

Onchocerciasis associated epilepsy and nodding syndrome research.



Richard Idro

Makerere University College of Health Sciences,
Kampala, Uganda

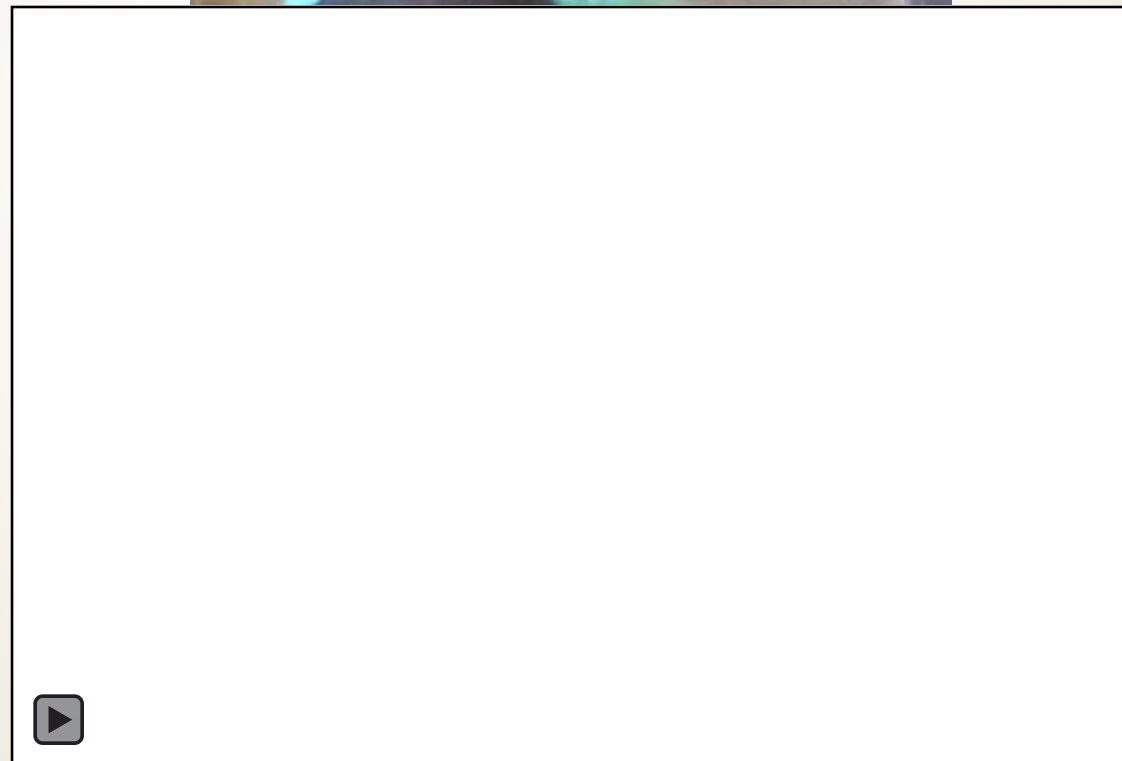


Objectives

- Describe the clinical, EEG, imaging features and short term outcomes of both NS and OAE in Uganda
- Determine if NS is a neuro-inflammatory disorder with antibodies to *O. volvulus* cross reacting with host neuron proteins
 - Determine if a similar relationship exists between OAE. May NS and OAE both be the same disease with different manifestations.
 - Can we develop a diagnostic test?
- Can Doxycycline be used for the treatment of nodding syndrome?

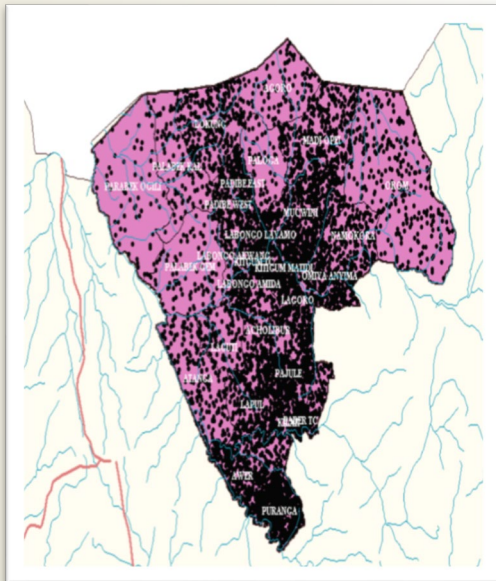


Head nodding in an adolescent



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

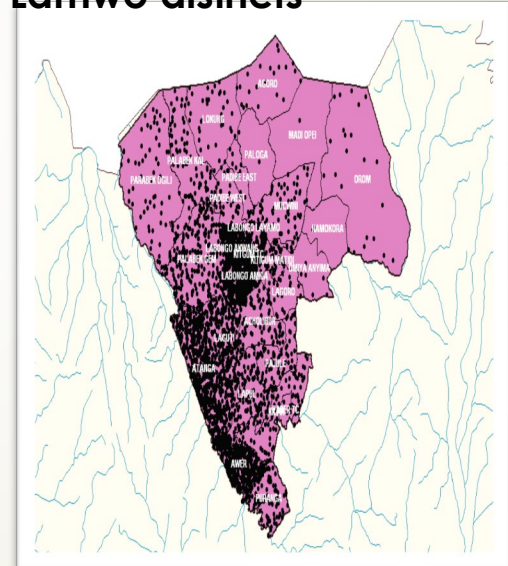
GPS locations of patients with epilepsy in Pader, Kitgum and Lamwo districts



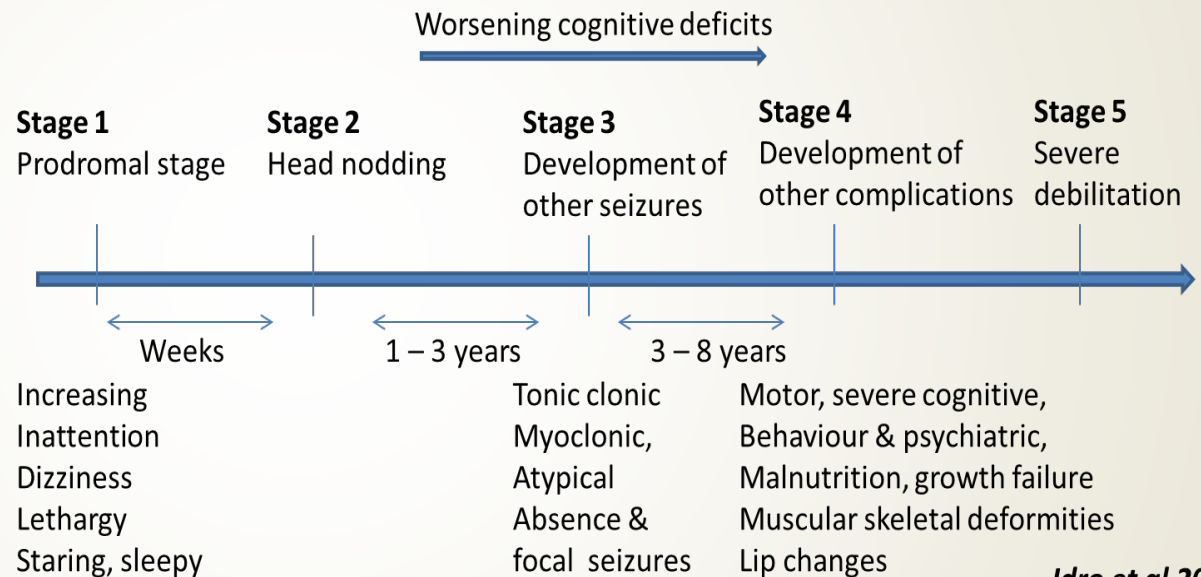
Map of Lamwo, Kitgum and Pader showing black fly breeding sites



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

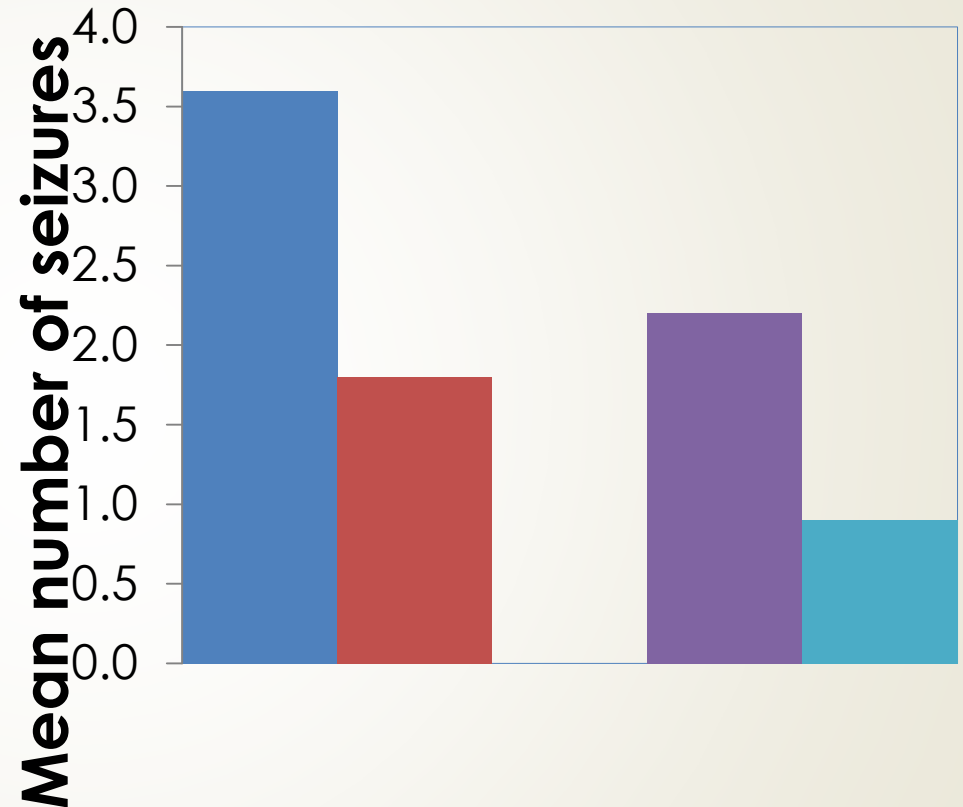
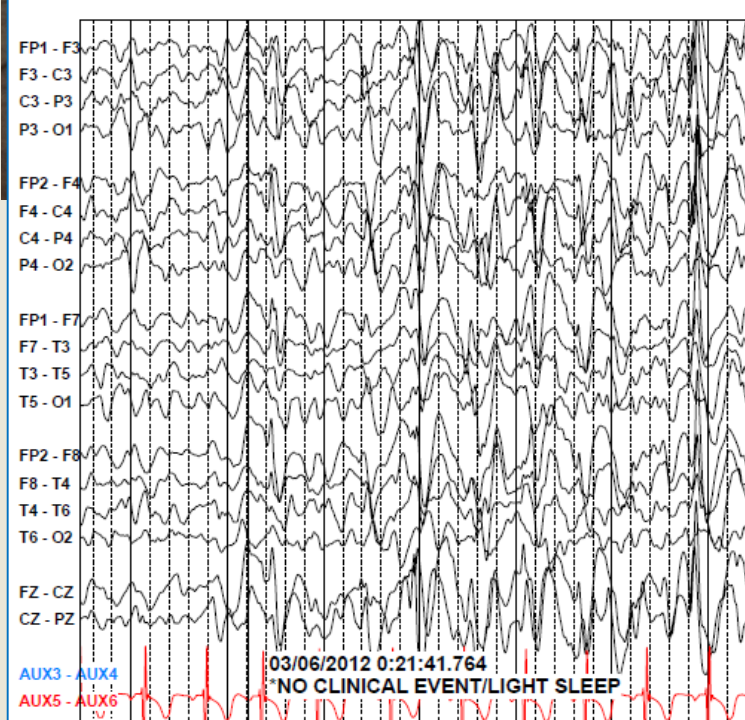
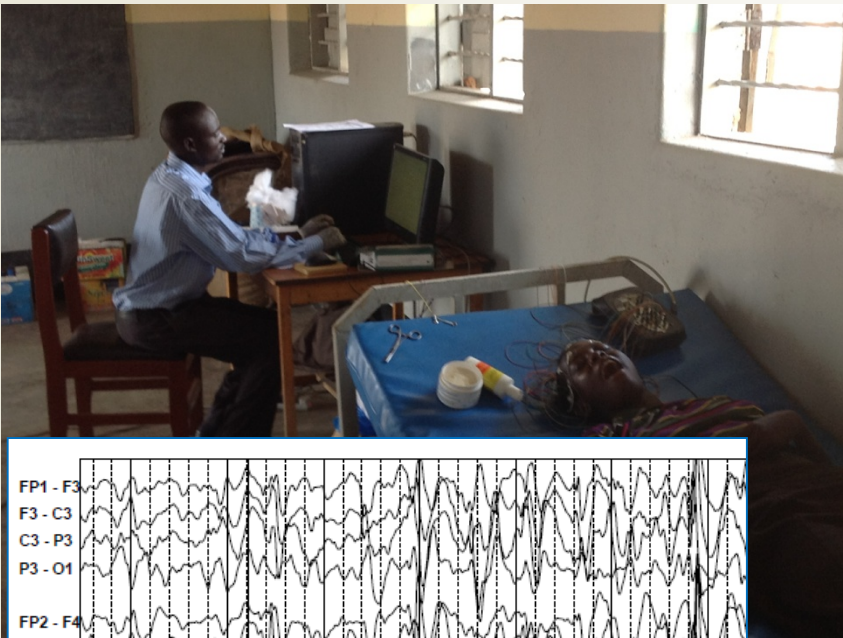


Natural history of untreated nodding syndrome



Idro et al 2013

Nodding syndrome is a neurological disorder characterized by epilepsy



No. of seizures 2-3 wks after starting sodium valproate

Principles of Management of Nodding Syndrome in Uganda

- ▶ Treatment guidelines developed by a multidisciplinary team **of clinicians, nurses, and therapists**
- ▶ **Trained health workers provide care in 17 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**



NODDING SYNDROME


HEALTH WORKERS' TRAINING MANUAL

MINISTRY OF HEALTH

DRAFT EDITION: February 2012

We assessed the outcomes of treatment one year after starting

	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



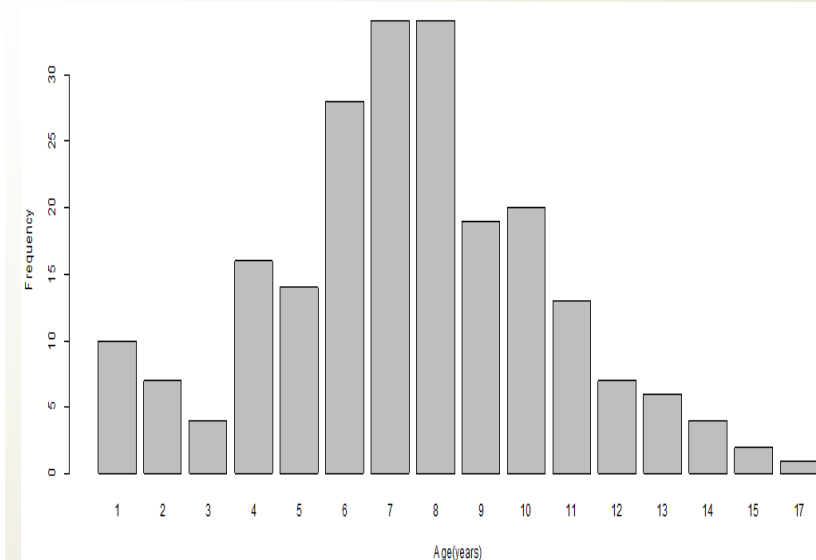
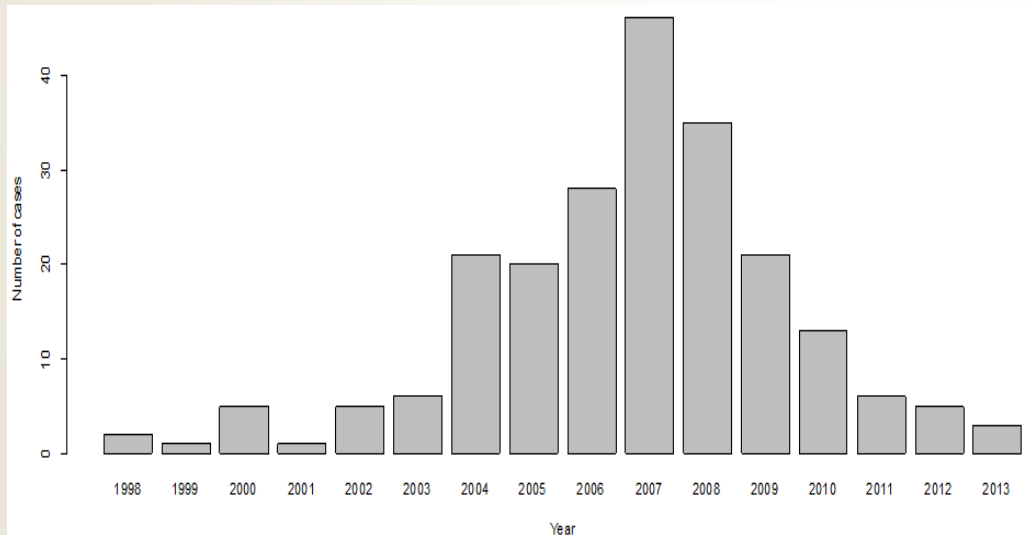
Nodding Syndrome in Uganda - 2017

District	Number of Cases	Deaths
Pader	806	81
Kitgum	544	33
Lamwo	339	10
Gulu and Omoro	323	1
Amuru	58	4
Lira	13	-
	2083	129

What causes nodding syndrome?

10

- We asked ourselves several questions?
 - Is it caused by a toxin or an environmental chemical in water or food?
 - Is it genetic?
 - Is it caused by an infection?
- We conducted a series of research to answer these questions.

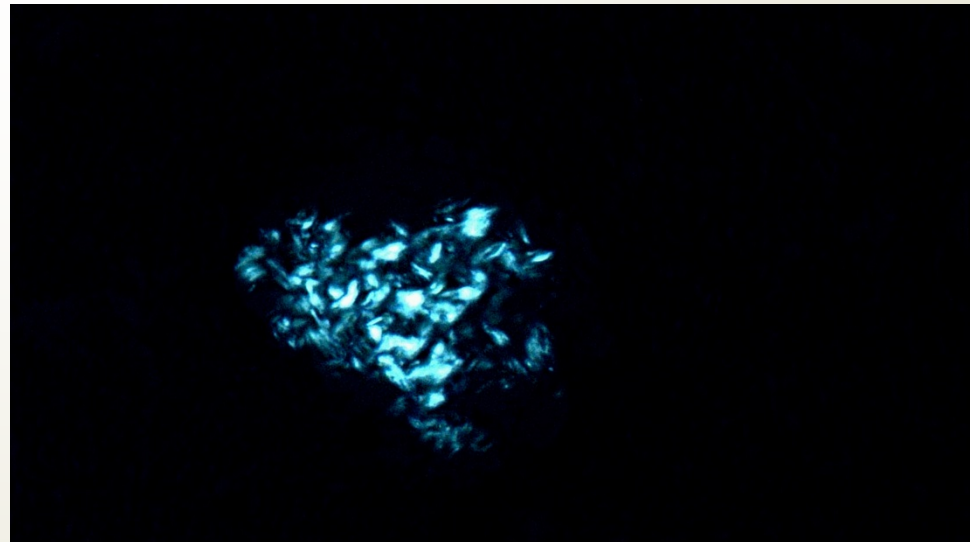
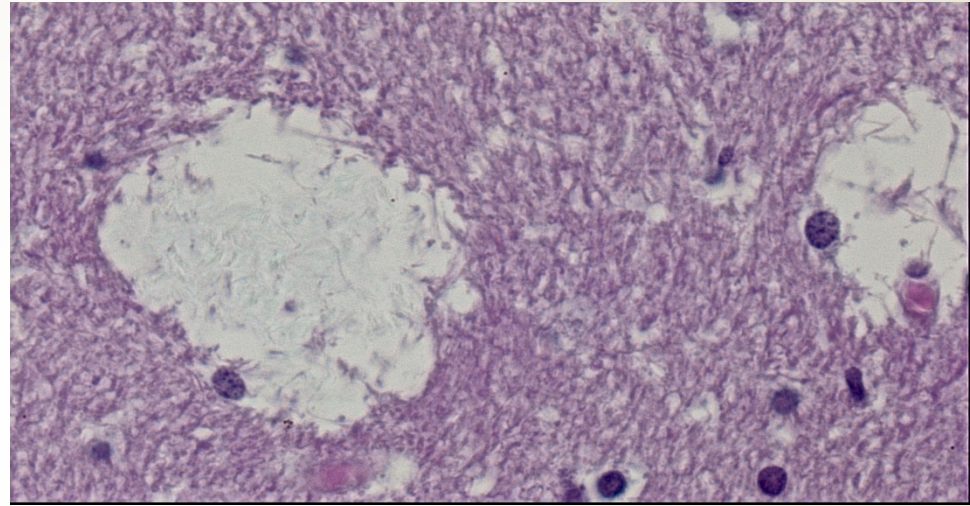


Postmortem examinations

First set of brain specimens – obtained late

Next $\frac{3}{4}$ specimens – high carbon density material

Similar findings in next set of brain specimens



Recent findings – Pollanen et al 2018

Acta Neuropathologica

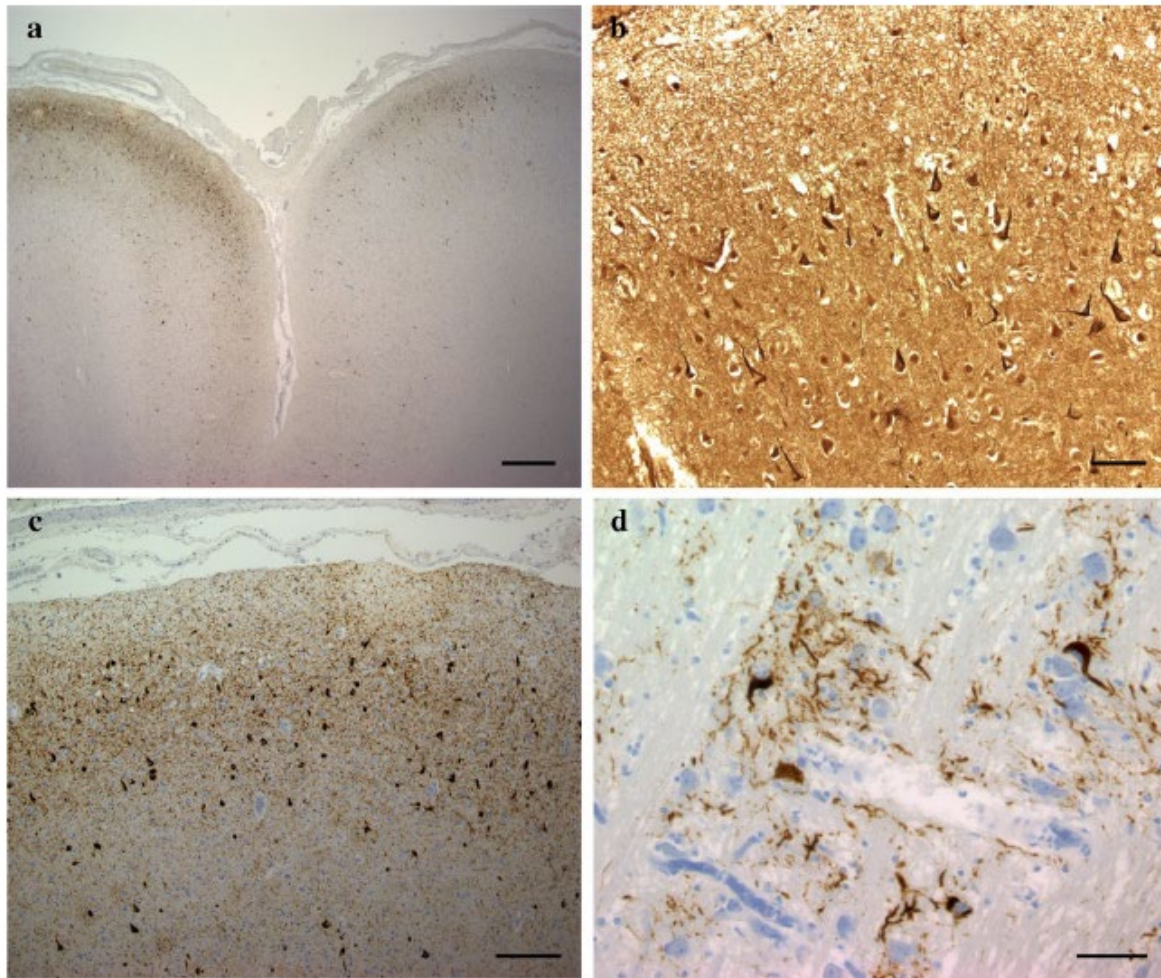
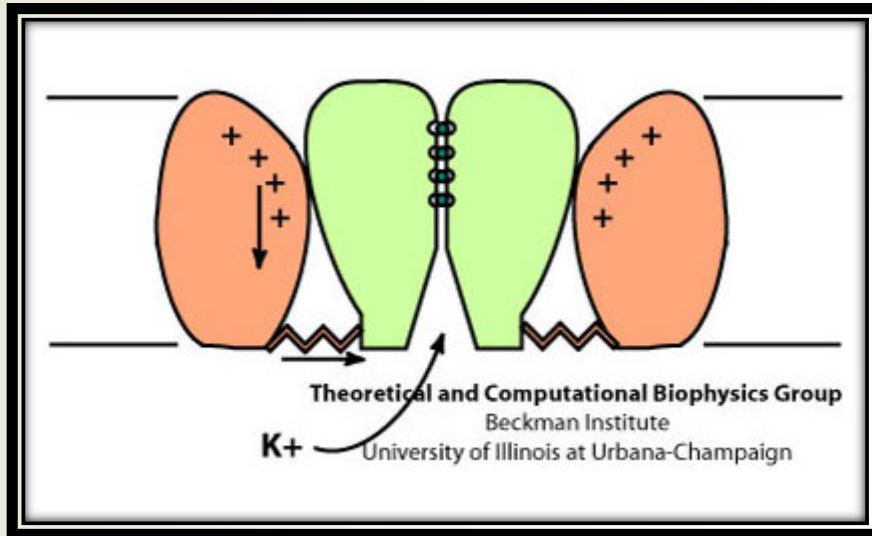


Fig. 2 Histologic findings in nodding syndrome. **a** Tau-immunoreactive in frontal cortex, mostly in gyral crowns (AT8, scale bar: 1000 μ m). **b** Cortical neurofibrillary tangles (Bielschowsky stain, scale bar: 100 μ m). **c** Neurofibrillary tangles, dystrophic neurites

and dot-like immunoreactivity containing phosphorylated tau in cerebral cortex (AT8, scale bar: 200 μ m). **d** Neurofibrillary tangles and dystrophic neurites in neurons in the base of pons (AT8, scale bar: 75 μ m)

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

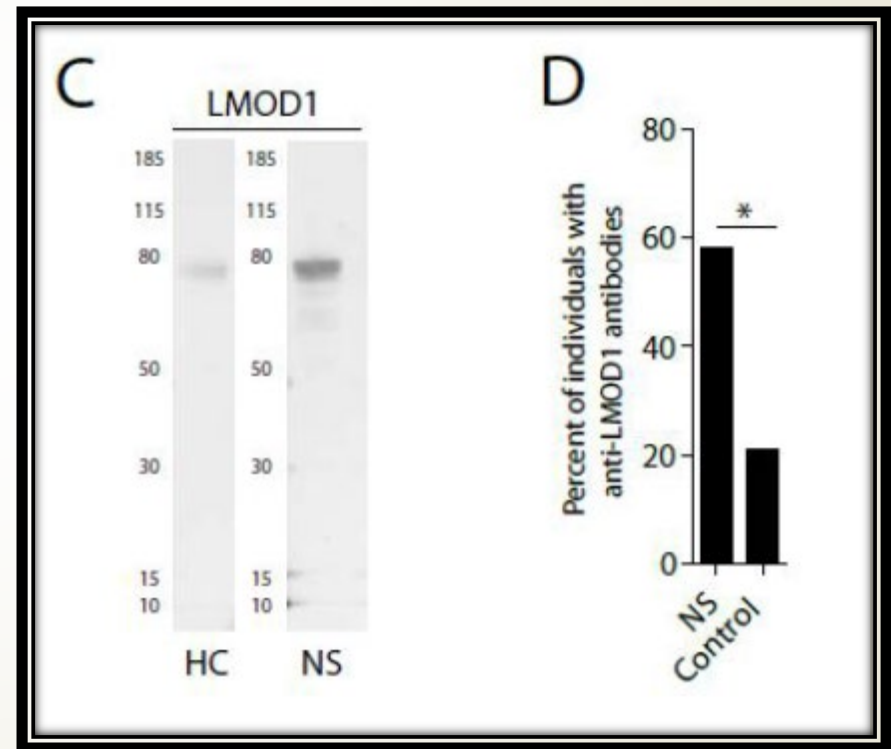


- VGKC are key in generation and propagation of electrical impulses in the CNS.
- We measured serum antibodies against VGKC-complex proteins in 31 patients and 11 sibling controls:
 - 15/31 (48.3%) established cases of NS tested positive for these antibodies compared to:
 - 1/11 (9.1%) controls

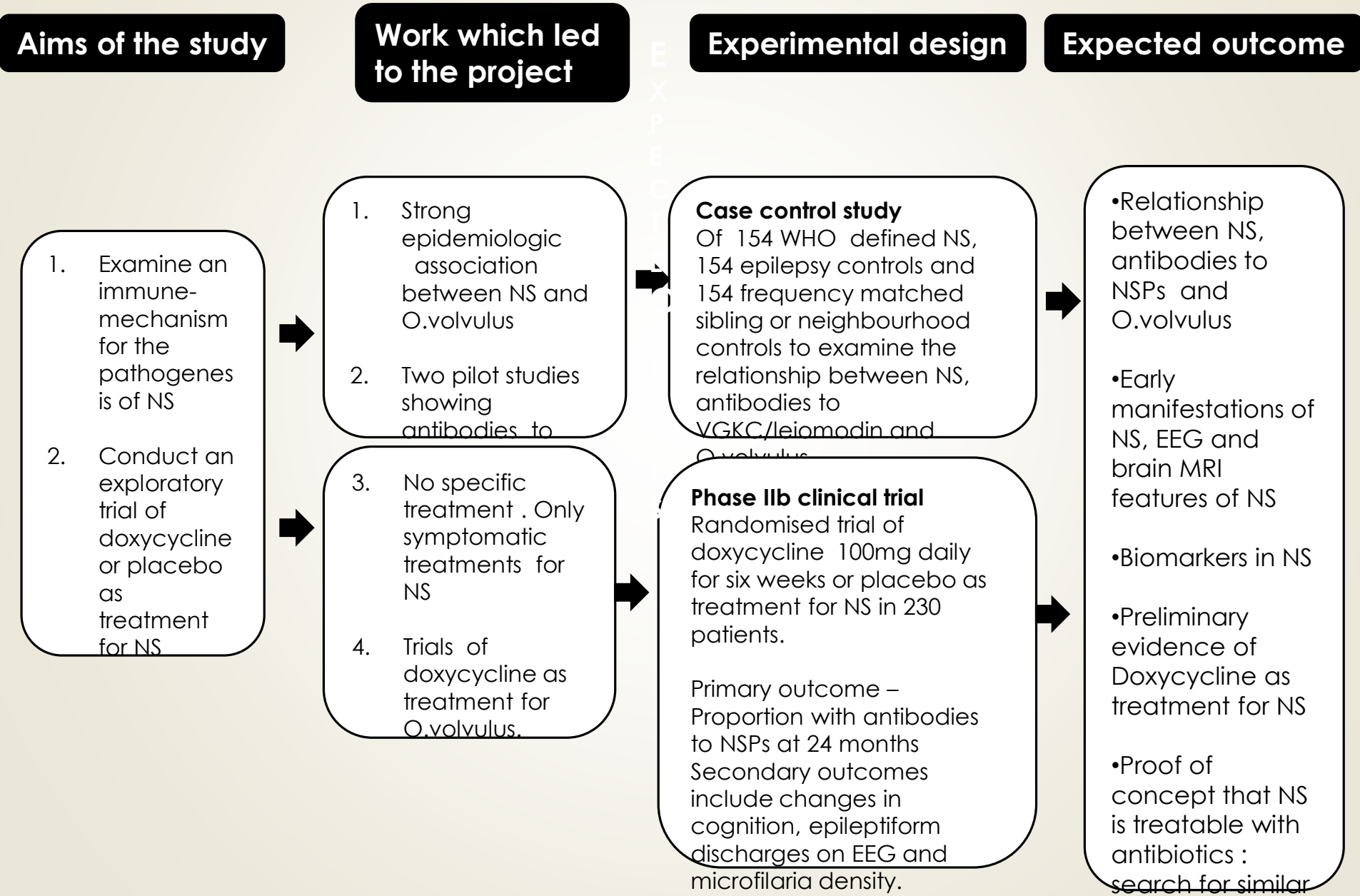
CDC measured antibodies to another protein – leiomodin and found an association with NS

- 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 neurotoxic in mice brain suggesting cross-reactivity.

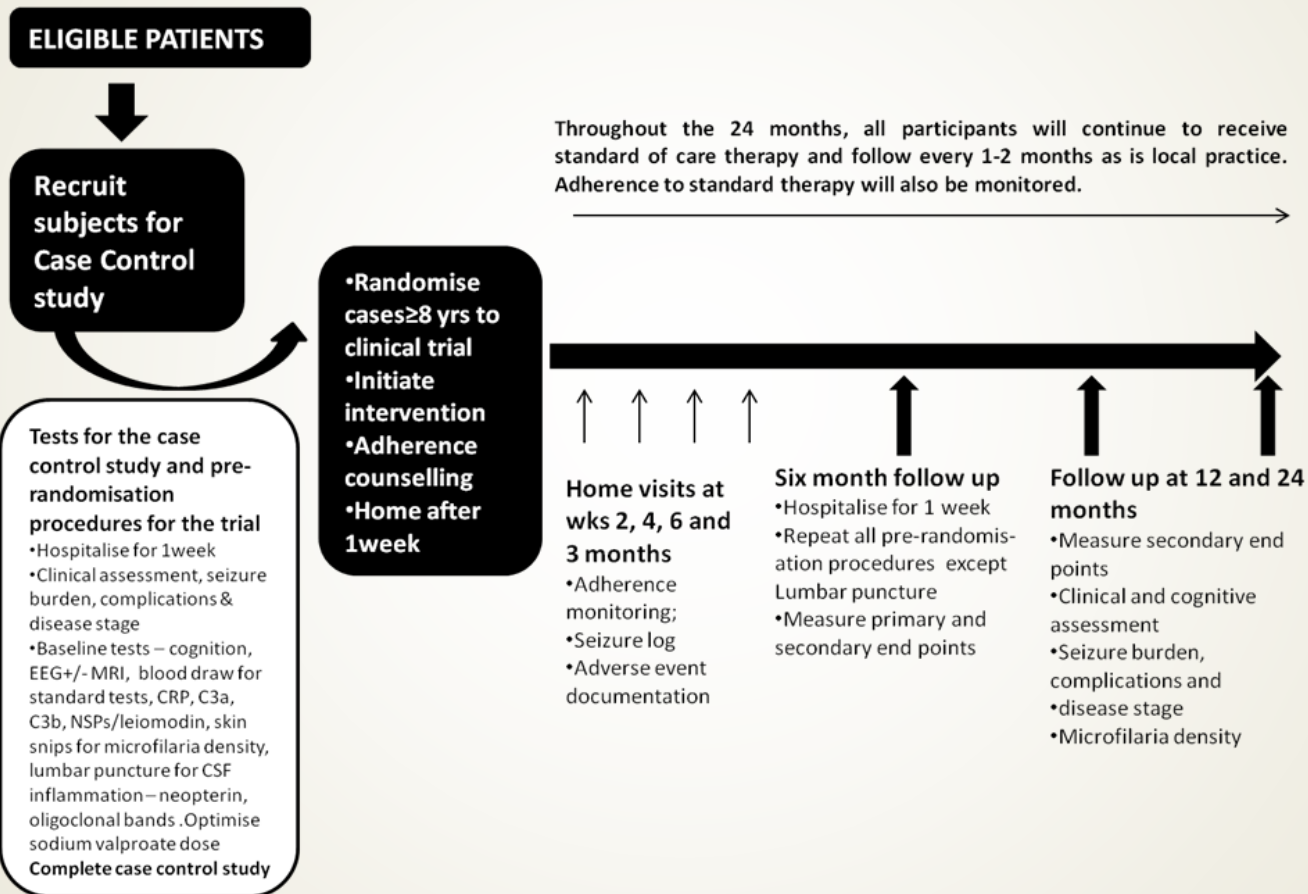
Johnson et al



Pathogenesis & treatment of NS project in Uganda



SUMMARY OF STUDY PROCEDURES





Current progress

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%

Recruitment is complete - Results expected beginning of 2020

Preliminary studies

1. Describe the clinical, EEG and corresponding 1.5 Tesla MRI features of NS. ----- 40 patients
2. Clinical, EEG and imaging studies and 2 yr outcomes of OAE epilepsy.
3. Examine the relationship between NS and antibodies to specific NSPs.
4. In cases, investigate for inflammatory markers in CSF and plasma and determine the relationship between these, *O.volvulus* specific IgG4 and antibodies to NSP-Abs/leiomodin and microfilaria density.
5. Describe types of *Wolbachia* super-groups in cases with NS and controls and examine the relationship between the super-groups and NS - Germany
6. Conduct an exploratory mass spectrometry study of plasma and CSF to identify potential diagnostic and prognostic biomarkers and explore mechanisms of disease.
7. Genetic studies

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

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

Proportion of nodding syndrome patients testing positive for *Onchocerca volvulus* microfilaria

Positive *O. volvulus* microfilaria
on skin snip testing

60

40

20

0

2009

2013

2017



Acknowledgments



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