment and rehabilitation strategies are urgently needed.

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