Onchocerciasis-related epilepsy
Clinical manifestations and case definition

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Content

1. Clinical manifestations
2. Technical investigations
   a) EEG
   b) MRI
3. Proposed case definition

Case study in Maridi, South Sudan

High epilepsy prevalence

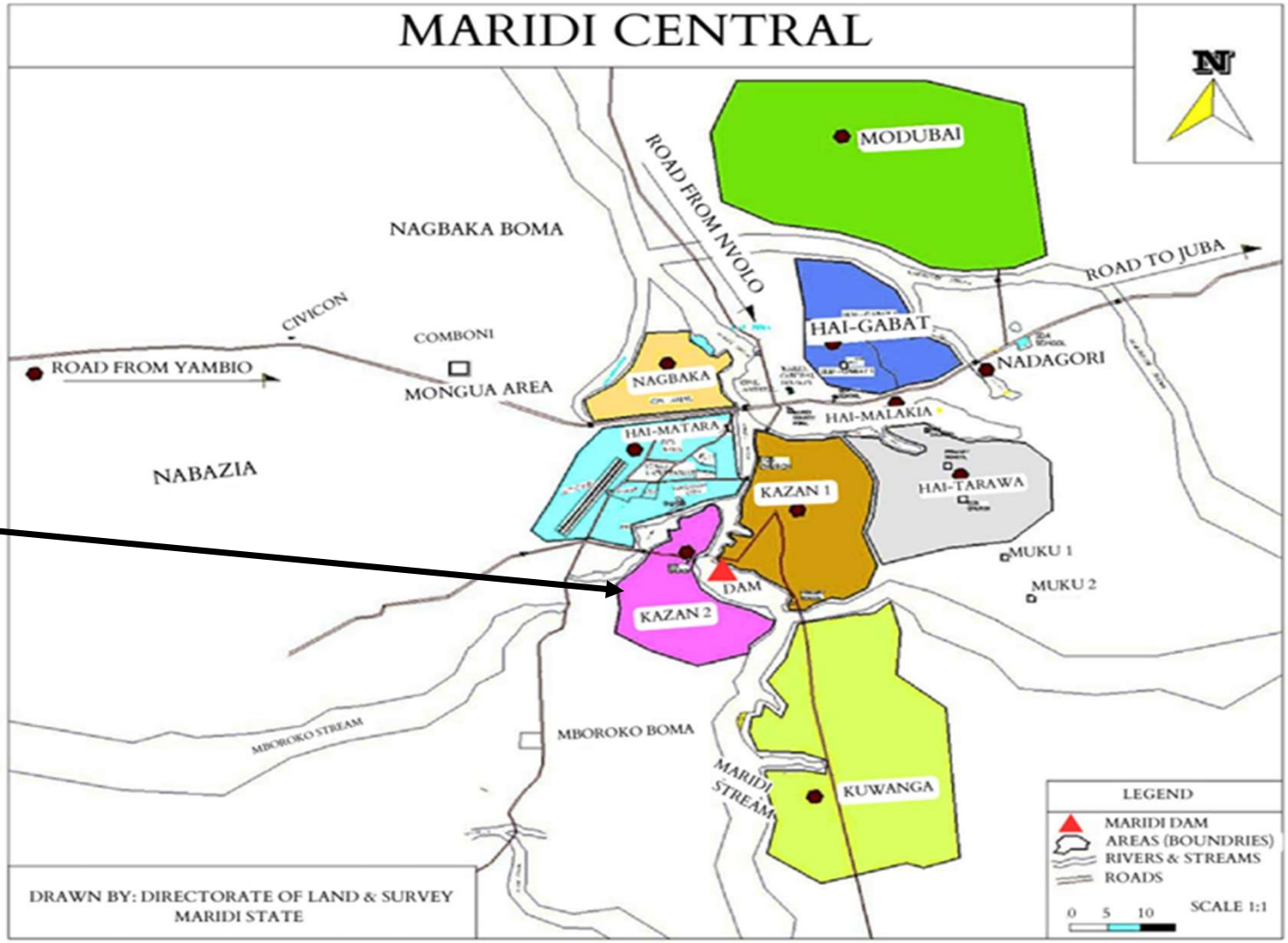
40,7 per 1000 (2022)

High onchocerciasis transmission

3–6 year-olds: 19,8% seroprevalence (2019)

7–9 year-olds: 33,3% seroprevalence (2019)

Maridi dam


MARIDI CENTRAL
N
MODUBAI
ROAD FROM NYOLO
NAGBAKA BOMA
ROAD TO JUBA
CIVICON
COMBONI
HAI-GABAT
ROAD FROM YAMBIO
NAGBAKA
NADAGORI
MONGUA AREA
HAI-MALAKIA
HAI-MATARA
NABAZIA
KAZAN 1
HAI-TARAWA
MUKU 1
DAM
MUKU 2
KAZAN 2
MBOROKO STREAM
MBOROKO BOMA
MARIDI STREAM
KUWANGA
LEGEND
MARIDI DAM
AREAS (BOUNDRIES)
RIVERS & STREAMS
ROADS
0 5 10
SCALE 1:1
DRAWN BY: DIRECTORATE OF LAND & SURVEY
MARIDI STATE

Family living in Kazana 2

Boy, 14 years
- Age of onset (y): 9
- Nodding seizures
- 1 seizure with generalized onset (tonic–clonic)

Girl, 16 years
- Age of onset (y): 9
- Nodding seizures
- Seizures with generalized onset (tonic–clonic)

Girl, 12 years
- Age of onset (y): 4
- Nodding seizures
- Focal aware seizures

Boy, 10 years
- Age of onset (y): 9
- 1 seizure with generalized onset (tonic–clonic)
- Focal seizures with impaired awareness (non-motor onset)

A closer look at a family in Kazana 2

Boy, 14 years
Probable nodding syndrome

Girl, 16 years
Probable nodding syndrome

Girl, 12 years
Probable nodding syndrome

Boy, 10 years

Reminder: case definition of NS[1]

Suspected	Reported head nodding in a previously healthy person
Probable	Age 3–18 y at onset of head nodding and nodding frequency 5–20 times/min + At least one of the following: other neurologic abnormalities, clustering in space or time with similar cases, triggering by eating or cold weather, delayed sexual or physical development, psychiatric manifestations
Confirmed	Probable case with documented head nodding episodes (by healthcare worker, by EEG/EMG, by video)

1 Dowell et al. 'Nodding Syndrome'. *Emerging Infectious Diseases* 19, nr. 9 (2013): 1374-84. https://doi.org/10.3201/eid1909.130401.

A closer look at a family in Kazana 2

Boy, 14 years
Probable nodding syndrome

Girl, 12 years
Probable nodding syndrome

Girl, 16 years
Probable nodding syndrome

Boy, 10 years
?
Combined focal and generalized epilepsy

Application of the OAE definition [1]

Minimal criteria

1. a history of two or more unprovoked epileptic seizures occurring at least 24 h apart
2. living in an onchocerciasis-endemic region for at least three years
3. living in a village with a high prevalence of epilepsy and PWE often clustered within certain households, that is, families having more than one child with epilepsy
4. no other obvious cause of epilepsy (e.g., perinatal asphyxia, history of severe malaria, measles, encephalitis or meningitis, or head injury with loss of consciousness in the five years before the onset of epileptic seizures
5. onset of seizures in childhood or adolescence (3 to 18 years)
6. normal neurological development before the onset of epilepsy

1 Van Cutsem G et al. . Case definitions for onchocerciasis-associated epilepsy and nodding syndrome: A focused review. Seizure. april 2023.

A closer look at a family in Kazana 2

Boy, 14 years
Probable nodding syndrome
OAE

Girl, 16 years
Probable nodding syndrome
OAE

Girl, 12 years
Probable nodding syndrome
OAE

Boy, 10 years
OAE

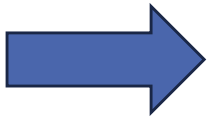
21 year old boy living in Kazana 2

- Onset nodding seizures at age 7
- Blind at age 10
- Body weight 27kg, height 130 cm
- 4 siblings with epilepsy, one died

Short recap

NAKALANGA SYNDROME

- Occuring in previously healthy children, clustering of cases
- Characterized by: stunting, wasting, retardation of sexual development and mental impairment
- Additional features: facial dysmorphia, kyphoscoliosis, epilepsy



Overlap in clinical features

Technical investigations

EEG

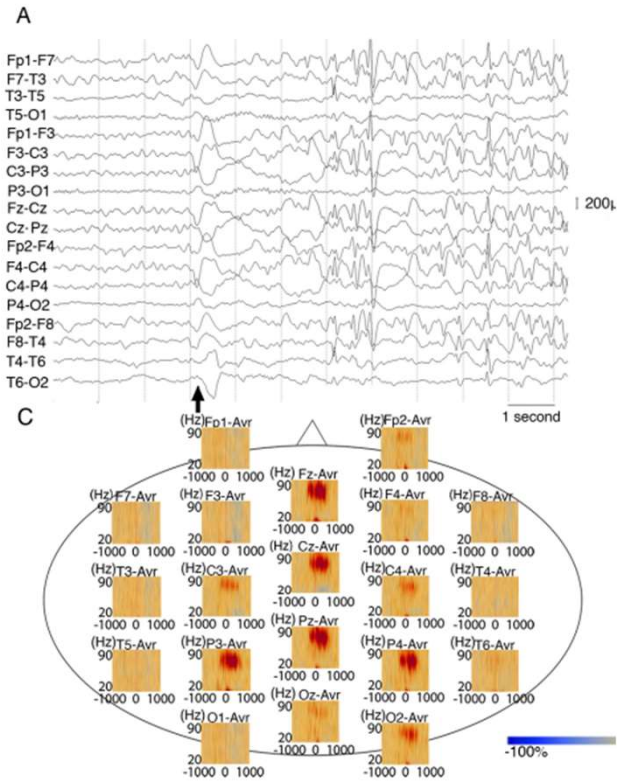
MRI

Interictal EEG

- Normal EEG[1,2]
- Slow background EEG activity (focal slowing, multifocal slowing, bilateral slowing, generalized slowing)[1, 2]
- Generalized interictal epileptic activity (intermittent generalized slowing and sharp wave activity)[1]
- Focal interictal epileptic activity (multifocal, bilateral, right temporal and left temporal)[2]

[1] Winkler et al. The Head Nodding Syndrome--Clinical Classification and Possible Causes. *Epilepsia* 2008-15.
[2] Ogwang et al. Epilepsy in Onchocerca Volvulus Sero-Positive Patients From Northern Uganda-Clinical, EEG and Brain Imaging Features' *Frontiers in Neurology* 2021: 687281.

Ictal EEG during nodding seizure[1]



A 7 year-old male with NS onset at age 6 years.

Ictal EEG shows generalized slow wave followed by electrodecrement. EEG background between each head nod is marked by generalized spike and wave discharges.

<u>Conclusions</u>

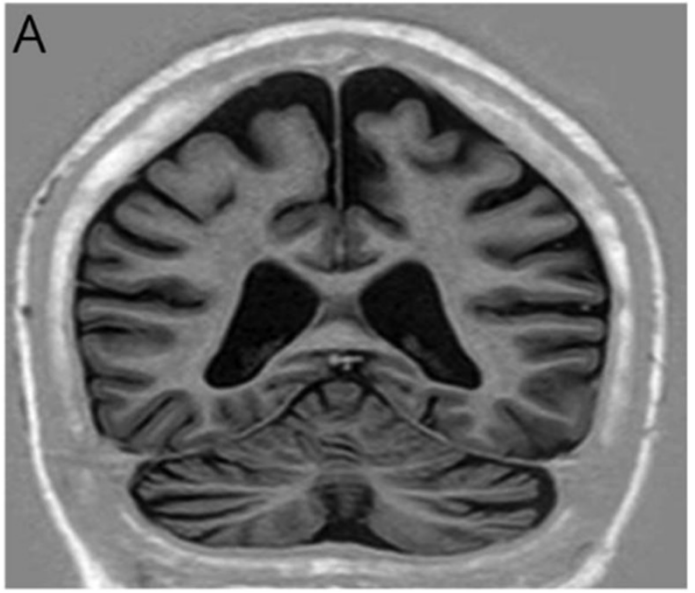
- shared electro-clinical features with the spectrum of developmental and epileptic encephalopathies

- unable to assess if the seizure onset zone in NS is focal or generalized

[1] Mazumder et al. Ictal Electroencephalographic Characteristics of Nodding Syndrome: A Comparative Case-Series from South Sudan, Tanzania, and Uganda. *Annals of Neurology* july 2022

MRI

- Similar findings NS and other forms of OAE in Uganda
- Most consistent: cerebral and cerebellar atrophy [1,2]
- More hemispheric asymmetry in cases of NS compared to other forms of OAE
- 12,5% (2/16) of cases meeting the OAE criteria had developmental malformations on MRI imaging



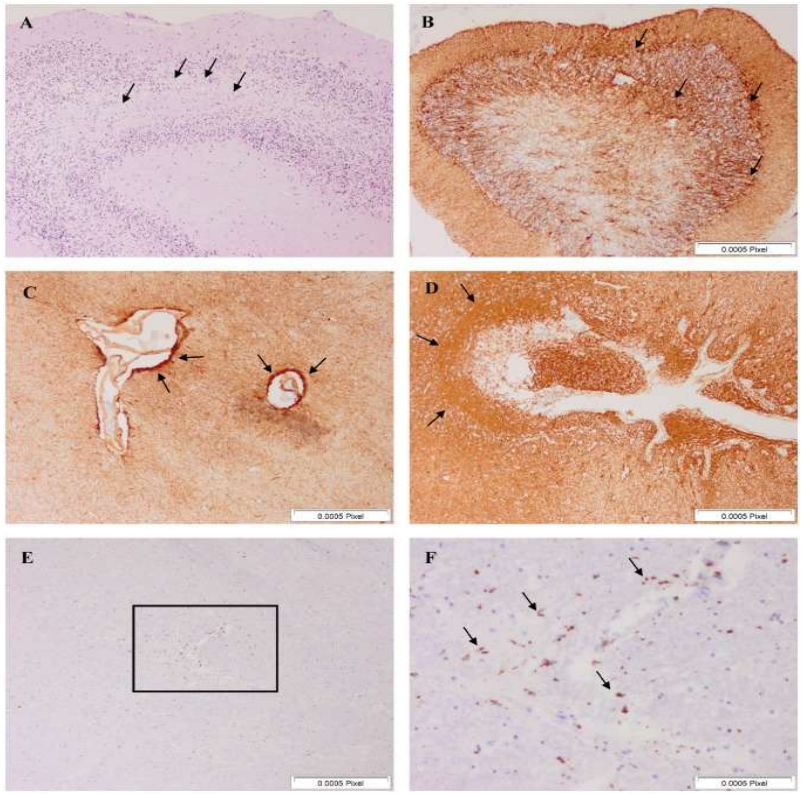
16-year-old girl with NS with global cerebral and cerebellar atrophy (T1- weighted inversion recovery)[1]

[1] Mazumder et al. 'Comparison of Structural Changes in Nodding Syndrome and Other Epilepsies Associated With Onchocerca Volvulus'. *Neurology(R) Neuroimmunology & Neuroinflammation. March 2023*

[2] Winkler et al. MRI Findings in People with Epilepsy and Nodding Syndrome in an Area Endemic for Onchocerciasis: An Observational Study' *African Health Sciences* June 2013

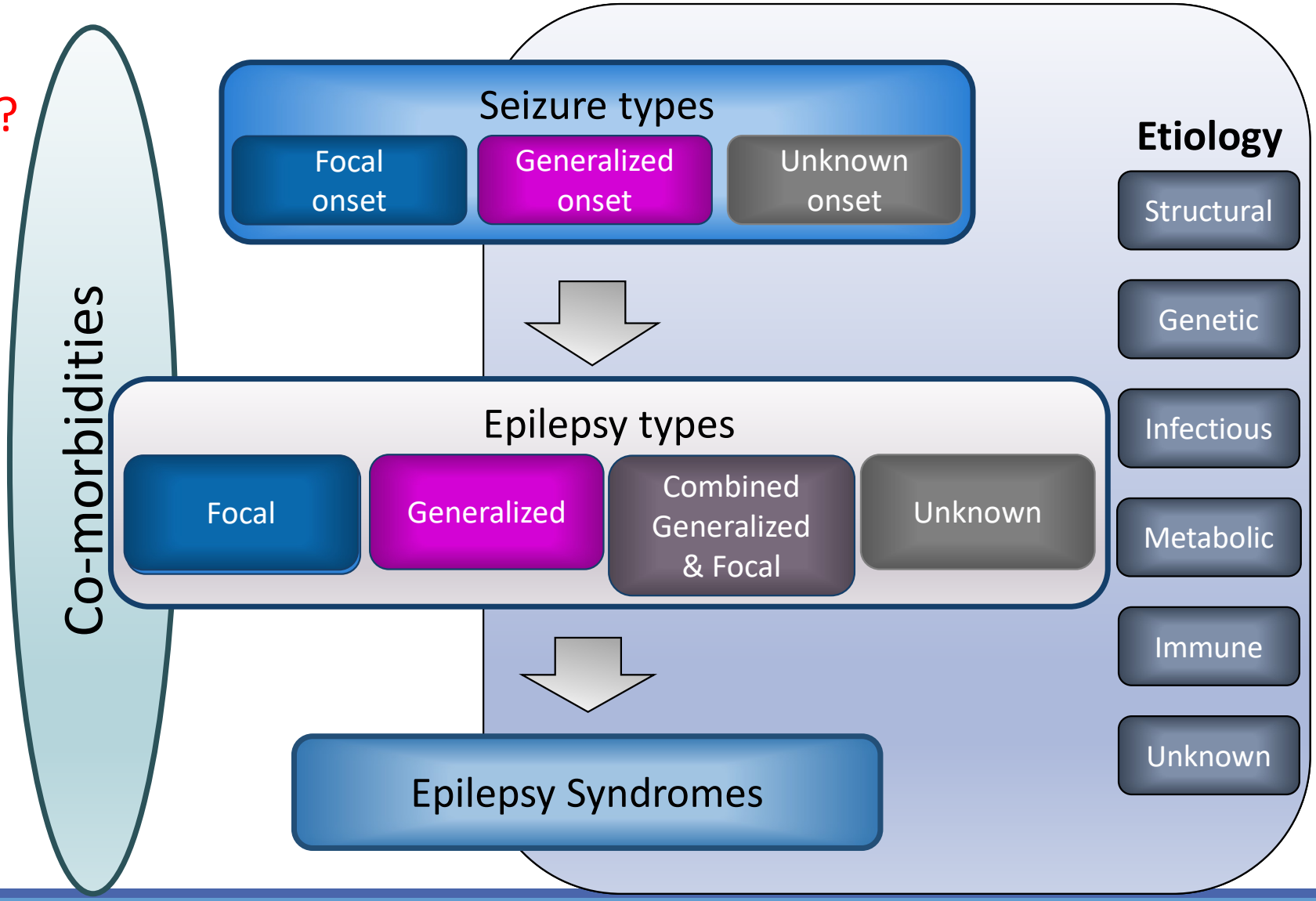
Anatomopathology

- Study in Uganda
- 5 cases of NS and 4 cases of other forms of OAE
- NS/OAE: similar pathological presentation signs of neuro-inflammation
- More Tau deposits in NS



Hotterbeekx et al, *J Neuropathol Exp Neurol* 2019

Nodding?


Co-morbidities
Seizure types
Focal onset
Generalized onset
Unknown onset
Epilepsy types
Focal
Generalized
Combined Generalized & Focal
Unknown
Epilepsy Syndromes
Etiology
Structural
Genetic
Infectious
Metabolic
Immune
Unknown

Proposed case definition

Proposed case definition of OAE[1]

Minimal criteria

1. a history of two or more unprovoked epileptic seizures occurring at least 24 h apart
2. living in an onchocerciasis-endemic region for at least three years
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1 Van Cutsem G et al. . Case definitions for onchocerciasis-associated epilepsy and nodding syndrome: A focused review. Seizure. april 2023.

Proposed case definition of OAE

Additional criteria suggesting OAE

1. a history of **head nodding seizures**, cognitive impairment or **Nakalanga features** (stunting without an obvious cause, skeletal deformities and absence of external signs of sexual development)
2. persons with these features in the same village
3. seropositivity for Ov16 onchocerciasis antibodies (Not a required criterion because both the Ov16 rapid diagnostic test (RDT) and the Ov16 ELISA test have a relatively low sensitivity (<85%) and many people in onchocerciasis hyperendemic areas have *O. volvulus* antibodies, potentially including persons with epilepsy with another aetiology)
4. for a person who has never taken ivermectin:
   a) a skin test positivity for microfilaria (microscopy or PCR)
   b) clinical manifestations of onchocerciasis, including leopard skin, onchodermatitis, ocular onchocerciasis and/or nodules

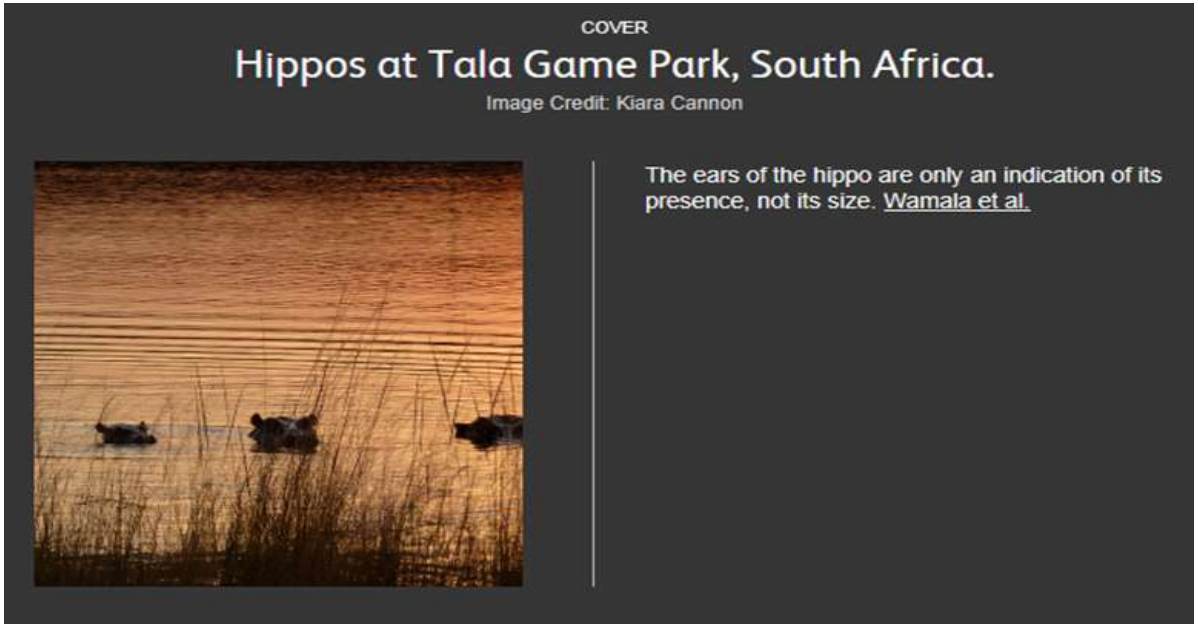
Proposed case definition of OAE

New additional criterion suggesting OAE

Knowledge that the area is or was onchocerciasis meso- or hyperendemic based on > 20% nodule prevalence in REMO surveys or > 35% prevalence of microfilaria in the skin

Conclusion

- OAE includes a spectrum of different types of seizures including nodding seizures



Nodding syndrome = the ears of the hippo

Conclusion

- OAE includes a spectrum of different types of seizures including nodding seizures
- OAE may present with Nakalanga features
- Other onchocerciasis skin and eye disease with potentially blindness at a very young age

Let’s talk!