Cerebral Amyloid Angiopathy-related inflammation

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CAA
Hemorrhage-Prone Vasculopathy


Sporadic cerebral amyloid angiopathy

CAA is very common in the elderly

<table>
<thead>
<tr>
<th>TABLE 1: Clinical and Pathologic Characteristics of Cohort</th>
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<tbody>
<tr>
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<td></td>
</tr>
<tr>
<td>Dementia (n = 181)</td>
</tr>
<tr>
<td>No Dementia (n = 223)</td>
</tr>
<tr>
<td>Total (n = 404)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Age at death, yr</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
</tr>
<tr>
<td>Education, yr</td>
</tr>
<tr>
<td>MMSE score proximate-to-death</td>
</tr>
<tr>
<td>AD pathology score</td>
</tr>
<tr>
<td>Cerebral infarct present, n (%)</td>
</tr>
<tr>
<td>Neocortical Lewy bodies present, n (%)</td>
</tr>
<tr>
<td>CAA present, n (%)</td>
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<tr>
<td>No-to-minimal CAA, n (%)</td>
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<tr>
<td>Mild-to-moderate CAA, n (%)</td>
</tr>
<tr>
<td>Moderate-to-very severe CAA, n (%)</td>
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</table>

Values are mean (SD) unless otherwise indicated.

aCAA severity score of 1 or more in any of the 5 brain regions.
bCAA pathology was measured in 5 brain regions using a 5-point scale (0–4), with 0 = none (no immunohistostaining for CAA), 1 = mild (scattered positivity in either leptomeningeal or cortical blood vessels), 2 = moderate (strong, circumferential positivity in some but not all leptomeningeal or cortical blood vessels), 3 = severe (widespread, strong, circumferential positivity in leptomeningeal and cortical blood vessels), and 4 = very severe (same as 3, but with additional changes of positivity emanating from vessels into surrounding neuropil).

AD = Alzheimer disease; CAA = cerebral amyloid angiopathy; MMSE = mini-mental state examination; SD = standard deviation.

Lobar Microbleeds are Common in AD

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Prevalence</th>
<th>Predominant Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cordonnier²</td>
<td>223</td>
<td>18 %</td>
<td>Lobar</td>
</tr>
<tr>
<td>Pettersen³</td>
<td>80</td>
<td>29 %</td>
<td>Lobar</td>
</tr>
<tr>
<td>Hanyu⁴</td>
<td>59</td>
<td>32 %</td>
<td>Lobar</td>
</tr>
<tr>
<td>Atri⁵</td>
<td>61</td>
<td>15 %</td>
<td>Lobar</td>
</tr>
<tr>
<td>Nakata⁶</td>
<td>38</td>
<td>18 %</td>
<td>Lobar</td>
</tr>
</tbody>
</table>

Topography of Lobar Microbleeds is Similar in AD and Sporadic CAA

### Comparison of Cerebrovascular versus Parenchymal Amyloid

#### TABLE 1: Comparison of Features of Cerebrovascular versus Parenchymal Senile Plaque Amyloid Deposition

<table>
<thead>
<tr>
<th>Feature</th>
<th>Cerebrovascular Amyloid Deposition</th>
<th>Senile Plaque Amyloid Deposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominant Aβ type</td>
<td>Aβ40</td>
<td>Aβ42 (particularly in diffuse plaques)</td>
</tr>
<tr>
<td>Location of Aβ deposition</td>
<td>Relative occipital lobe predominance</td>
<td>Frontal, parietal, temporal lobes</td>
</tr>
<tr>
<td>APOE allele risk factors</td>
<td>APOE ε4 (for amyloid deposition) and APOE ε2 (for vessel breakdown)</td>
<td>APOE ε4</td>
</tr>
<tr>
<td>Inflammatory subtype with reversible white matter hyperintensities</td>
<td>Occurs spontaneously as CAA-related inflammation</td>
<td>May occur iatrogenically as a result of amyloid immunotherapy or other candidate treatments targeting amyloid</td>
</tr>
<tr>
<td>Cerebral microbleeds</td>
<td>Lobar predominant, particularly occipital</td>
<td>Not associated with senile plaques</td>
</tr>
<tr>
<td>Location of white matter disease</td>
<td>Equal distribution between anterior and posterior subcortical regions (subgroup may have posterior-dominant white matter disease)</td>
<td>Equal distribution between anterior and posterior subcortical regions, but less extensive than advanced CAA</td>
</tr>
</tbody>
</table>

See text for more details discussion and details.

APOE = apolipoprotein E; CAA = cerebral amyloid angiopathy.

CAA-related inflammation (CAA-RI)

- 71 yr old woman, 1 yr progressive cognitive decline, then acute confusion
- CSF: protein 164, WBC 1
- MRI: Microbleeds, confluent white matter hyperintensities

+high-dose corticosteroids x 16d
CAA-related Inflammation (CAA-RI)

• Subacute cognitive changes, headaches, or seizures
• Pathology suggests anti-amyloid autoimmune reaction
Vasogenic Edema in Inflammatory CAA

- Subcortical white matter extending to grey
- Bright FLAIR, increased ADC, dark T1
- Often asymmetric
Changes in T2-hyperintensity over time in patients with Inflammatory CAA

Kinnecom Neurology 2007;68:1411
Inflammatory response after Aβ42 immunization resembles spontaneous CAA-related inflammation

Inflammatory response after Aβ42 immunization resembles spontaneous CAA-related inflammation.

CAA-RI patients may have increased levels of anti-Aβ1-40 and anti-Aβ1-42 autoantibodies in the CSF

DiFrancesco et al. Neurology 2011;76;842
Diagnostic Criteria cerebral amyloid angiopathy–related inflammation (CAA-RI)

• **Definite CAA-RI**: Tissue-based evidence of CAA-related inflammation in the cerebral vasculature.
  
  – CAA identified by Congo Red or immunostaining of pathological samples
  
  – Evidence of perivascular or vascular inflammatory infiltrate associated with CAA-affected blood vessels
  
  – No other causative lesion identified.
Diagnostic Criteria cerebral amyloid angiopathy-related inflammation (CAA-RI)

- **Probable CAA-RI**: Clinical and neuroimaging evidence strongly suggestive of CAA-related inflammation.
  
  - Pattern of hemorrhagic lesions consistent with probable CAA
  
  - MRI T2/FLAIR-sequence changes of confluent subcortical white matter hyperintensities and/or cortical sulcal hyperintensities
  
  - These above described changes are often focal or asymmetric, typically with little or no contrast enhancement
  
  - CSF abnormalities of mildly elevated protein and presence of leukocytes may be seen, but normal CSF does not rule out the diagnosis.
Treatment of cerebral amyloid angiopathy–related inflammation (CAA-RI)

• The strongest basis for treatment is the finding of Definite CAA-RI by brain/leptomeningeal biopsy.
  – Empiric treatment can also be considered for Probable CAA-RI when the neuroimaging features appear clear-cut.

• Five-day course of high-dose corticosteroids (e.g. IV methylprednisolone 500mg-1g / day) as an inpatient or outpatient followed by outpatient treatment with a tapering oral corticosteroid dose (e.g. PO prednisone 40-60 mg/day, reduced in weekly increments to a target of approximately 10 mg/day).

• Re-imaging and clinical follow-up approximately 3-4 weeks after initial treatment to monitor radiographic changes and clinical status.
  – If there is radiographic resolution of the subcortical/sulcal hyperintense lesions, it is reasonable to consider continuing the downward steroid taper with the goal of discontinuing.
Treatment of cerebral amyloid angiopathy–related inflammation (CAA-RI)

- Radiographic resolution may precede or occur in the absence of clinical change. In these cases, other reasons for clinical impairment (progression of underlying Alzheimer’s or CAA pathology) should be sought.

- Consider repeat lumbar puncture on follow-up, especially in cases with baseline CSF abnormalities and ambiguous neuroimaging and clinical response to treatment.

- If there is no or poor radiographic and clinical improvement after approximately 8 to 10 weeks of steroid treatment, consider changing the immunosuppressive regimen to cyclophosphamide, 1-2 mg/kg/day PO for 2 weeks. In this situation, it is also reasonable to consider confirming Definite CAA-RI by brain biopsy prior to initiating cyclophosphamide.

- Other immunosuppressive agents may be further alternatives in highly refractory cases, although clinical experience with these agents remains very limited.
Conclusions

• CAA-RI is an inflammatory disorder occurs in subset of patients with CAA and is associated with cognitive symptoms, seizures, headaches, T2-hyperintense MRI lesions, and neuropathologic evidence of vascular inflammation

• MRI evidence shows
  – Subcortical white matter extending to grey
  – Bright FLAIR, increased ADC, dark T1
  – Often asymmetric

• CAA-RI is not dissimilar to the inflammatory response after Aβ42 immunization in Alzheimer’s disease therapy trials

• Definite diagnosis requires pathologic confirmation, but clinical and neuroimaging evidence may be strongly suggestive of the disease

• Corticosteroids treatment is the mainstay of therapy, but other immusuppressants may be tried in refractory cases