Neuroinflammation and not tauopathy is a predominant pathological signature of nodding syndrome

An Hotterbeekx
Introduction

Onchocerciasis (river blindness) caused by the filarial nematode *Onchocerca volvulus*

- Skin disease
- Eye disease (blindness)
- Epilepsy

Blackfly (*Simulium* spp.) vector

**Nodding syndrome** = epileptic disorder with repetitive forward dropping of the head

- Seizure onset between 3-18 years
- Previously normal
- No obvious cause of epilepsy
- High prevalence of epilepsy in the village
- Person living in onchocerciasis endemic region for at least 3 years and high microfilarial loads
Nodding and Nakalanga syndrome occur together with other forms of epilepsy

Logo, Ituri, Democratic Republic of Congo

Mvolo, South Sudan

Cameroon

Mean microfilarial load 155/mg
The pathological mechanism is currently unknown

Is nodding syndrome an auto-immune disease?
- Cross reactivity between *O. volvulus* antigens and human Leiomodin-1
- Neurotoxic antibodies in the CSF in samples from Uganda

However:
- Not in all cases
- Also in controls without epilepsy
- Not in cases from the DRC

Are parasites crossing the blood-brain barrier?
- Microfilariae are not found in the CSF

MRI findings:
- Generalized atrophy of cerebral cortex and cerebellum
- Gliotic lesions
- Subcortical abnormalities

Post mortem study in northern Uganda

People who died with **Nodding syndrome** (5) or **Other forms of epilepsy** (4)

Complete post mortem examination + collection of clinical data

Histology of the brain:
- H&E
- GFAP (astrocytes)
- CD68 (macrophages)
- AT8 (tau- NFTs)
- Ubiquitin
- P62
- α-synuclein
- TDP-43
- 4G8 (amyloid β)
Demographic and clinical information

No main pathological difference between nodding syndrome and other forms of epilepsy

- **External examination:**
  - 5 wasted (dehydration + reduced subcutaneous fat and muscle mass)
  - 3 Nakalanga features

- **Internal examination:**
  - Abnormalities in the lungs (fibrinous adhesion, congestion, edema, gastric contents)
  - No common abnormality in the other visceral organs

- **Demographic findings**
  - People with OFE were older at disease onset and death
  - 7/9 have siblings with NS or OFE
  - 8/9 have also generalized tonic clonic seizures

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NS</th>
<th>OFE</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Age of onset</td>
<td>8</td>
<td>12</td>
<td>0.006</td>
</tr>
<tr>
<td>Age of death</td>
<td>18</td>
<td>20</td>
<td>0.021</td>
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</table>
Neuropathological findings

- Neuronal loss
  - Cerebral cortex
  - Purkinje cells (A)

- Hyperplasia of Bergmann glia (B) and gliotic lesions (cortex and mesencephalon)

- Signs of past ventriculitis/ependymitis granularis (C&D)

- Foci of activated microglia (E&F)

- Hippocampus normal!

- Foci of tau NFTs
  - Cortical regions
  - The top of the gyri
  - Mesencephalon
  - Thalamic and hypothalamic regions
# Neuropathological findings

## Nodding syndrome

<table>
<thead>
<tr>
<th>Histological findings</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
<th>Case 8</th>
<th>Case 9</th>
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<tbody>
<tr>
<td>Loss Purkinje cells</td>
<td>±</td>
<td>±</td>
<td>3+</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>3+</td>
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<tr>
<td>Hyperplasia Bergmann glia</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
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<tr>
<td>Activated microglia</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>NA</td>
<td>±</td>
<td>±</td>
<td>±</td>
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<tr>
<td>Loss of neurons</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Lymphocytes in meninges</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>-</td>
<td>NA</td>
<td>NA</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Cerebellum atrophy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<td>Gliosis</td>
<td>-</td>
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<td>2+</td>
<td>±</td>
<td>±</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<td>Neurofibrillary tangles</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
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<tr>
<td>Past ventriculitis or meningitis</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</table>
The presence and abundance of tau-reactive NFTs is dependent on the severity of disease.
Abundant tau NFT focus

Hotterbeekx et al, 2019
Comparison other neurological disorders

Primary tauopathies
• Tau dysfunction the primary pathological event
• Alzheimer’s disease; fronto-temporal dementia; progressive supranuclear palsy
• **No similarity with NS**
  • Different distribution
  • Different abundance
  • Often linked to genetic mutations (MAPT)

Tau pathology as a secondary neuropathological event
• P-tau deposition result of neuronal death after other event
• Chronic traumatic encephalopathy; temporal lobe epilepsy; post-infectious neurological disorders (like SSPE)
• **Similarities with NS**
  • Localization (cortical layers)
  • Focal distribution (in other forms of epilepsy)
• **Differences with NS**
  • SSPE involvement of hippocampus and more diffuse distribution
To conclude

Similar pathological characteristics indicate NS and OAE are different clinical manifestations triggered by the same disease mechanism.

Post mortem findings suggest NS/OAE could be a neuroinflammatory disease.

Many questions remaining!
Acknowledgements

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Nodding case from Uganda
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
<th>Case 8</th>
<th>Case 9</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>18</td>
<td>20</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>23</td>
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<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
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<td>Male</td>
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<tr>
<td>District</td>
<td>Kitgum</td>
<td>Kitgum</td>
<td>Kitgum</td>
<td>Kitgum</td>
<td>Pader</td>
<td>Kitgum</td>
<td>Pader</td>
<td>Kitgum</td>
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<tr>
<td>Secondary sexual characteristics</td>
<td>Underdeveloped; stunted</td>
<td>Fully developed</td>
<td>Fully developed</td>
<td>Fully developed</td>
<td>Fully developed</td>
<td>Underdeveloped; stunted</td>
<td>Stunted</td>
<td>Fully developed</td>
<td>Fully developed</td>
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<td>Clinical notes</td>
<td>Wasted</td>
<td>Well nourished</td>
<td>Wasted</td>
<td>Well nourished</td>
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<td>Wasted</td>
<td>Well nourished</td>
<td>Wasted</td>
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<tr>
<td>Cause of death</td>
<td>Septicaemia secondary to lung infection</td>
<td>Asphyxia due to aspiration of gastric contents during seizures</td>
<td>Asphyxia due to aspirations of gastric content during seizures</td>
<td>Carbamazepine overdose</td>
<td>Asphyxia due to aspirations of gastric content during seizures</td>
<td>Septicaemia</td>
<td>Severe dehydration following gastroenteritis</td>
<td>Suffocation during seizures</td>
<td>Liver failure, generalized metastatic Burkitt lymphoma</td>
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<td>History of severe disease/febrile illness</td>
<td>Measles</td>
<td>Severe malaria at 2 years</td>
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<td>Severe malaria</td>
<td>Malnutrition as baby</td>
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<td>Modified Rankin score</td>
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<td>3</td>
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<td>1</td>
<td>5</td>
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<td>Nodding seizures</td>
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<td>Yes</td>
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<td>Age at seizure onset</td>
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<td>5</td>
<td>4</td>
<td>8</td>
<td>9</td>
<td>11</td>
<td>Childhood</td>
<td>12</td>
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<td>Duration of disease (years)</td>
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<td>12</td>
<td>9</td>
<td>9</td>
<td>9</td>
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<td>8</td>
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<td>Antiepileptic drugs</td>
<td>Sodium Valproate, Carbamazepine and folic acid</td>
<td>Sodium valproate, carbamazepine and folic acid</td>
<td>Sodium valproate, carbamazepine and folic acid</td>
<td>Sodium valproate and carbamazepine</td>
<td>Sodium valproate and carbamazepine</td>
<td>Sodium valproate</td>
<td>Carbamazepine and folic acid</td>
<td>Carbamazepine and folic acid</td>
<td>Carbamazepine</td>
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<td>Seizure frequency</td>
<td>Several/week</td>
<td>2-3/week</td>
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<td>1/month</td>
<td>Several/month</td>
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<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
<td>No</td>
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<tr>
<td>Family member with NS/OFE</td>
<td>2 brothers with OFE, 1 sister with NS</td>
<td>1 brother and 1 sister with NS</td>
<td>No</td>
<td>1 sister with NS; 2 sisters with OFE</td>
<td>2 brothers with NS</td>
<td>1 brother with NS; 1 brother with OFE</td>
<td>2 siblings with NS</td>
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<td>1 brother with NS</td>
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