Niemann-Pick Type C: The Young Adult’s Tauopathy

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RMH: A Strange Attractor
Niemann-Pick Type C Disease

• Rare recessive inherited lysosomal storage disorder
• Progressive and invariably fatal
• Characterised by abnormal intracellular lipid trafficking
• Accumulation of cholesterol and glycosphingolipids (mainly GM2 and GM3 gangliosides), mostly in the brain
  • Causing functional and structural damage to neurons
• Other tissues may also be affected (e.g., liver, spleen)
• Wide range of clinical manifestations

Molecular genetics of NPC

- Autosomal recessive inheritance
- 90–95% of cases due to mutations in *NPC1*
- Mutations in *NPC2* can also cause NPC
- *NPC1* and *NPC2* have roles in intracellular lipid trafficking

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosomal locus</th>
<th>Frequency of mutations</th>
<th>Protein size</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>NPC1</em></td>
<td>18q11–q12</td>
<td>90–95% of cases (sequence alterations)</td>
<td>1278 amino acids (transmembrane protein)</td>
</tr>
<tr>
<td><em>NPC2</em></td>
<td>14q24.3</td>
<td>4% of cases (sequence alterations)</td>
<td>132 amino acids (soluble protein)</td>
</tr>
</tbody>
</table>

Patterson MC. *Gene reviews* 2007.
Effect of mutations in *NPC1* and *NPC2*

Mutations in the *NPC1* or *NPC2* genes lead to

- Impaired trafficking of multiple intracellular lipids
- Accumulation of cholesterol and glycosphingolipids in various tissues
  - Particularly gangliosides in neurons
- Beta-amyloid aggregation
- Tau accumulation in neurofibrillary tangles
- Altered cellular autophagy
- Altered calcium & other biometal homeostasis

2. Pacheco CD, Lieberman AP. Autophagy 2007
Neuropathology of NPC

- Accumulation of $G_{M2}$ and $G_{M3}$ ganglioside causes aberrant neural function – esp in cerebellum, thalamus
- Neurofibrillary tangles contribute to neurodegeneration in hippocampus, basal ganglia, thalamus
- Significant alterations to myelination and axonal structure
- Cortical atrophy may be seen in later stages of disease

Suzuki K et al. Acta Neuropathol (Berl) 1995
Walkley SU, Suzuki K. Biochim Biophys Acta 2004
Increased perinuclear cholesterol
Enlarged axon hillock
Ectopic dendritogenesis
Neurofibrillary tangles
Activation of microglial pro-inflammatory cytokine secretion
Axonal spheroids in axons
Reduced differentiation of oligodendrocyte precursors
Destabilisation of axonal microtubules
Reduced myelination
Altered synoptic vesicle turnover and transmission
# Adult NPC Neuropsychiatric Presentation

## Age of Neurological Onset

<table>
<thead>
<tr>
<th>0-15</th>
<th>15-30</th>
<th>30-50+</th>
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</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>Schizophrenia</td>
<td></td>
</tr>
<tr>
<td>Autism Spectrum</td>
<td>Bipolar Disorder</td>
<td></td>
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<tr>
<td>D/O</td>
<td></td>
<td></td>
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<tr>
<td>Depression</td>
<td></td>
<td></td>
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<tr>
<td>Learning Disorder</td>
<td>Dysexecutive Syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subcortical ➔ Cortical Dementia</td>
<td></td>
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</tbody>
</table>

Psychiatric: |

Cognitive: |
Neuropsychiatry of NPC

NPC1/2 dysfunction

- Impeded cholesterol transport and availability
  - Impaired myelination, axonal growth, and remyelination
    - Axonal dystrophy and eventual loss
- Cholesterol and ganglioside accumulation
  - Alterations in dendritic microtubular proteins
  - Ectopic dendritogenesis, reduced dendritic arborization
- Altered kinase activity and protein phosphorylation
  - Reduced production of neurosteroids
  - Increased γ-secretase activity and increased Aβ42 formation
  - Hyperphosphorylation of tau
    - Neuronal amyloid deposition
    - Neuronal neurofibrillary tangle formation

Neuronal Disconnection
- Psychosis ± Mania

Neuronal Dysfunction and Loss
- Dementia

Early → Late

Magnetic Resonance Imaging of Volume & Microstructure
Voxel-Based Morphometry: Global Grey Matter

Tract-Based Spatial Statistics: White Matter Microstructure

Walterfang et al. Neurology 2010
Corpus Callosum

Subcortical Grey Matter

Cerebellar Grey Matter On Miglustat

Untreated Patients (n=2) vs Treated Patients

Treated:  -87.18(±54.01)mm³/month
Untreated: -410.73mm³/month

Bowman et al. *J Neurol*, 2015
Relationship with Symptoms, Ataxia, and Saccadic Gain

A: $p=0.03^*$

B: $p=0.80$ $p=0.67$

C: $p=0.01$ $p=0.02^*$

Bowman et al. *J Neurol*, 2015
Longitudinal Tract-Based Spatial Statistics

- Splenium of callosum
- Inferior fronto-occipital fasciculus
- Anterior thalamic radiation

- Corticospinal tracts
- Inf/Sup fronto-occipital fasciculi
- Superior longitudinal fasciculus

- Superior longitudinal fasciculus
- Inferior fronto-occipital fasciculus
Horizontal Saccadic Parameters

Horizontal Saccadic Gain
On Miglustat

- Patients on treatment showed a significant increase in gain across sessions ($p=0.037$)
- Patients not on treatment showed a significant decrease across sessions ($p<0.001$)

Abel et al. *Orphanet J Rare Dis* 2015
PET Imaging of PHF Tau
Tau in Human NPC Neuropathology

- First described in two histopath series in 1995
- Seen in cx, HC, thalamus, brainstem, SN (most affected by storage)
- Seen in patients as young as 4

Love et al. *Brain* 1995
Tangles Across the NPC Lifespan

Zhang et al. *Brain Pathol* 2010
Tau Across the NPC Lifespan

Zhang et al. *Brain Pathol* 2010
Tau in the NPC Mouse Model

• In NPC null mice – tangle formation not seen but elevations of hyperphosphorylated tau shown by AT8 staining

• Site-specific phosphorylation of Ser-396 and Ser-404 – results in loss of tau-mediated tubulin polymerization – destabilising microtubules

• MAPK activated, GSK-3B and CDK5 inactive in one mouse study

• Similar findings seen in heterozygotes in a further study

• However CDK5 shown to be upregulated in a second mouse study, and p25 co-accumulated with CDK5 with hyperphosphorylated tau in axonal spheroids, progressing with age

• ?Role of tau dephosphorylation as therapeutic intervention

Bu et al. J Neurosci 2002
Treiber-Held et al. J Pathol 2003
Ab & tau imaging in ageing and Alzheimer’s disease

**HC**

- **18F-FLUTEMETAMOL**
  - RT.LAT
  - LT.LAT
  - RT.MED
  - LT.MED

- **18F-THK5117**
  - RT.LAT
  - LT.LAT
  - RT.MED
  - LT.MED

**AD**

- **18F-FLUTEMETAMOL**
  - RT.LAT
  - LT.LAT
  - RT.MED
  - LT.MED

- **18F-THK5117**
  - RT.LAT
  - LT.LAT
  - RT.MED
  - LT.MED
Our Analysis

• 8 patients and 7 controls
• $^{18}$F -AV1451 tau imaging and $^{11}$C -PiB or $^{18}$F -florbetapir for Ab-amyloid binding
• Global and regional tau burden – SUVR using cerebellar cortex as reference, using MeTeR classification
• Z-scores generated using age-matched control groups
• Association between $^{18}$F -AV1451 binding and clinical/cognitive parameters through regression analyses
MeTeR Classification
Subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>HC&lt;25yo*</th>
<th>NPC&lt;25yo</th>
<th>HC&gt;25yo</th>
<th>NPC&gt;25yo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Age</td>
<td>23.3±2.1</td>
<td>21.5±3.3</td>
<td>42.1±8.8</td>
<td>39.4 ± 8.2</td>
</tr>
<tr>
<td>Gender (M-F)</td>
<td>1-2</td>
<td>2-1</td>
<td>1-3</td>
<td>2-3</td>
</tr>
<tr>
<td>Age of Onset</td>
<td>15.3±3.2</td>
<td></td>
<td></td>
<td>31.8 ± 8.4</td>
</tr>
<tr>
<td>Symptoms Duration</td>
<td>6.1 ± 4.5</td>
<td></td>
<td></td>
<td>7.6 ± 3.0</td>
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<tr>
<td>Illness Scale Score</td>
<td>9.7±3.5</td>
<td></td>
<td></td>
<td>6.6 ± 1.8</td>
</tr>
<tr>
<td>NUCOG Score (&gt;80/100)</td>
<td>60.5 ± 14.8</td>
<td></td>
<td></td>
<td>72.7±20.6</td>
</tr>
</tbody>
</table>
Results

• All subjects were Ab-
• 2 NPC patients presented with high tau burden – 21yo female and 39yo male, show high neocortical burden
• 40yo female showed high burden in mesial temporal and temporoparietal cortices
• Correlation between tau burden in mesial temporal lobe and age of symptom onset (p=0.015)
• Correlation between frontal tau and duration of symptoms (p=0.025)
• No significant correlation with the NUCOG
High MeTeR SUVR

Neocortical

Me

Te

R

HC<25yo  NPC<25yo  HC>25yo  NPC>25yo

HC<25yo  NPC<25yo  HC>25yo  NPC>25yo

HC<25yo  NPC<25yo  HC>25yo  NPC>25yo

HC<25yo  NPC<25yo  HC>25yo  NPC>25yo
Aβ & tau imaging in Niemann-Pick type C

51 yo F

**18F-AV1451**

- Hippo: 1.05
- Amygdala: 1.01
- TransEnt: 0.85
- Fusiform: 0.96
- Inf Temp: 0.90
- Supramarg: 1.00
- Angularis: 0.91
- Frontal: 0.91
- Sensorimot: 0.82

**11C-PiB**

Neocortical SUVR 1.16
A\beta & tau imaging in Niemann-Pick type C

40 yo M

**18F-AV1451**

- Hippo: 1.39
- Amygdala: 1.41
- TransEnt: 1.20
- Fusiform: 1.43
- Inf Temp: 1.35
- Supramarg: 1.35
- Angularis: 1.41
- Frontal: 1.21
- Sensorimot: 0.90

**11C-PiB**

*Neocortical SUVR 0.98*
Tau imaging in Niemann-Pick type C.

40 yo F NPC

43 yo F HC

$^{18}$F-AV1451
**Implications?**

- Marker of illness stage - late
- Sensitivity of tracer
- Ultrastructural differences between PHFs in NPC and AD

![Immunohistochemical stain images showing Aβ and tau proteins.](image)
PET Imaging of Neuroinflammation
Microglia and NSAIDs in NP-C

Smith et al. Neurobiol Dis 2009

Cologna et al. J Inher Met Dis 2015
Imaging Glial Activation in vivo: TSPO

- Translocator protein/peripheral benzodiazepene receptor (PBR)
- Differs to CBR – regulation of cell death, chemotaxis, cell growth; cholesterol transport at mitochondrial membrane
- Normal brain usually only expresses in choroid plexus, ependymal layer (found abundantly in other organs)
- Significant increase in expression on outer membrane of mitochondria in microglial cells
- Extent of expression relates to extent of injury
PK 1195 in Pediatric NPC

• 8 NPC patients (4-16 years) and 7 adult controls (mean 27.4±7.5 years)
• Increased binding potential (BP) in:
  • basal ganglia (0.22 vs 0.14, p=0.02)
  • thalamus (0.42 vs 0.30, p=0.006)
  • cerebelleum (0.18 vs 0.09, p=0.15)
• PK abnormalities correlated with clinical manifestations
• Suggests TSPO binding detectable in NPC patients

Kumar et al. J Nuc Med Assoc 2010
PK 1195 in Adult NP-C: Method

• 9 patients recruited, age range 18-52; compared to 9 age-matched controls

• Part of a larger study examining different stages of schizophrenia (n=46), Huntington’s disease (n=6+) and NPC patients vs controls (n=28)

• Undertook C11-PK1195 PET imaging, MRI scan (DTI, volumetry), and illness rating scale
Results

- NP-C – significantly higher $\text{BP}_{ND}$ in total WM ($p<0.01$)
- Reduced GM in thalamus ($p<0.001$)
- FA reduced in 39/48 white matter regions – esp fornix, external capsule, uncinate fasciculus ($p<0.05$ FDR)
- Significantly reduced FA in total WM ($p<0.01$)
- Negative correlation between $\text{BP}_{ND}$ and FA in WM – and driven by NP-C patients
- No relationship with age or clinical severity
**BP\textsubscript{ND} Changes in NP-C vs Controls**

<table>
<thead>
<tr>
<th></th>
<th>HC</th>
<th>S.D.</th>
<th>NPC</th>
<th>S.D.</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total GM</td>
<td>0.99</td>
<td>0.02</td>
<td>0.98</td>
<td>0.04</td>
<td>-1.01</td>
<td>0.34</td>
</tr>
<tr>
<td>Total WM\textsuperscript{*}</td>
<td>0.78</td>
<td>0.03</td>
<td>0.84</td>
<td>0.06</td>
<td>3.06</td>
<td>0.01</td>
</tr>
<tr>
<td>Medial temporal</td>
<td>0.85</td>
<td>0.04</td>
<td>0.89</td>
<td>0.07</td>
<td>1.59</td>
<td>0.14</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.97</td>
<td>0.05</td>
<td>1.00</td>
<td>0.06</td>
<td>1.39</td>
<td>0.19</td>
</tr>
<tr>
<td>Striatum</td>
<td>0.85</td>
<td>0.05</td>
<td>0.84</td>
<td>0.08</td>
<td>-0.32</td>
<td>0.75</td>
</tr>
</tbody>
</table>
White Matter FA Changes

![Bar chart comparing mean FA in total WM for Healthy controls and NPC groups.](chart1)

![Scatter plot showing the relationship between Mean FA in total WM and Mean BP_{ND}.](chart2)
Neuropsychology in Adult NPC

[Chart showing neuropsychological test scores for different domains and patient groups (Early Onset vs. Late Onset).]

[Graph showing changes in scaled scores over time for various patients.]
Florey Collaborations: Biometals and Beyond
Altered Cu Homeostasis in NPC Patients

* p < 0.05; ** p < 0.01; *** p < 0.0001; **** p < 0.00001
Heterozygous NPC Mice: Intermediate Phenotype

Hung et al *Neurotherapeutics* 2016

**Linear trend**

**Vertical count**

**Stereotypic count**

**Ambulatory time: total arena**

**Ambulatory time: Centre**

* p < 0.05; ** p < 0.01; *** p < 0.0001; **** p < 0.00001
White Matter Loss in NPC Mouse

A

WT

NPC1^-/

FA

T2

T2*

B

Corpus callosum

Hippocampus

Caudate Putamen

Thalamus

T2* (ms)

***

T2* (ms)

T2* (ms)

T2* (ms)
MRI analysis: trend to iron accumulation in affected NP-C brain regions

n (WT) = 3; n (Npc1) = 2
Cyclodextrin
Other Directions
Thank you!

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Acknowledgements