Tropical Spastic Paraparesis

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Human models of self-limiting toxic motor neuron diseases vs. progressive MNDs

- Konzo
- Lathyris
- Primary Lateral Sclerosis (PLS)
- ALS (Familial and Sporadic cases)
- ALS/PDC
- Different from: HTLV-I or HIV associated myelopathy

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TSP/HAM (Tropical Spastic Paraparesis/HTLV-I Associated Myelopathy)

• Historically,
  – Jamaica in 1964: syndrome called TSP
  – In 1985, 60% of TSP cases of in Martinique HTLV-1 positive
  – Lately: named TSP/HAM

• Most endemic regions
  – Japan
  – South America (Brazil)
  – Colombia
  – Caribbean
  – Africa

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Konzo and Lathyrysm in Africa

- D.R. Congo
- Mozambique
- Central African Republic
- Tanzania
- Cameroon
- Uganda
- Angola
- Lathyrysm: Ethiopia and Eritrea, other parts of the world.

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Pathogenesis
Exploring the lesion in MNDs

• Causal agent (infectious vs. toxic) agents, clinical features
• Electrophysiology helpful
  – Electroencephalography
  – Motor and sensory nerve conduction studies
  – Transcranial electrical and magnetic stimulation
    • ++ Pre-synaptic failure (SCN involvement and common mechanisms konzo/lathyrism?)
  – Visual evoked potentials (not reported here)
• Neuropathology
• Imaging
TSP/HAM

- transfusion, and injecting drug use Causes by HTLV-I (HTLV stands for human T cell lymphotropic virus)
  - Note: Two molecularly distinct types for HTLV: HTLV-I and HTLV-II
- HTLV-I infects T lymphocytes
- Transmission through breast feeding, sexual contact, blood

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HTLV infection

• While HTLV infection is lifelong, fewer than 5% of those infected develop related disease

• First symptoms occur several years, maybe decades, after initial infection

• Clinically, HTLV-I may cause:
  – adult T cell lymphoma (ATLL) – an aggressive, drug resistant malignancy, with a median survival of less than 12 months (post diagnosis)
  – HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP) – a chronic progressive inflammatory neurological disease that leads to a reduction in mobility and general limb function (late onset, average age 40 years)
HTLV infection

• First symptoms occur several years, maybe decades, after initial infection: leg weakness and/or walking difficulties

• Other: pain, paraesthesia, bladder dysfunction, progressive course

• Signs: progressive spastic paraparesis, loss of touch and pain sensations.

• Clinically, HTLV-I may cause:
  – adult T cell lymphoma (ATLL) – an aggressive, drug resistant malignancy, with a median survival of less than 12 months (post diagnosis)

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Mechanisms involved in HAM/TSP

- Lack of correlation between seroprevalence rates and occurrence in same country: genetic and/or co-environmental factors?
- In situ PCR of HTLV-I proviral DNA: CD4+ preferential virus reservoir in the CNS
- Interferon-γ, II-6, IL-1, and TNF-α play a role
- Lesions: mostly in pyramidal tracts thoracic spinal cord
  - Severe demyelination, perivascular and parenchymal mononuclear infiltrates (T and B lymphocytes and macrophages), reactive astrocytosis, microglial proliferation, loss of axons.
Mechanisms involved in HAM/TSP

• However, the promoter of the disease remains unclear
• Cytotoxic and auto-immune hypotheses (indirect mechanisms via infection of T lymphocytes migrating to the CNS)
Konzo – an upper motor neuron associated with cyanogenic exposure.

Cycasin

Linamarin

Lotaustralbin

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Cassava (*manihot esculenta*)
Cassava roots: insufficiently processed (left) and well done (right)
Metabolism of Linamarin

Cassava Processing
Linamarin → Cyanohydrin → HCN → Dietary protein

Gastro-intestinal tract
Linamarin → Cyanohydrin → HCN → CN⁻ + H⁺ → Sulfur amino acids: Methionine and cysteine

Blood and tissues
Linamarin → 2-iminothiazoline-4-carboxylic acid? → CNO? → CN⁻ → MethHb-CN → S-S-R → Sulfur amino acid pool → Protein synthesis → Protein degradation

Urine
Linamarin → SCN⁻ → SO₄²⁻
Candidates for neurotoxicity in konzo

- Linamarin (enter neurons via glucose transporter ?)
- Cyanide CN⁻ and metabolites
  - Thiocyanate SCN (AMPA agonist)
  - Cyanate OCN (carbamoylating agent)
  - 2-iminothiazolidine-4-carboxylic acid (?)
Neurolathyrism – a toxic motor neuron associated with the grass pea *lathyrus sativus*
Guam ALS/PDC – an upper motor neuron associated with use of cycad seeds
Cyanogenic compounds and MNDs

The last two: linamarin (93%) and lotaustralalin (7%) are found in cassava, cycasin (MAM metabolite) is associated with ALS/PDC
Summary

- TSP/HAM: HTLV-I infection, indirect CNS (+ systemic damage) via Infection of T lymphocytes, progressive non-pure MND
- To differentiate from: HIV vacuolar myelopathy, konzo and lathyrisim (non-progressive toxic pure MNDs, NO RETROVIRUSES), and ALS/PDC (progressive toxic neurodegeneration)
- Treatment: based on the pathogenesis.