TOWARDS A PHENOTYPIC CHARACTERIZATION OF ARGYROPHILIC GRAIN DISEASE

A. Rabano¹, I. Santa-Maria², C. Guerrero³, R. Cuadros², A.B. Rebolledo³⁴, O. Calero⁵, M. Calero⁵⁶, A. Kun⁷, J. Avila²

¹Neuropathology, Alzheimer Disease Research Unit, CIEN Foundation, Carlos III Institute of Health - Alzheimer Center Reina Sofia Foundation, ²Centro de Biología Molecular “Severo Ochoa”, CSIC-UAM., Madrid, ³Hospital Universitario Fundación Alcorcón, Alcorcón, ⁴Alzheimer Disease Research Unit, CIEN Foundation, Carlos III Institute of Health - Alzheimer Center Reina Sofia Foundation, ⁵CIBERNED (Spain), ⁶Carlos III Institute of Health, Madrid, Spain, ⁷DPAN-IIBCE & Facultad de Ciencias- Universidad de la República, Montevideo, Uruguay

Introduction: Argyrophilic grain disease (AGD) is a 4R-tauopathy characterized by the presence of 4-8 μm intraneuronal (dendritic) inclusions and glial pathology, involving limbic brain regions. Its incidence increases with age and it may contribute to dementia in 5% of cases.

Aims: Characterization of clinical, neuropathological (NP) and molecular profiles in a series of AGD cases from two brain banks. Analysis of subgroups derived from clinical and morphological variables.

Methods: All cases with a NP diagnosis of AGD and stage of AG pathology ≥ II were included. Several cortical and subcortical brain regions were studied by tau immunohistochemistry (AT8, AT100, AT180, PHF-1, 7.51, RD3 and RD4) in paraffin-embedded tissue, and by Western-blot, tau filament isolation and immunoelectron microscopy in fresh-frozen tissue. APOE and H1/H2 haplotypes were determined.

Results: Fifteen cases of AGD were identified (8 M / 7 F, mean age: 77.3 y.), with a 1st neuropathological diagnosis of AGD in 7 and a 2nd diagnosis in 8 cases (Table).

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Gender</th>
<th>Age</th>
<th>Dementia</th>
<th>Rapidly progressive</th>
<th>AGD stage (mean)</th>
<th>APOE status</th>
<th>H1/H2 status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st NP diagnosis of AGD</td>
<td>7</td>
<td>3 M / 4 F</td>
<td>81 (±9.4)</td>
<td>100%</td>
<td>71.4%</td>
<td>3.57</td>
<td>83.3% E3/E3 16.7% E3/E4</td>
<td>66.7% H1/H1 33.3% H1/H2</td>
</tr>
<tr>
<td>2nd NP diagnosis of AGD</td>
<td>8</td>
<td>5 M / 3 F</td>
<td>74 (±10.2)</td>
<td>62.5%</td>
<td>0%</td>
<td>3.25</td>
<td>83.3% E3/E3 16.7% E3/E4</td>
<td>83.3% H1/H1 16.7% H1/H2</td>
</tr>
</tbody>
</table>

Main clinical, NP and genetic data

Rapidly progressive course and CERAD score were significantly higher in the 1st diagnosis Group. Distribution of pathology was highly regular in all cases, and molecular analysis demonstrated a predominance of 4R1N isoform.
Conclusions: AGD shows a highly homogeneous neuropathological profile, may present as a rapidly progressive neurological disease, and is associated to a predominance of 4R1N isoform.