Artyrophilic grain disease
a late-onset dementia

Markus Tolnay, MD
Institute of Pathology (Neuropathology)
University Hospital Basel, Switzerland

Agenda

- Epidemiology
- Neuropathology
- Genetics
- Clinical features
- Unresolved questions
1987 first described as a neurodegenerative dementia (Braak and Braak).

- ArGs in 10% - 43% of brains from subjects older than 65 years.
- AgD is a late-onset dementia (often > 80 years).
- AgD is a progressive neurodegenerative disorder.
- 5% - 9% of all dementia cases.
- Second most common cause of degenerative dementia among the oldest-old in Japan.

Argyrophilic grain disease - macroscopy
Argyrophilic grain disease - macroscopy

Severe involvement of ambient gyrus in dementia with grains
Argyrophilic grain disease - distribution of grains
AgD - voxel-based morphometry

AgD + dementia  AgD - demetia

Argyrophilic grain disease is a 4-repeat tauopathy

Togo et al. JNEN 2002; 61: 547-56
Argyrophilic grains are formed in dendrites and axons of limbic „pretangle“ projection neurons
Glial tau pathology in argyrophilic grain disease (oligodendrocytes and astrocytes)
### Argyrophilic grain disease - diagnostic criteria

<table>
<thead>
<tr>
<th>Diagnostic findings</th>
<th>Associated changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Argyrophilic grains</td>
<td>• Ballooned neurons</td>
</tr>
<tr>
<td>(dendritic, axonal)</td>
<td>• Tau-positive astrocytes</td>
</tr>
<tr>
<td>• Coiled bodies</td>
<td>• Alzheimer-type changes</td>
</tr>
<tr>
<td>(oligodendroglial)</td>
<td>- Neurofibrillary tangles</td>
</tr>
<tr>
<td>• Tau-immunoreactive</td>
<td>early Braak stages I-III</td>
</tr>
<tr>
<td>„pretangle“ neurons</td>
<td>- Senile plaques</td>
</tr>
<tr>
<td>(4R-tauopathy)</td>
<td>absent in 1/4 of cases</td>
</tr>
<tr>
<td></td>
<td>• Spongiosis, Gliosis (rare)</td>
</tr>
</tbody>
</table>
Risk factors and Genetics

- Age (increased frequency of AgD cases with older age).
- ApoE E4 allele no risk factor for AgD (E2 allele?).
- Polymorphisms of the LRP (low-density lipoprotein receptor-related protein) and A2M (alpha-2 macroglobulin) genes associated with AgD?
- Tau H1 haplotype associated with CBD, PSP and AgD (?)
- Mutant ubiquitin (UBB+1) expressed in ArGs.
- No (rare?) familial cases.
- Novel MAPT S305I mutation with AgD-like features.
MAPT S305I mutation: implications for argyrophilic grain disease

Gabor G. Kovacs · Alan Pittman · Tamas Revesz · Connie Luk · Andrew Lees · Eva Kiss · Peter Tariska · Lajos Laszlo · Kinga Molnár · Maria J. Molnar · Markus Tölnay · Rohan de Silva

Acta Neuropathol 2008; 116: 103-118
**MAPT S305I mutation: implications for argyrophilic grain disease**

Gabor G. Kovacs · Alan Pittman · Tamas Revesz · Connie Luk · Andrew Lees · Eva Kiss · Peter Tariska · Lajos Laszlo · Kinga Molnár · Maria J. Molnar · Markus Tölnay · Rohan de Silva

Acta Neuropathol 2008; 116: 103-118
Progressive late-onset dementia.

ADL (activities of daily living)/behavioral and affective symptoms early in disease course (but comparable with AD) (Steuerwald et al. 2007)

Cognitive symptoms (e.g. language and problem solving difficulties) later than in AD

„Symptom load“ of cognitive symptoms lower than in AD (attention, verbal expression, articulation, recent and past memory, problem-solving, judgment).

High proportion of cases with ArGs in MCI and MCI progressing to dementia (Petersen et al.; Jicha et al. 2006; Jicha et al. 2006).

AgD and associated pathologies

• **AD changes (Aβ-amyloidosis, NFTs)**
  ArGs lower the threshold for dementia in the presence of moderate amounts of AD-related pathology (Thal et al. 2005; Josephs et al. 2008).

• **Tauopathies**
  Progressive supranuclear palsy, corticobasal degeneration, senile dementia with tangles.

• **α-Synucleinopathies**
  Parkinson’s disease, dementia with Lewy bodies, multiple system Atrophy.

• **Prionosis**
  Creutzfeldt Jakob disease.

• **TDP-43** (Fujishiro et al. 2008).
• AgD - separate entity of variant of another tauopathy?
• Impact of associated lesions (tau, α-synuclein, TDP-43)?
• Clinical features that allow to distinguish AgD from AD
• Therapeutic options (tau as major target)
• Familial form (MAPT S305I mutation)
• Transgenic mouse model
Temporospatial spreading in tauopathies

AD Stage I-II

AD Stage III-IV

AD Stage V-VI

AgD Stage I

AgD Stage II

AgD Stage III
P301S and Alz17 tau transgenic mice

P301S mouse (tangle)
Allen et al., J Neurosci 2002

- Expression of P301S mutant human tau
- Thy-1.2 promoter
- Robust “tangle pathology”
- Insoluble, fibrillar tau (Gallyas staining)

Alz17 mouse (pretangle)
Götz et al., EMBO J 1995
Probst et al., Acta Neuropathol 2000

- Expression of normal human tau
- Thy-1.2 promoter
- Robust “pretangle” pathology
- Soluble, no fibrillar tau (no Gallyas staining)
Alz17 “host” tau aggregates when seeded with P301S tau
Spreading of tau pathology at the injection level

15 months postinjection

1: dorsal thalamus
2: optic tract
Temporospatial spreading of tau pathology

antero-posterior

Fibrillar tau

X X

Fimbria

Hippocampus