Update on Onchocerca Associated Epilepsy in Uganda

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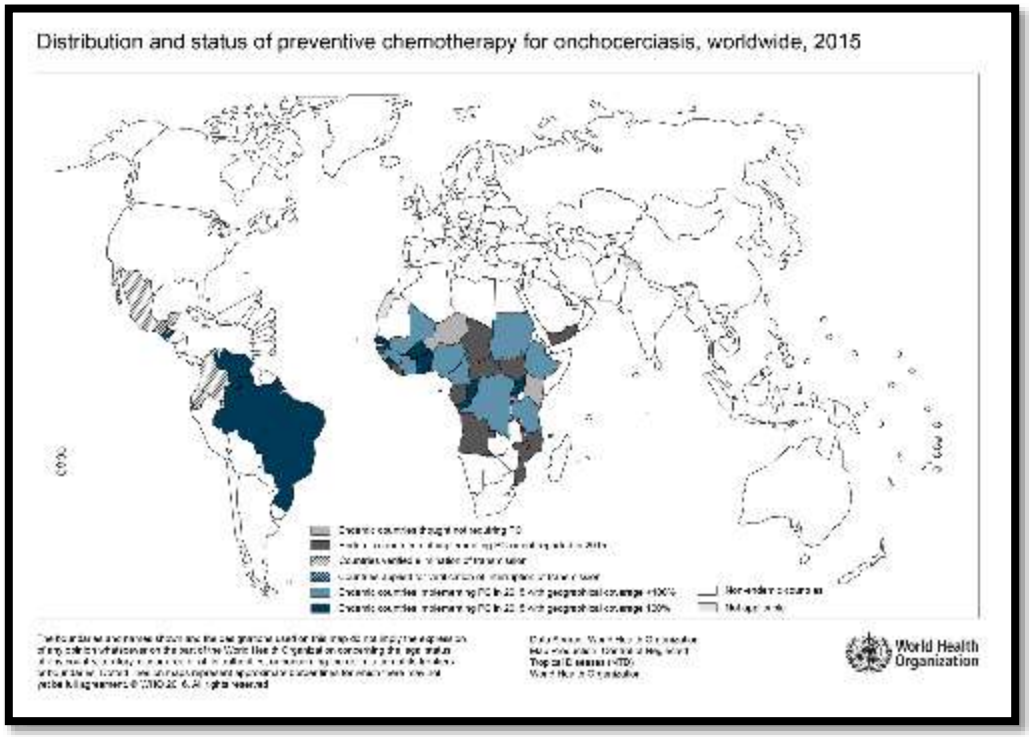
On Behalf of the nodding syndrome investigators

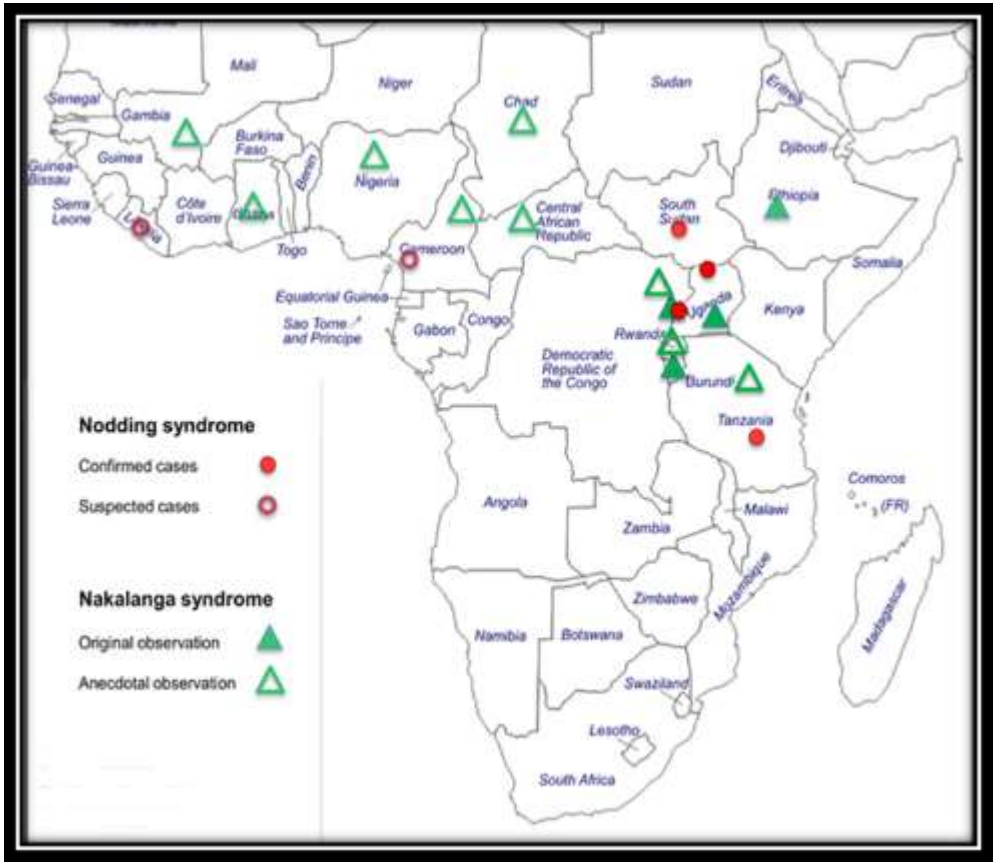
Onchocerciasis



- Onchocerciasis occurs mainly in tropical areas.
- More than 99% of infected people live in 31 countries in sub-Saharan Africa:
  - Angola, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Republic of Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Gabon, Ghana, Guinea, Guinea-Bissau, Kenya, Liberia, Malawi, Mali, Mozambique, Niger, Nigeria, Rwanda, Senegal, Sierra Leone, South Sudan, Sudan, Togo, Uganda, United Republic of Tanzania.

Nakalanga Syndrome in Uganda

- An acquired condition resulting in arrested growth
- Reported in the 1950s and 1960s from along the Nile near Jinja in eastern Uganda.
- Growth arrest beginning around age 6–10 years
- This became known as Nakalanga dwarfism, and an association with onchocerciasis was postulated.
- After control of onchocerciasis through larvaciding in this area some 30 years ago, no new cases have been noted.



Föger K, Gora-Stahlberg G, Sejvar J, Ovuga E, Jilek-Aall L, et al. (2017) Nakalanga Syndrome: Clinical Characteristics, Potential Causes, and Its Relationship with Recently Described Nodding Syndrome. PLOS Neglected Tropical Diseases 11(2): e0005201. https://doi.org/10.1371/journal.pntd.0005201

The Nakalanga syndrome in Kabarole District, Western Uganda

- A new focus

- Case control study
  - 31 persons with short stature, ≥15 years, identified through household surveys in Kabarole – an area with a high prevalence of onchocerciasis.

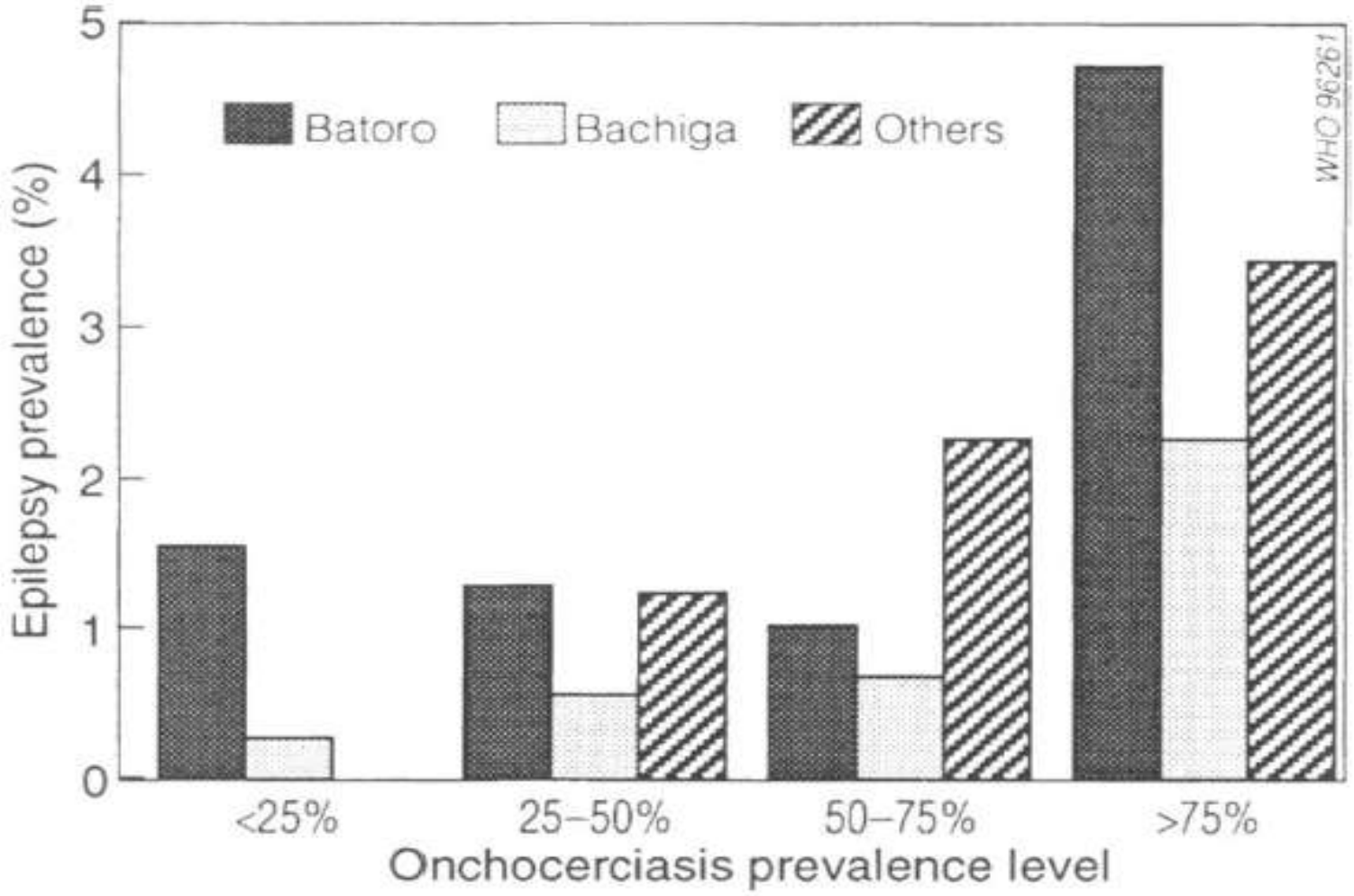
- Cases matched with controls for age, sex and the nearest household.
- Cases of Nakalanga syndrome
  - The Z scores for weight-for-age, weight-for-height, height-for-age, and body mass index were significantly less among cases.
  - Other features included absence of secondary sexual characteristics, skeletal deformities, dental caries, and mental retardation.
  - All cases and 22 (79%) controls had Onchocerca volvulus microfilaria in skin snips.
  - All community thought it was acquired sometime after birth.

The prevalence of epilepsy follows the distribution of onchocerciasis in a West Ugandan focus

C. Kaiser,[1] W. Kipp,[2] G. Asaba,[3] C. Mugisa,[4] G. Kabagambe,[5] D. Rating,[6] & M. Leichsenring[7]

Epidemiological surveys indicate that the prevalence of epilepsy is higher in developing countries than in industrialized countries. Except for neurocystocercosis due to Taenia solium*, little is known about possible underlying causes. This article reports the relationship between epilepsy and onchocerciasis in an* Onchocerca volvulus *endemic area in West Uganda. Individuals complaining of seizures were identified by means of a population census in 12 villages. Active epilepsy was confirmed in 61 of 4743 inhabitants (crude prevalence rate = 1.3%; age-standardized rate = 1.1%). Distribution of epilepsy in the study area was clustered, ranging from a prevalence of 0.2% to 3.4% in different villages. Age-specific prevalence was highest between 10 and 19 years, with a rate of 3.6% for the study area as a whole, and up to 10.0% in villages of high epilepsy prevalence. The prevalence of onchocerciasis in the 10–19-year-old age group was assessed by skin-snip biopsy and ranged from 15% to 85% in different villages. Epilepsy was significantly more frequent in the three villages with the highest levels of* O. volvulus *endemicity than in other villages (*$P < 0.0001$*). Serological testing for* T. solium *infection was positive in one and borderline in three of 53 epilepsy patients tested. The significant correlation between epilepsy and onchocerciasis did not change when these four patients were excluded from the analysis. These findings suggest a strong association between epilepsy and onchocerciasis in this area. This could have significant implications for the concept of morbidity due to* O. volvulus.

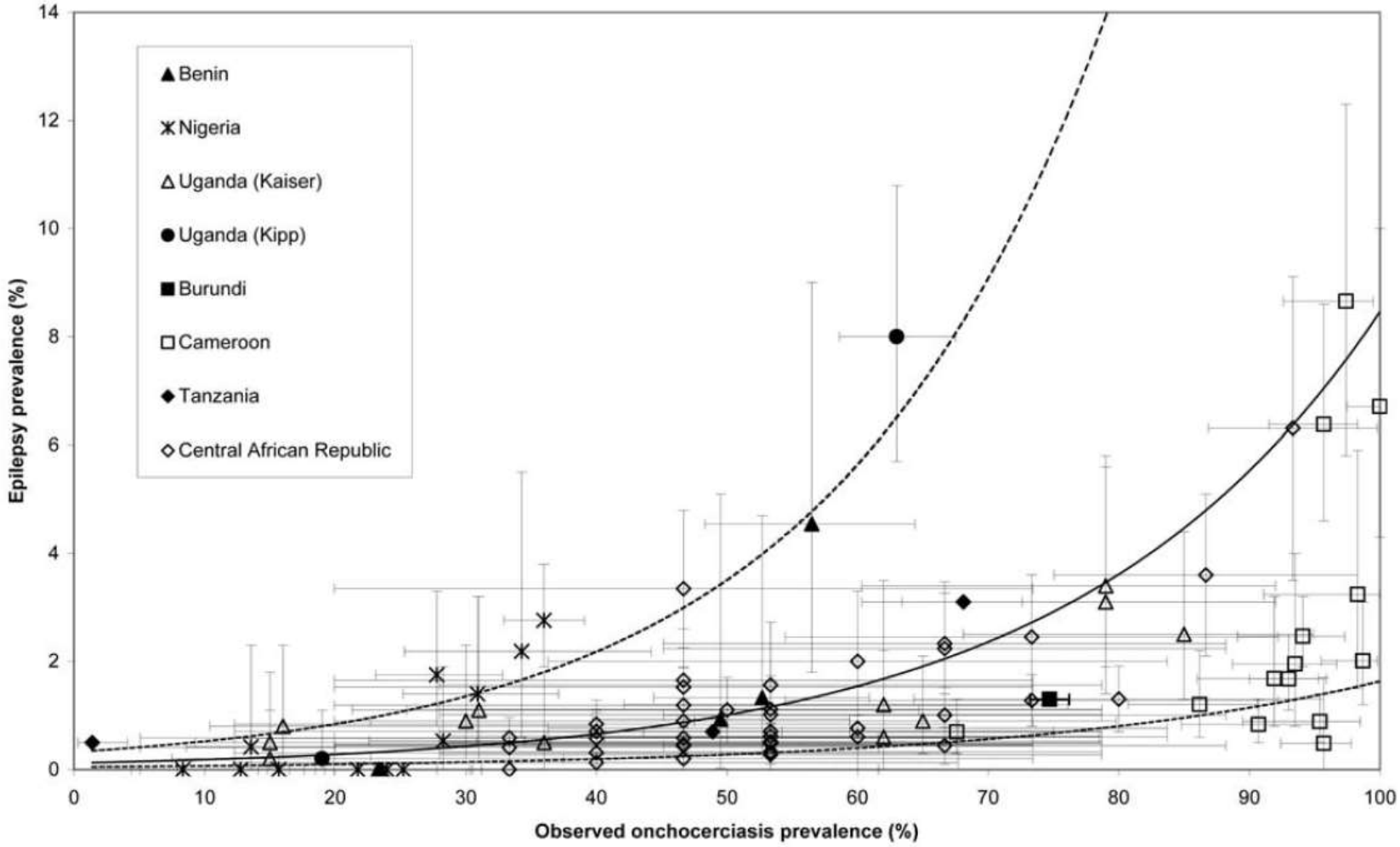
Fig. 2. **Epilepsy prevalence, by ethnic group, in zones of different *Onchocerca volvulus* endemicity.**



Bulletin of the World Health Organization, 1996, **74** (4): 361–367

Epilepsy in Onchocerciasis Endemic Areas: Systematic Review and Meta-analysis of Population-Based Surveys

Sébastien D. S. Pion[1]*, Christoph Kaiser[2], Fernand Boutros-Toni[3], Amandine Cournil[1], Melanie M. Taylor[4], Stefanie E. O. Meredith[5], Ansgar Stufe[6], Ione Bertocchi[7], Walter Kipp[8], Pierre-Marie Preux[3], Michel Boussinesq[1]



Am. J. Trop. Med. Hyg., 93(1), 2015, pp. 198–202
doi:10.4269/ajtmh.14-0838

Case Report: Nodding Syndrome, Western Uganda, 1994

Christoph Kaiser,* Tom Rubaale, Ephraim Tukesiga, Walter Kipp, and George Asaba

Basic Health Services, Kabarole and Bundibugyo Districts, Fort Portal, Uganda; Vector Control Unit, Ministry of Health, Fort Portal, Uganda; Department of Public Health Sciences, University of Alberta, Edmonton, Canada

Abstract. Nodding syndrome (NS) is a poorly understood condition, which was delineated in 2008 as a new epilepsy syndrome. So far, confirmed cases of NS have been observed in three circumscribed African areas: southern Tanzania, southern Sudan, and northern Uganda. Case–control studies have provided evidence of an association between NS and infection with *Onchocerca volvulus*, but the causation of NS is still not fully clarified. We report a case of a 15-year old boy with head nodding seizures and other characteristic features of NS from an onchocerciasis endemic area in western Uganda, with no contiguity to the hitherto known areas. We suggest that the existence of NS should be systematically investigated in other areas.

Apart from the north, Nodding syndrome has also been reported in other parts of Uganda

Nodding syndrome in Northern Uganda –

Slide courtesy of MOH

- March 2009 – MoH received reports of cases among pupils of Layamo Agwara Primary School, Kitgum and were described as Narcolepsy/ **"Post traumatic stress disorder"**

- From 23rd to 28th August 2009, MoH sent a team composed of CHS/NDC, a Physician, a Laboratory expert & Biostatistician to verify the strange disease in Kitgum

- In December 2009, the MoH, supported by WHO, CDC/Atlanta, CDC/Uganda, AFENET, TPO conducted further investigations in Kitgum

- Follow-up investigations were done in August 2010 in Kitgum, Lamwo & Pader district.

- GOU/APG meeting 2011 – comprehensive program

Head nodding in a child with NS

Nodding syndrome Response Plan

- NS response areas - paraphrased
  - Definition of the epidemic
  - Developing a program of Clinical care
  - Research
  - Multisectoral Community intervention, rehabilitation and prevention strategies

1st International Scientific Meeting on NS 2012 Joint WHO, CDC, UKAID and Uganda MOH

Decided on

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

Where and how many children have been affected?

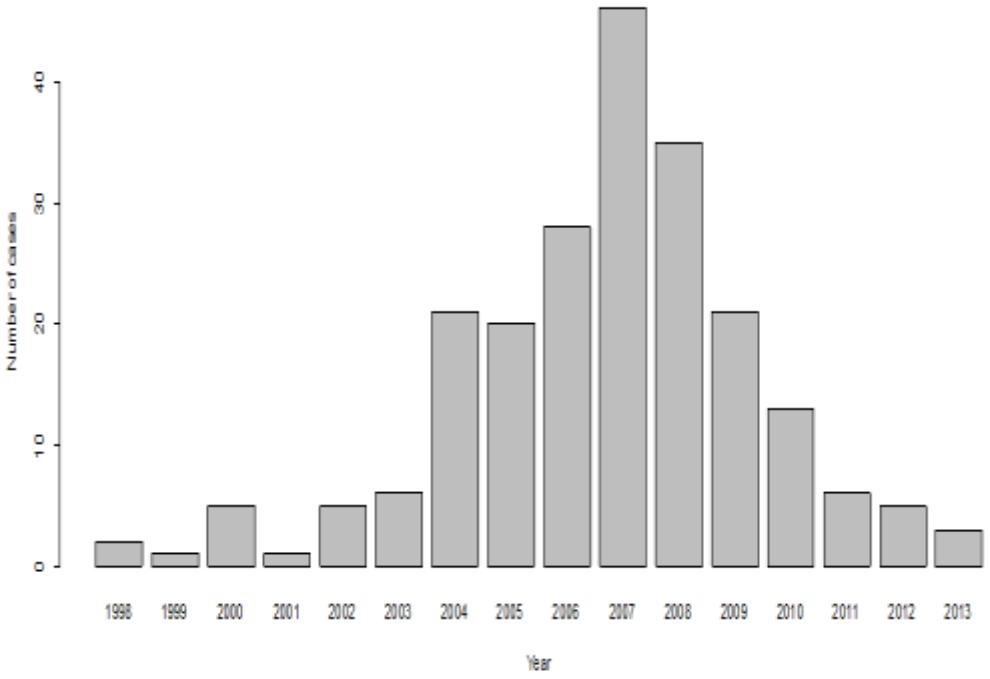
Over 10,000 children are affected mainly in E Africa (Uganda, Tanzania and South Sudan)

In Uganda, 3320 patients are receiving treatment in 17 centres

Areas in South Sudan, Northern Uganda and southern Tanzania where NS has been reported

When did the first cases appear? What is the burden of nodding syndrome in Uganda?

Epidemic curve of nodding syndrome in the sub counties Atanga and Awere in Pader District, Uganda, 1998-2013

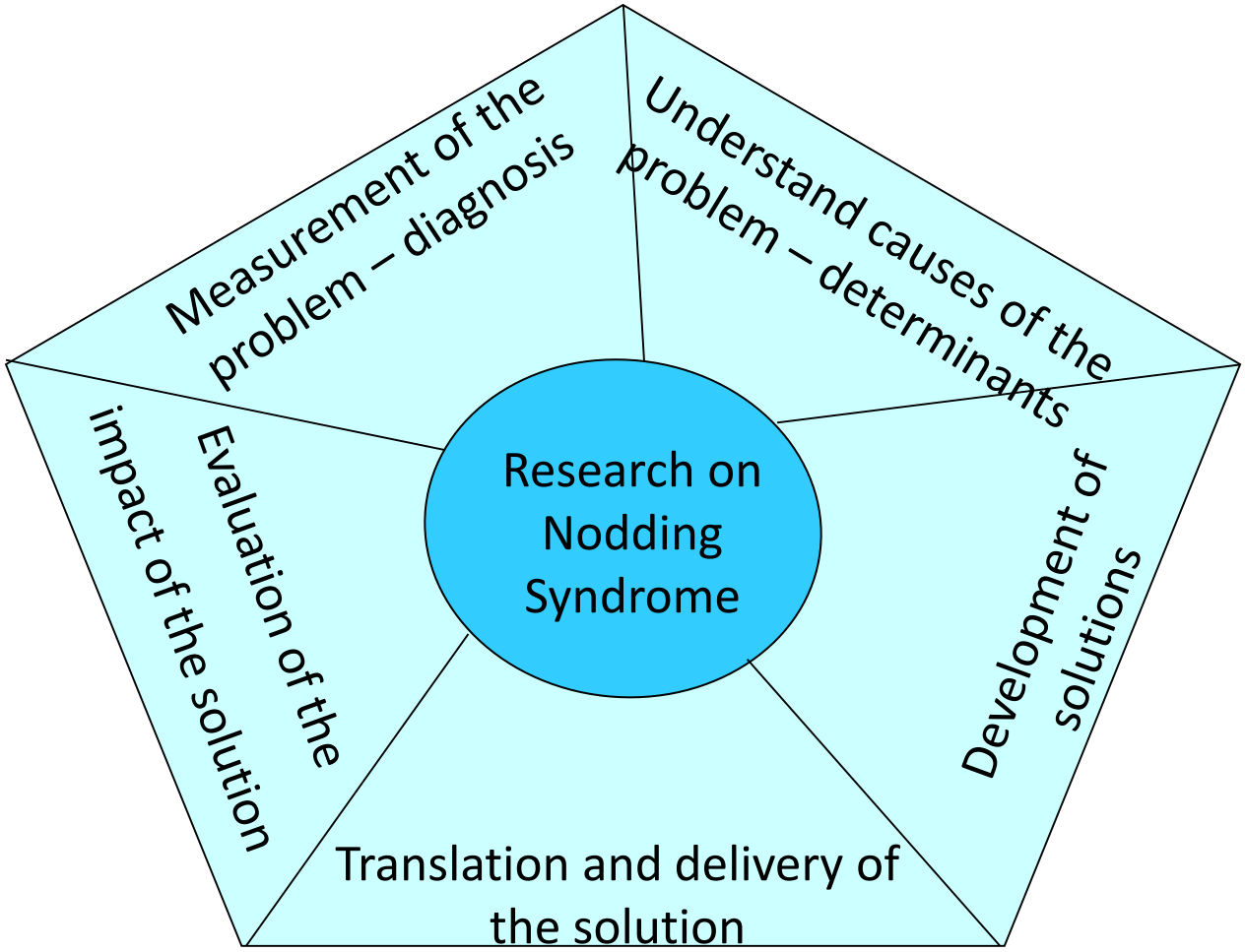


Luwanda et al, Unpublished

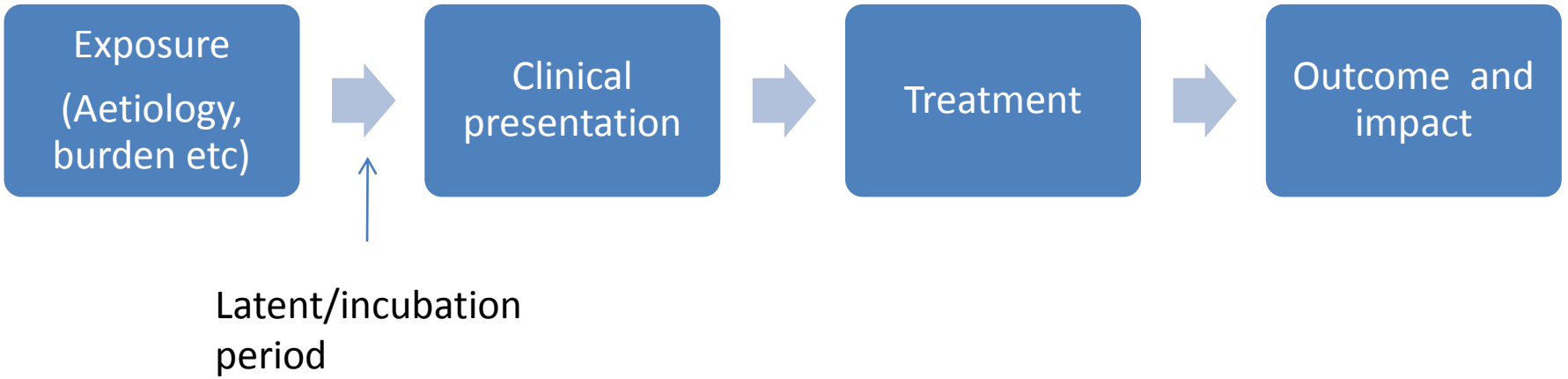
District	Epilepsy	Nodding syndrome cases in treatment centres
Amuru	200	61
Gulu	515	333
Kitgum	2,034	1,321
Lamwo	122	349
Lira	344	13
Pader	1,354	1,210
Oyam	860	8

Ministry of Health, District reports

A Framework for Research Priorities on Nodding Syndrome; **Five generic areas of activity**



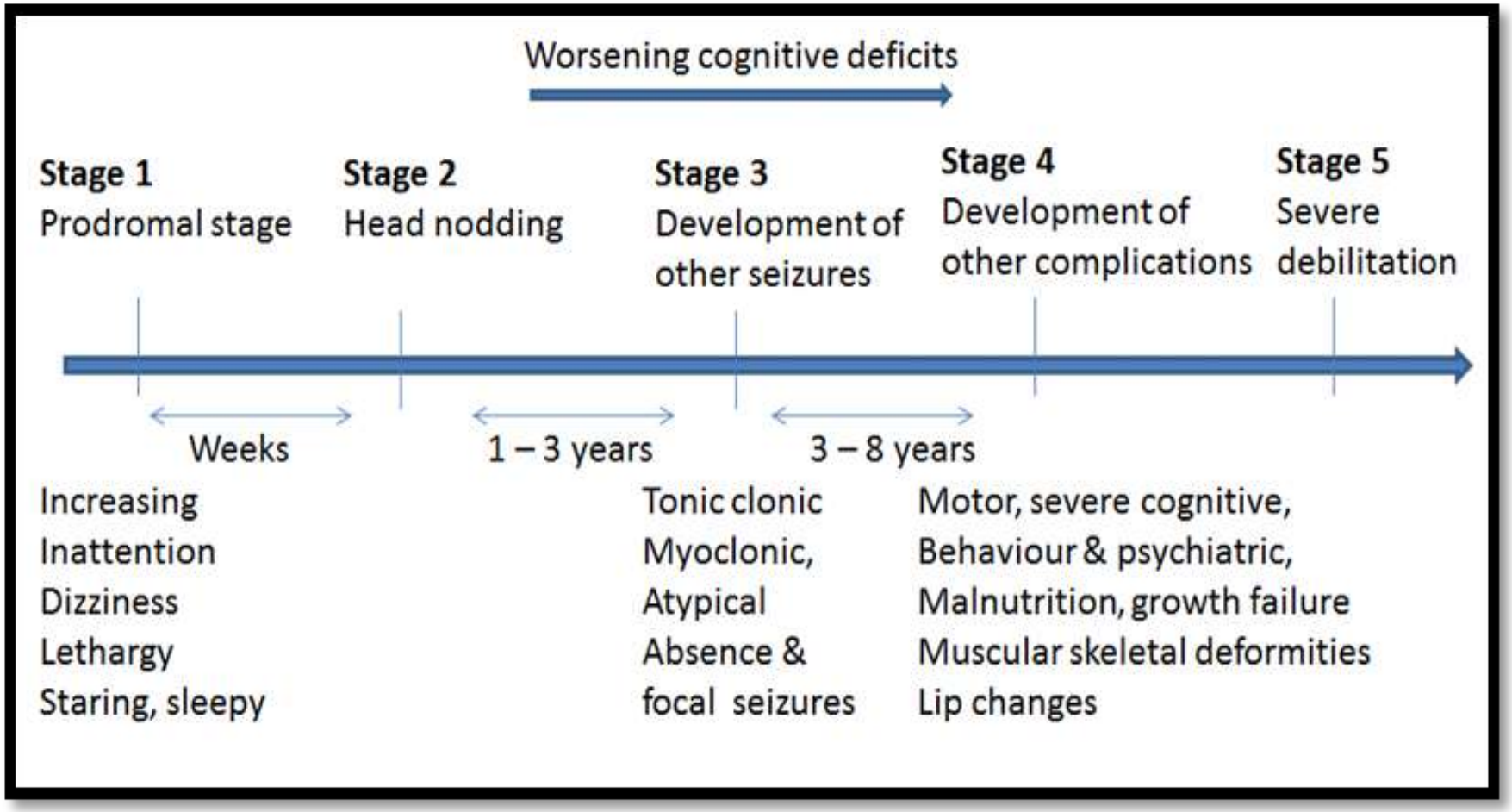
Research agenda:
Based on natural history of disease



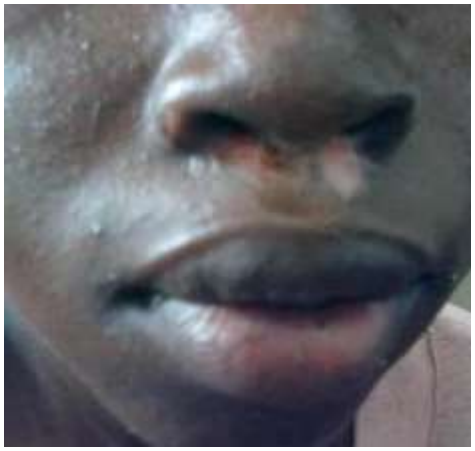
Nodding Syndrome Studies

- Burden and incidence
- Prospective longitudinal cohort
  - Determine course of illness, natural history, stages of illness
- Pathogenesis and genetics
  - Obtain high-quality biological specimens for analysis of pathology, possible etiologies
- Clinical studies, best approach to management / treatment
  - Perceptions
- Mortality surveillance
  - Identify decedents with NS as quickly as possible

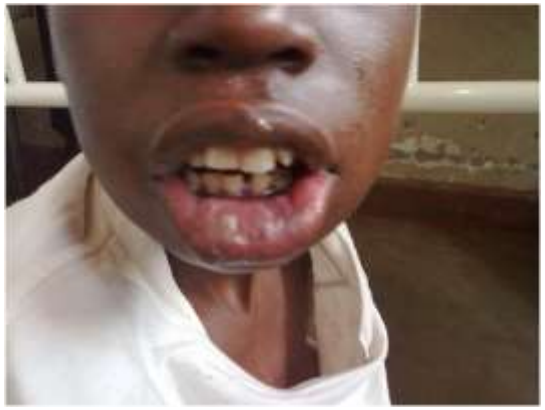
Probable Natural history of untreated nodding syndrome



Lip Changes in nodding syndrome

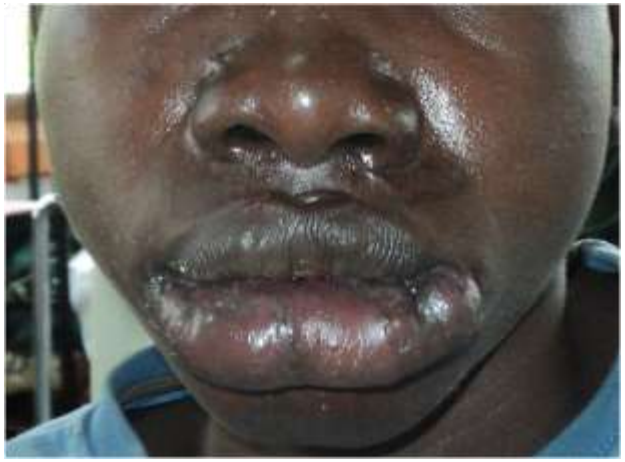


Lip Changes stage 1



Lip Changes stage 2

Lip Changes stage 3



Lip Changes stage 4

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

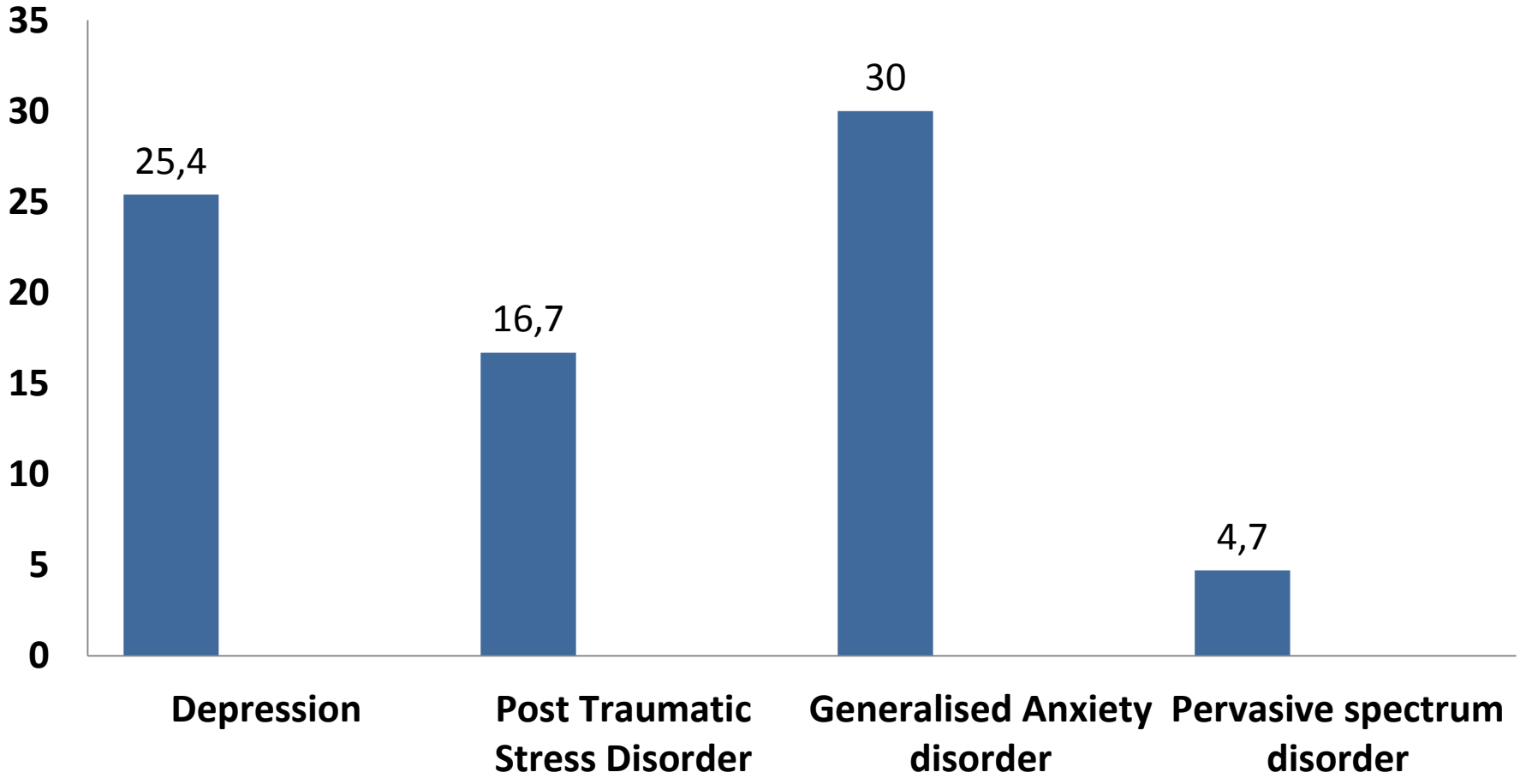
Domain	Patient 1 Male 13 years		Patient 2 Male 15 years		Patient 3 Male 15 years	
	Score	Age equivalent in years	Score	Age equivalent in years	Score	Age equivalent in years
Working memory	8	<5	7	<5	21	=5
Planning	7	<8	1	<5	3	<5
Learning	28	<5	28	<5	54	=5
Visual spatial	0	<5	0	<5	31	<5
Knowledge	11	<5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

Behaviour and psychiatric features

- **Wandering behaviour or running away**.
  - Some tied with ropes at home to restrain them.
  - Aggressive behaviour
- **Emotional problems**
- **Mood problems**
  - Clinical depression
  - Insomnia
- **Psychotic symptoms + disorganised behaviour**

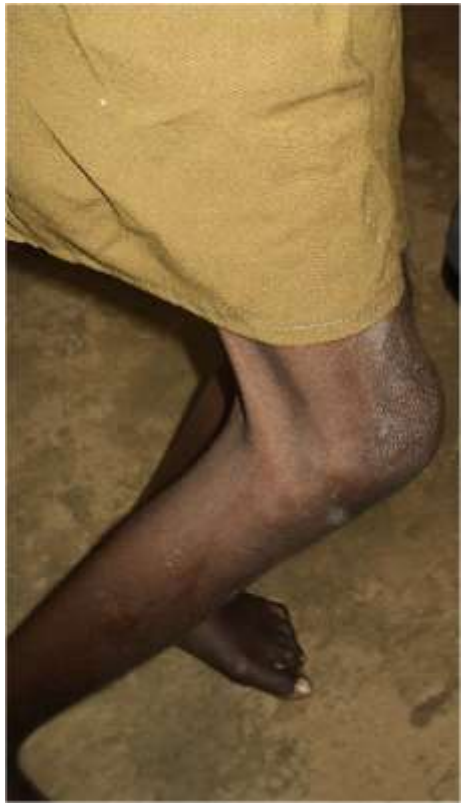
Idro et al 2013

Bar graph showing Psychiatric diagnosis in children with nodding syndrome

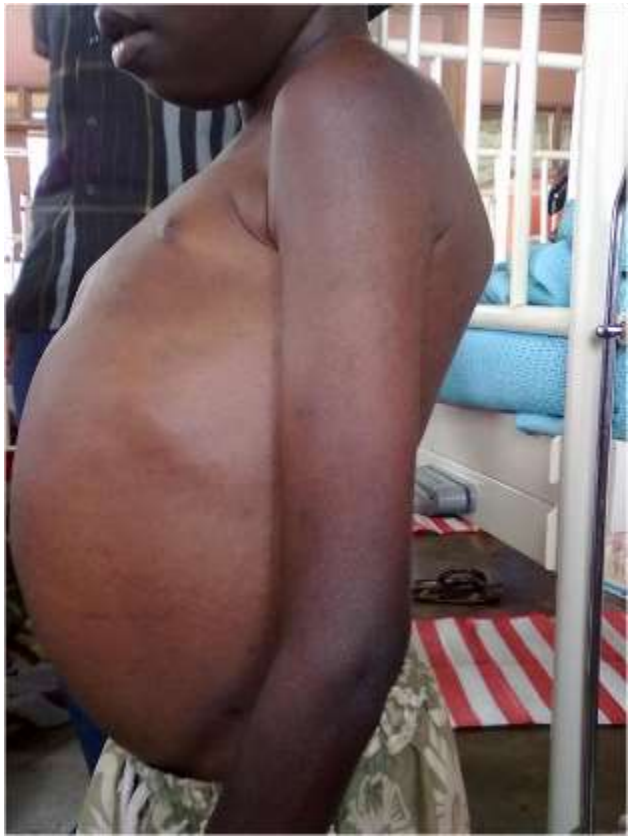


Preliminary study of Disability in NS

Functional Domain	No.	%
Gross motor difficulties and physical deformities	100/220	45.5%
Flat feet, contractures, spasticity, physical deformities		
Speech difficulties	60/220	27.3%
Difficulties 37, Loss of speech 2, slurring 3, understanding 5, unintelligible 2, slow 11		
Visual impairment	4/50	8%
Optic atrophy 2, retinal detachment 1 and night blindness 1		
Hearing impairment	6/52	11.5%
Mild 3 and severe 3		
Dental caries	14/38	36.8%
Oral lesions	5/37	13.5%
Independence of basic activities of daily living	53/220	24.1%



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

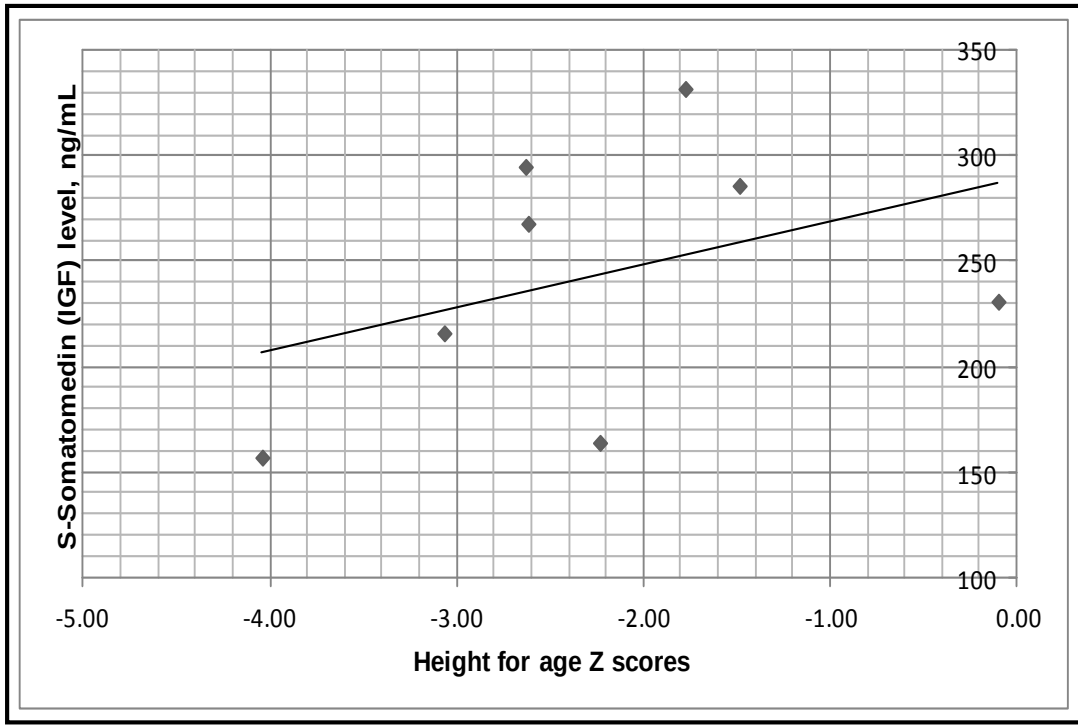


Kyphosis and pectus deformity o the chest

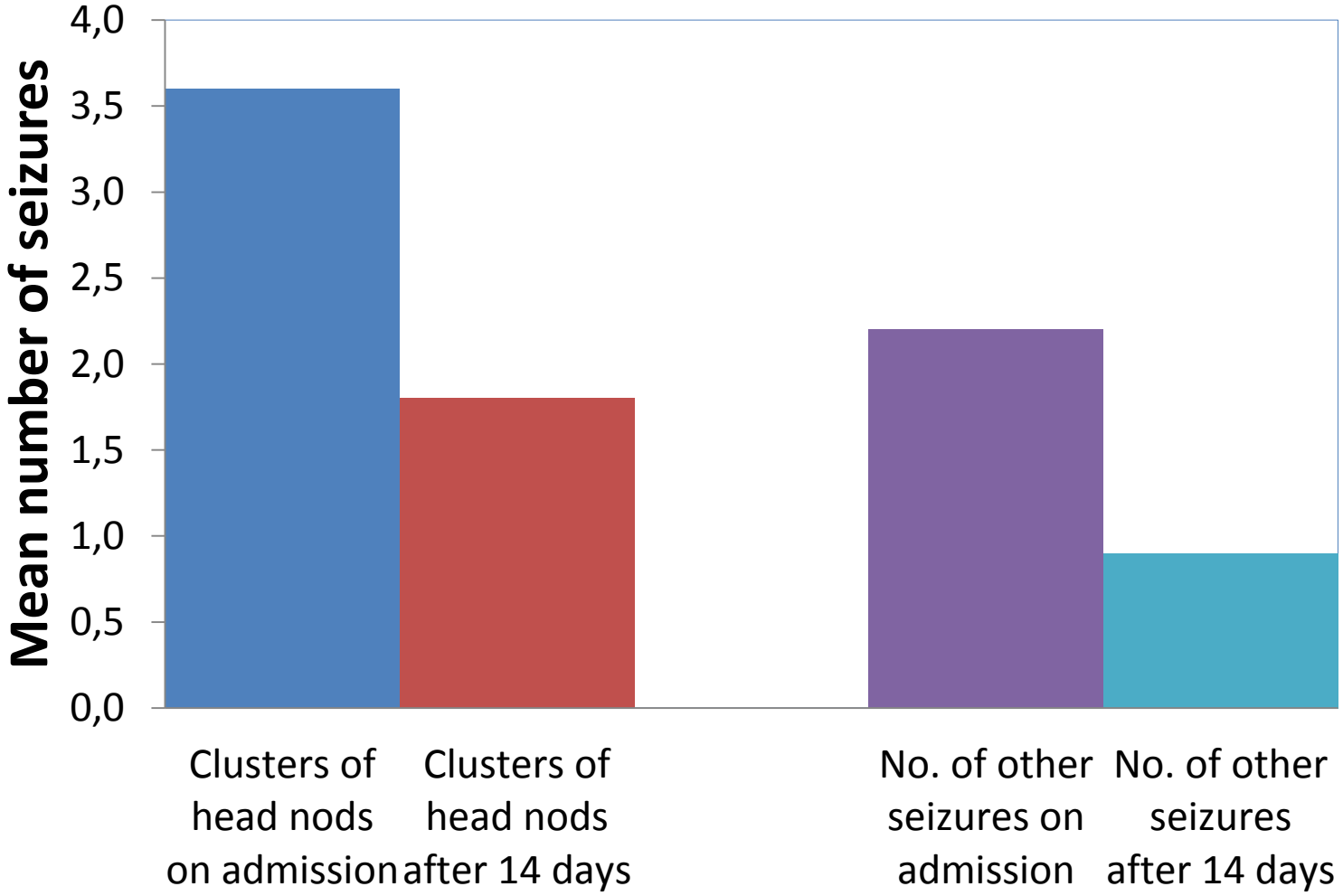
Growth Failure is associated with deficiencies in IGF

Three siblings: 13 yr old boy with NS and severe stunting together with his 16 yr and 17yr old siblings

Serum S-Somatomedin (IGF) levels and Height for age Z scores in 8 adolescents with nodding syndrome



Developing the present symptomatic therapies: Reduction in head nodding and convulsions 2-3 wks after starting treatment with Sodium valproate



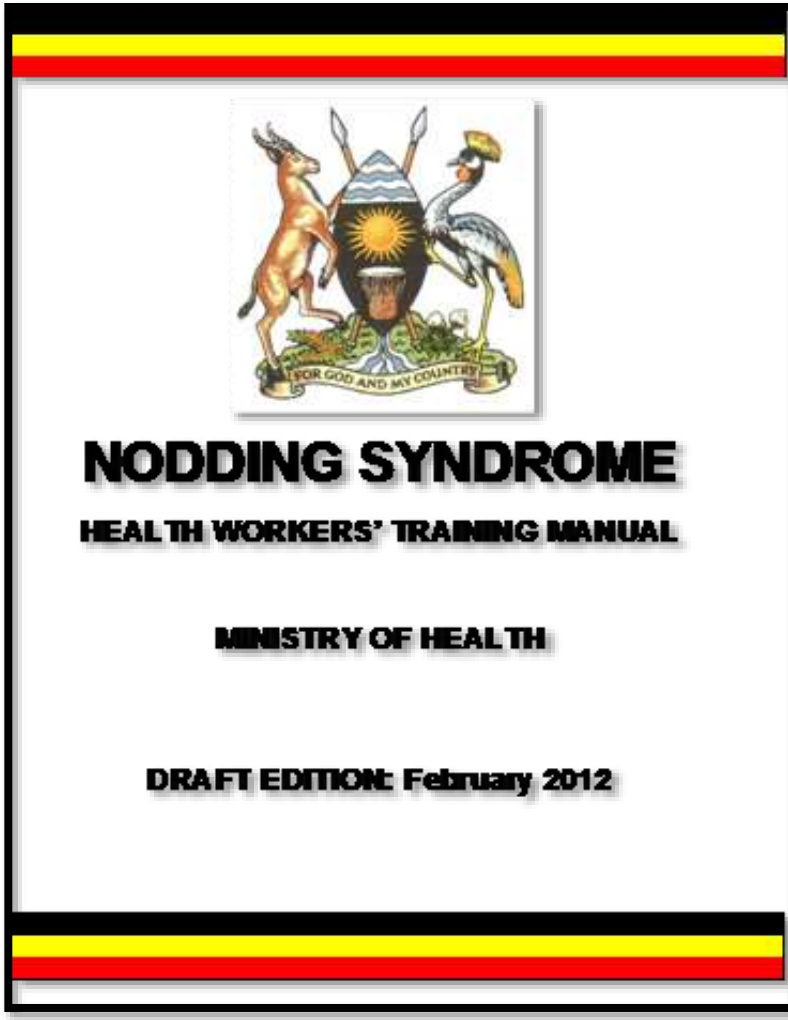
Principles of Management of Nodding Syndrome in Uganda

- 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**.



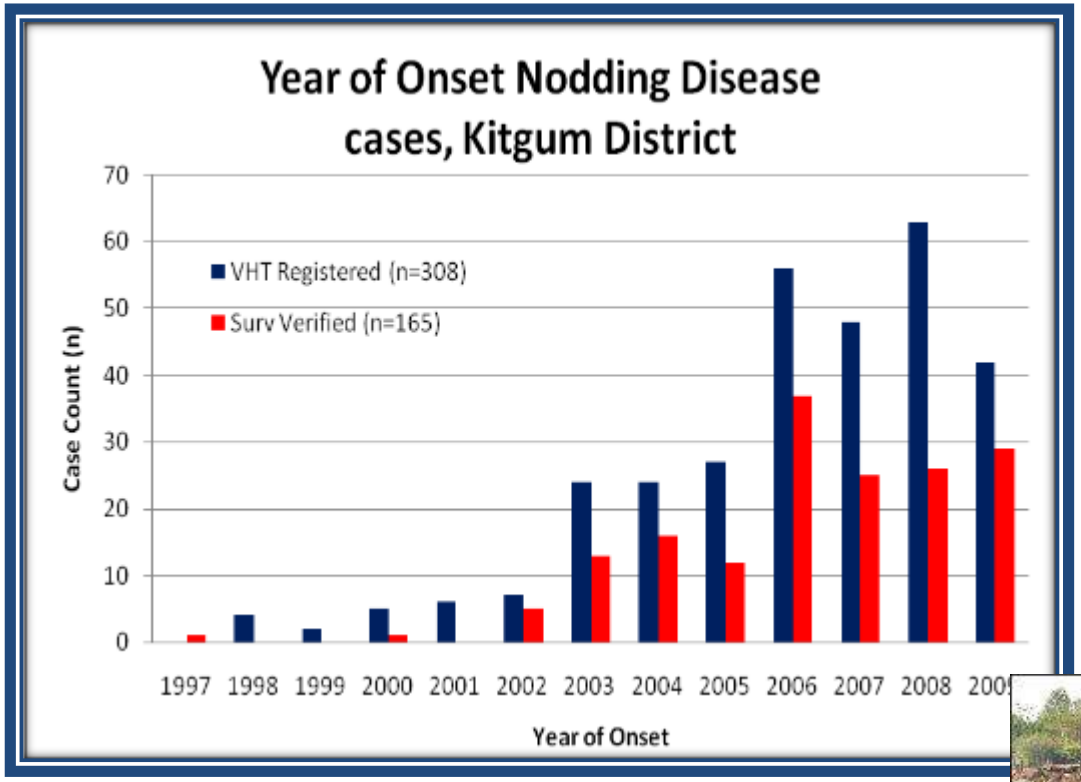
We audited the outcomes of treatment 1 year after starting treatment in 2013

	Nodding syndrome, N=484			Other convulsive epilepsies, N=476		
	Before	**After**	**P value**	**Before**	**After**	**P value**
Seizure free > 30 days	8 (1.7%)	**121 (25.0%)**	<0.001	8 (1.7%)	**243 (51.1%)**	<0.001
Daily clusters of head nods, median (IQR)	4 (IQR 3,6)	**1 (IQR 0,2)**	<0.001			
Behaviour and emotional difficulties	327 (67.6%)	**133 (27.5%)**	<0.001	206 (43.3%)	**105 (22.1%)**	<0.001
Independence in basic self care	174 (36.0%)	**402 (83.1%)**	<0.001	206 (43.3%)	**397 (83.4%)**	<0.001
Attending school	107 (22.1%)	**193 (39.9%)**	<0.001	170 (35.7%)	**250 (52.5%)**	<0.001

What causes nodding syndrome?

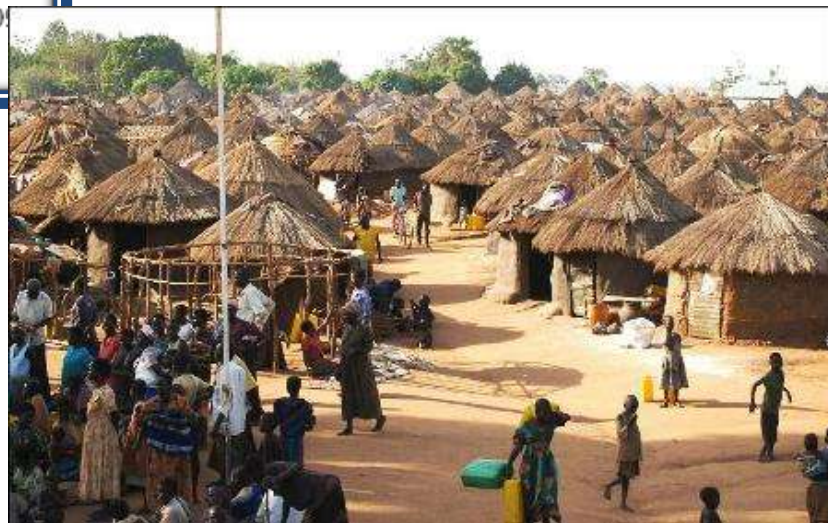
- We asked ourselves several questions?
  - Is it caused by a toxin or chemical in the environment, water or food eaten in the area?
  - Is it in the genes?
  - Is it caused by an infection?
- We conducted a series of research to answer these questions.

Is it associated with displacement, environmental toxins or war associated toxic injuries?



Heavy metals
Environmental poisons
Unusual food
Mycotoxins
War chemicals

Water, food, soil testing



Is it genetic?

- Nodding syndrome is a new problem in Uganda so unlikely inherited.

- Exon sequencing of two children
  - One from Uganda and one Sudan no genes that are usually associated with epilepsy.

- No epilepsy genes found in three families - **Families of patients with nodding syndrome taken to USA**
  - Studied grand parents, parents, affected and unaffected children

- **Additional genetic testing in Oct 2017 – Sept 2018 at UCL neurogenetics centre**

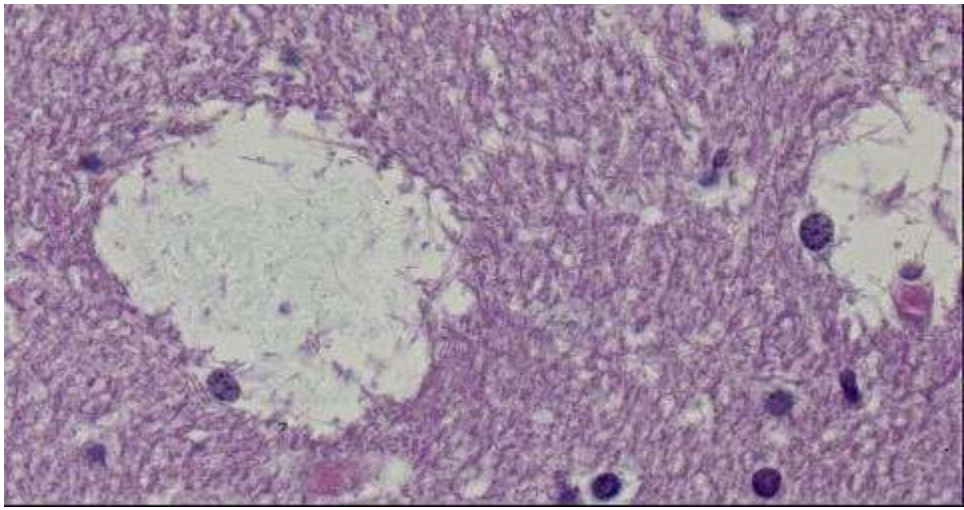
Postmortem examinations

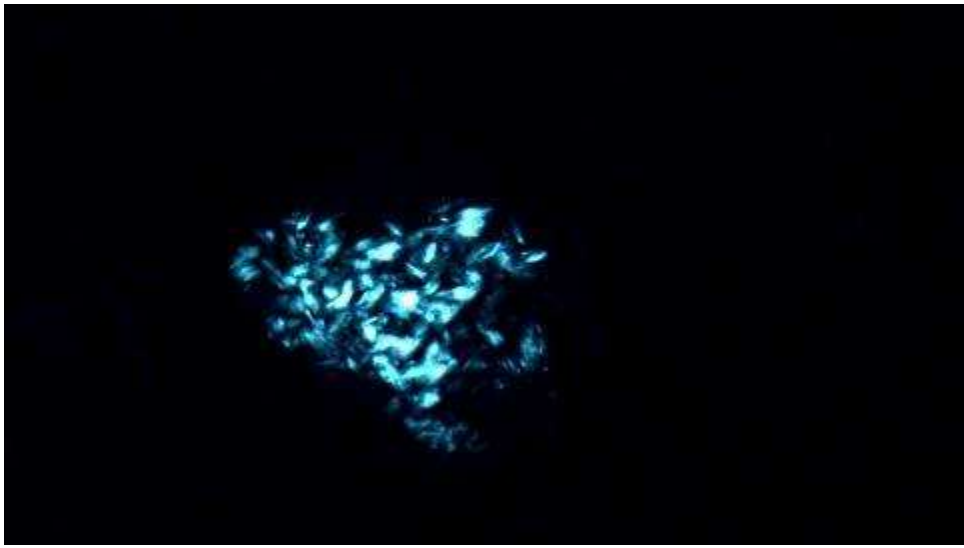
Pathology colleagues need to complete this study

First set of brain specimens – obtained late

Next ¾ specimens – high carbon density material

Similar findings in next set of brain specimens





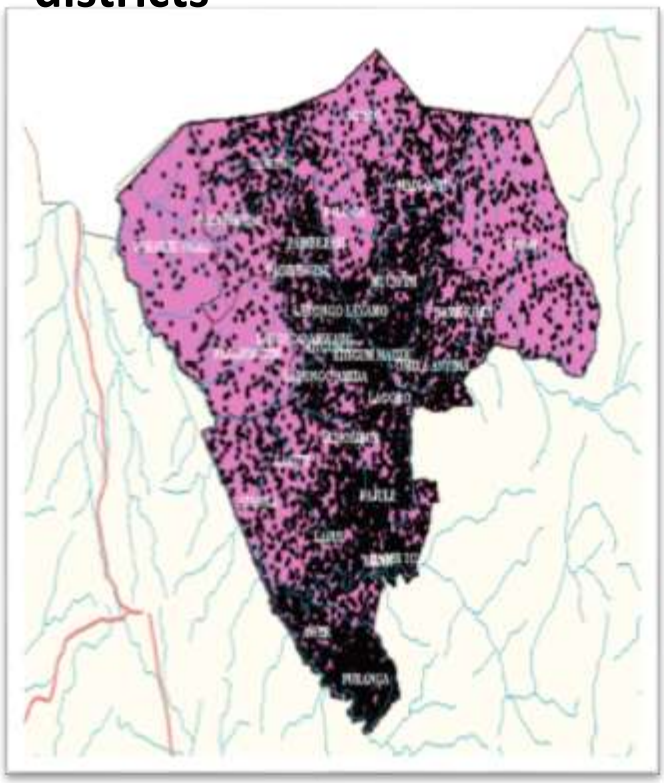
Is it due to an infection?

- No association with multiple parasitic infections (malaria, trypanosomiasis, neurocycticercosis etc) except the extracranial filarial parasite *Onchocerca volvulus*.

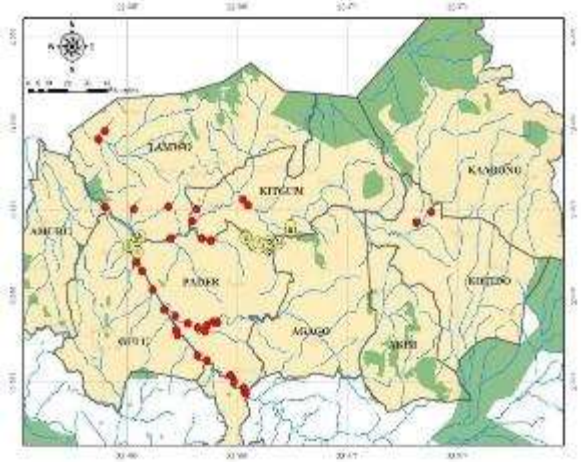
- CDC performed exploratory studies for 19 virus families – none identified
  - Initial suggestion of a co-transmitted neurotropic virus no confirmed.
  - No evidence of prion disease

Where in the northern Uganda are the patients nodding syndrome found?

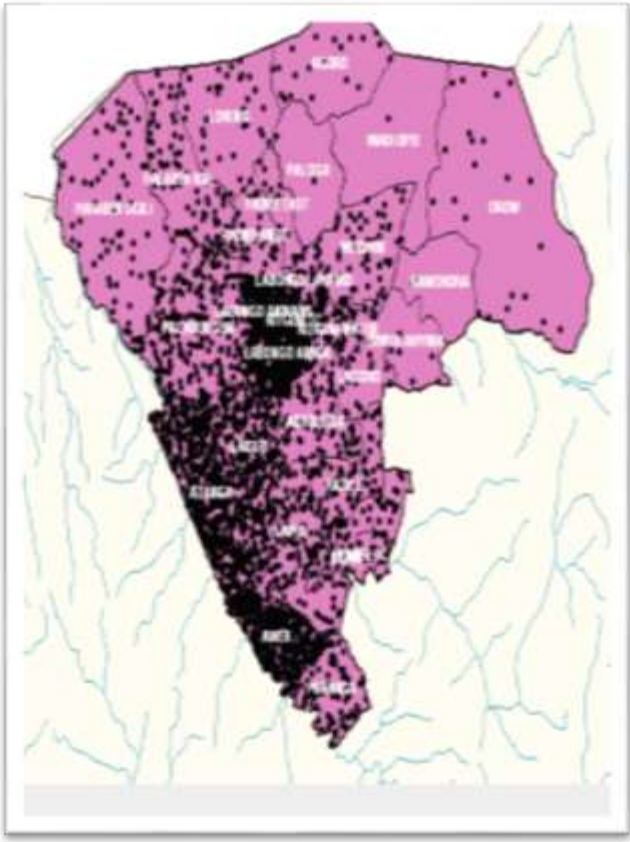
GPS locations of patients with epilepsy in Pader, Kitgum and Lamwo districts



Map of Lamwo, Kitgum and Pader showing black fly breeding sites



GPS locations of patients with NS in Pader, Kitgum and Lamwo districts



How may Onchocerca cause nodding syndrome?

- *O.volvulus* is endemic in many parts of Africa, Central and South America but nodding syndrome occurs in only few localised areas.

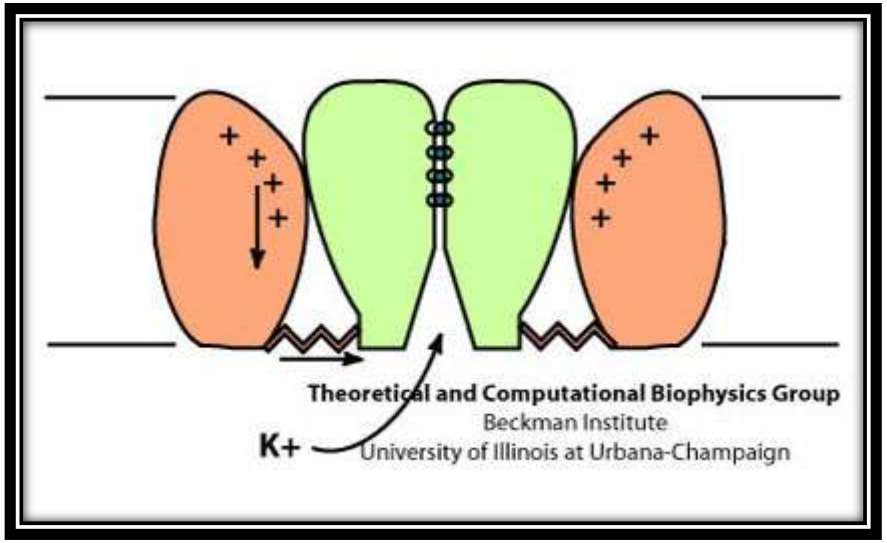
- How would it cause brain injury as it has never been found in the brain?

- **Nodding syndrome is an *O.volvulus or Wolbachia* induced inflammatory epileptic encephalopathy with cross reacting antibodies or auto-antibodies against neuron surface proteins.**

  - **Antibodies to *Onchocerca volvulus* proteins cross-reacting with host neuron proteins**

  - **Antibodies to mutant *Wolbachia* proteins cross-reacting with host neuron surface proteins**

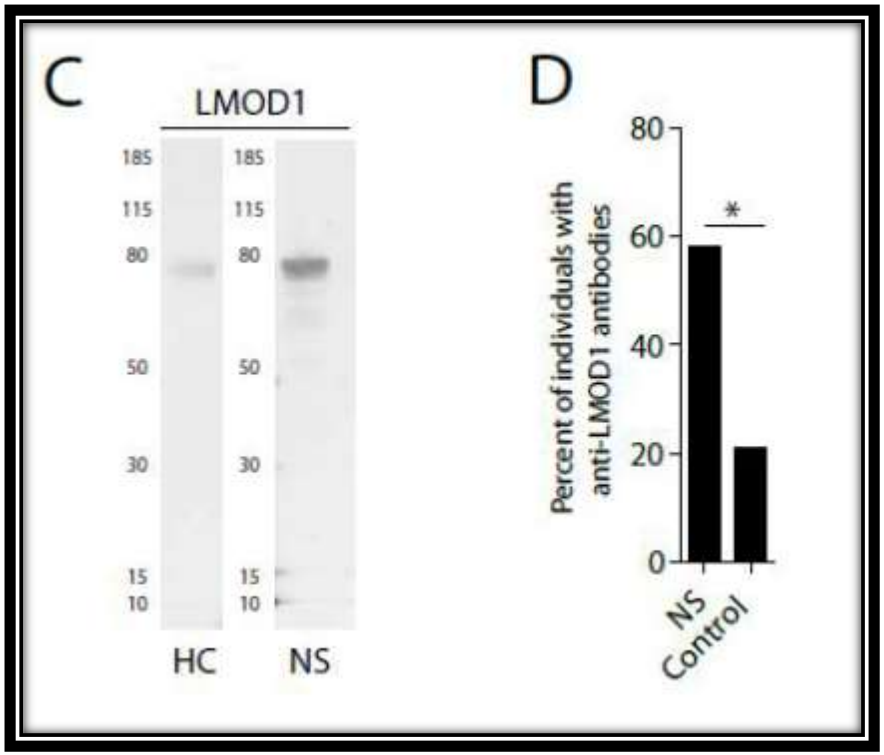
The relationship between antibodies to voltage gated potassium channel (VGKC) complex proteins and nodding syndrome



- VGKC are key in generation and propagation of electrical impulses in the CNS.
- We measured serum antibodies against VGKC-complex proteins in 31 patients and 11 sibling controls:
  - 15/31 (48.3%) established cases of NS tested positive for these antibodies compared to:
  - 1/11(9.1%) controls

CDC measured antibodies to a muscle protein and found an association with NS

- Antibodies against leiomodin-1 were found in 11/19(58%) cases
- LMOD1 shares 83% sequence similarity with a conserved region of *O. volvulus* tropomyosin.
- The antibodies were neuro-toxic in mice brain suggesting cross-reactivity.
  - **Tory Johnson**



Current studies in Kitgum & Pader; DFID/MRC 2015 ARL Award

- **Goal**
  - To understand the pathogenesis of NS and develop specific interventions for the disease.

- **Objectives**
  - Examine if nodding syndrome is an *Onchocerca volvulus/Wolbachia* induced neuro-inflammatory disorder.
  - Whether other non NS epilepsy patients with *Onchocerca* have similar findings*?*
  - Whether there is a genetic risk factor?
  - Whether we can use biomarkers to develop a rapid diagnostic test?
  - Whether doxycycline may be used as treatment.

CASE CONTROL
General objectives

1. Determine the relationship between NS and antibodies to host neuron surface proteins (NSPs) or leiomodin and infection by *O.volvulus*;

2. Determine if a similar relationship exists between *O.volvulus* and non-nodding syndrome associated epilepsy in NS endemic areas. ***May both be the same disease with different manifestations?***

Biomarkers in nodding syndrome and *Onchocerca volvulus* associated epilepsy

- Two approaches
  - Mass Spect in KEMRI starting with CSF to identify unique proteins.
  - Further testing to help develop a diagnostic test.
- Collaborative work with a EU funded work in DR Congo, Cameroon to:
  - Identify unique proteins that can inform therapeutic targets.

Doxycycline for the treatment of Nodding Syndrome trial

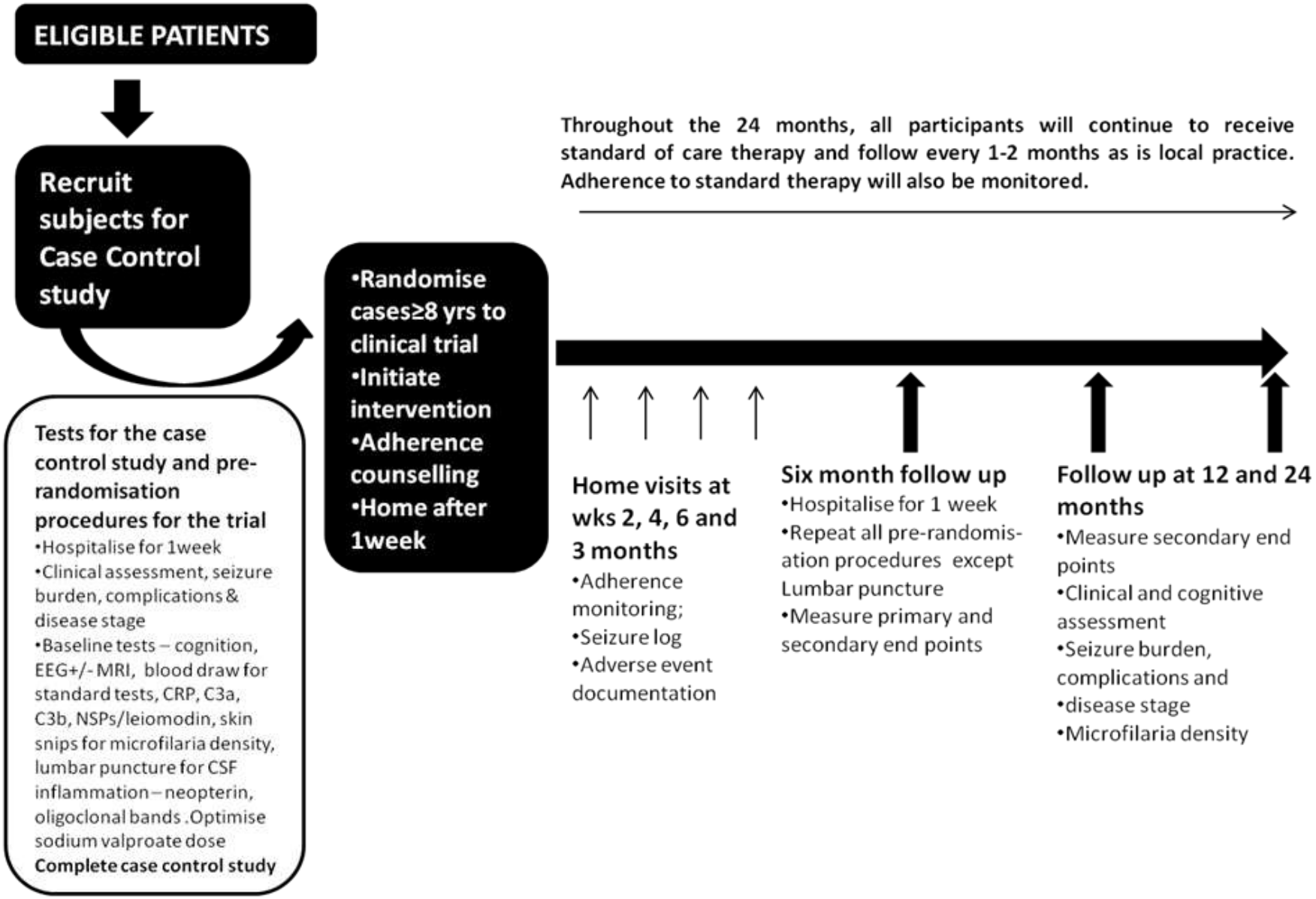
Two-arm, placebo-controlled, Randomized Phase II trial of oral doxycycline 100mg daily Or placebo in 230 patients for Six weeks and 24 month follow up

TRIAL
Hypothesis

- There is no specific treatment for adult Onchocerca
  - Ivermectin, kills only microfilaria.
  - Killing the adult worms may alter the course of NS.

- **Oral doxycycline 100mg daily for six weeks will resolve the antibodies and seizures and improve cognitive function in NS**
  - Achieved by targeting Wolbachia; Antibiotic depletion of Wolbachia results in extensive apoptosis in O.volvulus' germ-line and somatic cells of embryos leading to;
    - Reduced dermal microfilaria density, sterilisation and premature death of adult parasites
    - Six-wks Doxycycline (100mg/day), results in >90% reduction in Wolbachia levels in filarial tissue and dermal microfilaria density over 6-11 months & early death of adult parasite.

SUMMARY OF STUDY PROCEDURES



Completed enrollment – as of 01st October 2017

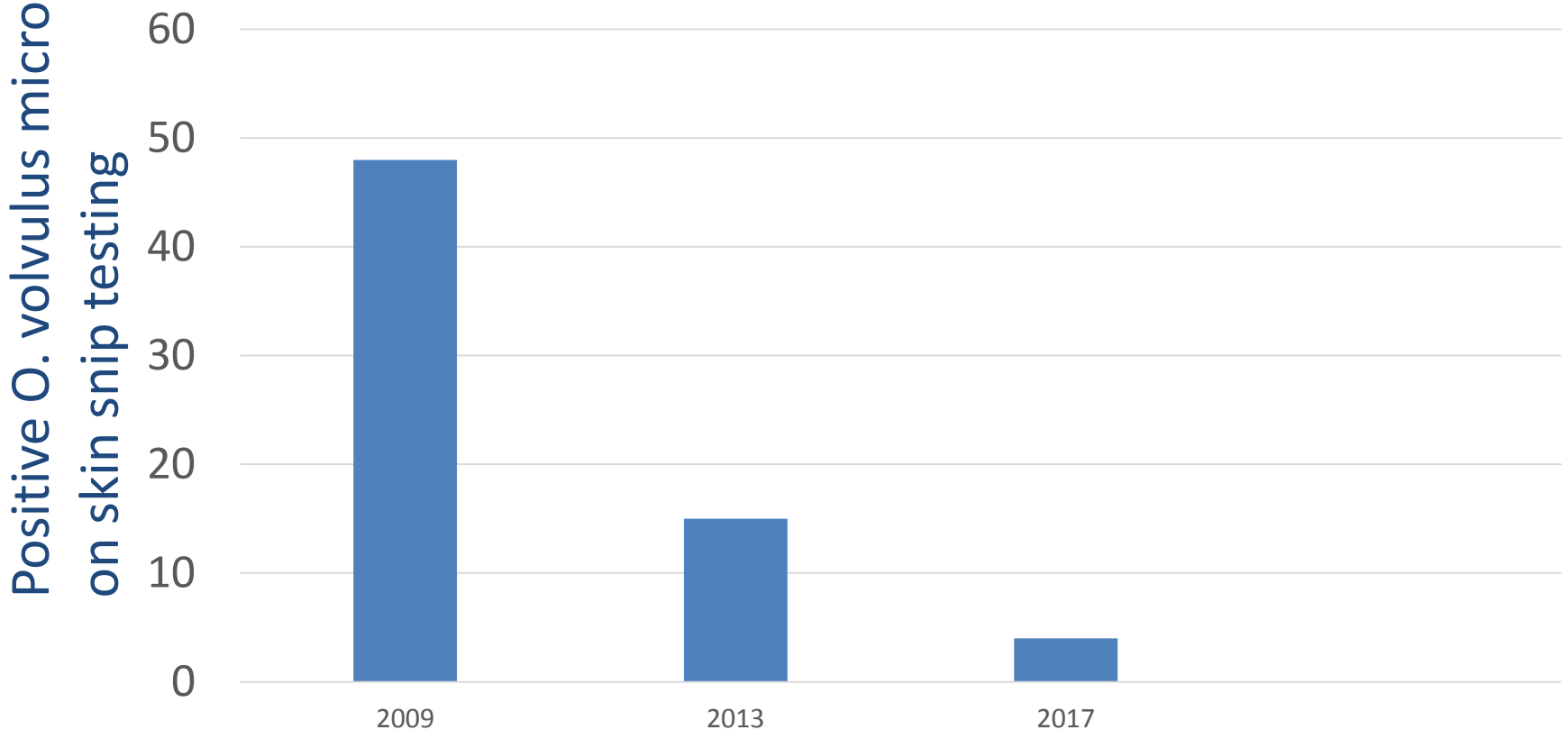
Participant Group	No. to be enrolled, N	No. enrolled	% enrolled
Nodding syndrome patients – also randomized to doxycycline or placebo	230	240	>100%
Non nodding syndrome epilepsy controls	154	154	100%
Normal community controls	154	154	100%

Expected recruitment completion date is September 2017

Other than research, what is the Ministry of Health doing?

- **Plan to eliminate Onchocerciasis**
  - Aeriel spraying
  - Twice yearly ivermectin to everybody
  - River douching/larvaciding

Proportion of nodding syndrome patients testing positive for Onchocerca volvulus microfilaria



Prevalence and Annual Incidence of Nodding Syndrome and Other forms of Epilepsy in Onchocerciasis Endemic areas of Northern Uganda

Mbonye M, Gumisiriza N, Opar, B, Lakwo T, Colebunders R et al

Acknowledgments

CENTRE FOR TROPICAL NEUROSCIENCE

UNIVERSITY OF OXFORD

REPUBLIC OF UGANDA
MINISTRY OF HEALTH

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