Neuroimaging Markers of Cerebral Amyloid Angiopathy in the Absence of Symptomatic Lobar Intracerebral Hemorrhage.

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Disclosures

• None
Cerebral amyloid angiopathy

- Deposition of β-amyloid peptide over media and adventitia of cortical and leptomeningeal arteries.
- Sporadic and hereditary forms
- Prevalence increases with age (85% of population over 80 have some degree, 20% have moderate/severe) — Arvanitakis et al. Ann Neurol 2011
- Strong association with Alzheimer’s disease (CAA more frequent and severe)
- Classic presentation: symptomatic lobar ICH (most common cause in the elderly) Other: cognitive impairment, TFNE, silent forms
How we currently diagnose CAA

• **Invasive:** Brain pathological exam – only way to confirm Dx

• **Non-invasive:** - Boston Criteria
  – Pathologically validated
  – 1 lobar hemorrhage (“possible CAA”) vs ≥2 strictly lobar hemorrhages (“probable CAA”)
  – Highly specific (probable >possible)
  – Applies strictly to individuals with at least 1 lobar ICH

*Greenberg et al. Stroke 1996
Knudsen et al. Neurology 2001*
CAA is more than just ICH...

- In the elderly, CAA prevalence is way superior to prevalence of lobar ICH – non-hemorrhagic forms
- The finding of incidental lobar MB is more frequent than lobar ICH
- CAA, through vascular dysfunction, can also cause ischemia.
- Initial stages of CAA pathophysiology may involve issues in drainage of interstitial fluid (ISF) along perivascular spaces, potentially detectable on MR imaging
Alternative approaches to a non-invasive diagnosis of CAA

• APOE genotype?
• PET-amyloid imaging?
• fMRI?...

Promising but not currently applicable in clinical practice. Not sensitive and specific enough.

• MRI markers that have been there for a long time...and quite overlooked.
  – Lobar MB (in the absence of lobar ICH)
  – A-P distribution of WMH
  – Dilated perivascular spaces in the white matter (WM-DPVS)
Research interests (I)

• **Lobar MB in the absence of lobar ICH** Radiological-pathological study on MGH and Framingham cohorts
  (Martinez-Ramirez et al. 2014. Under review in Alzheimer’s & Dementia)

• **A-P distribution of WMH**
  Center of WMH mass is more posteriorly located in CAA individuals compared to non-CAA individuals, even in the absence of lobar MB.
  (Thanprasertsuk/Martinez-Ramirez et al. Neurology 2014;83:1–7)

• **WM-DPVS**
Rationale behind the association between WM-DPVS and CAA

- BG-DVPS are more strongly associated with classic long-standing hypertension markers than WM-DPVS, in patients with ischemic stroke (Doubal et al. 2010, Rouhl et al. 2008) and general population (Yakushiji et al. 2014).

- There is a relative increase of water content in the WM of AD patients. (van Swieten et al. 1991)

- One pathologic study focused on the association between the retention of ISF within DPVS and the presence/severity of CAA (Roher et al. 2003).

In CAA, blockage of ISF drainage by vascular amyloid could favor the retrograde dilation of PVS into the white matter.
Research interests (II)

- **WM-DPVS**

  In memory clinic patients, high burden of BG-DPVS is independently associated with hypertension. High burden of WM-DPVS is independently associated with lobar MB count. (Martinez-Ramirez et al. Neurology 2013;80:1–6)

  ![Graph showing age-adjusted prevalence of severe EPVS](image1)

  *Charidimou et al. JNNP 2013*

  **WM-DPVS postulated as potential new CAA markers on a recent review on Lancet Neurology**

  ![Box plots of the AP center of WMH by DPVS category](image2)

  *Thanprasertsuk/Martinez-Ramirez et al. Neurology 2014*
Study aims

– To confirm the associations between WM-DPVS and CAA in cases with definite diagnosis of the disease.

– To explore differences in WM-DPVS burden between different CAA subgroups:
  – CAA with no hemorrhage
  – CAA with only MB
  – CAA with lobar ICH (+/- MB)

– To introduce a new quantitative method for DPVS assessment that might offer advantages compared to visual rating.
Study description

• In collaboration with Leiden University Medical Medical Center.
• To confirm and refine the association of WM-DPVS with CAA (considering CAA phenotypic spectrum).
  – Parallel study in both sporadic and hereditary CAA cohorts
    • **Sporadic:** pathological diagnosis, common form but plenty of interference by vascular risk factors and associated brain damage. **MGH cohort**
    • **Hereditary:** genetic diagnosis, rare form but less confounding by vascular risk factors. **Leiden cohort (CAA Dutch mutation)**
  – MGH cohort: subanalysis comparing WM-DPVS burden between macrobleeders (lobar ICH) vs microbleeders (only lobar MB) vs. non-bleeders
  – Leiden cohort: subanalysis comparing WM-DPVS burden between symptomatic carriers vs. asymptomatic carriers vs. non-carriers (controls)
  – Utilizing semi-quantitative DPVS measurements instead of visual rating
Study cohorts

• MGH cohort (sporadic CAA)
  – Modified from the original cohort for the MB-only Boston Criteria validation study.
  – 63 subjects

• Leiden cohort (hereditary CAA)
  – Symptomatic and Asymptomatic mutation carriers:
    • CHA (Cerebral Hereditary Angiopathy) outpatient clinic (LUMC)
    • Patient association
    • All DNA proven
  – 2 Control groups (comparable age)
  – 57 subjects
DPVS quantitative measurement
DPVS quantitative measurement

Relative CSO-DPVS area in a given brain slice:
CSO-DPVS area(cm²) / total brain area (cm²) x100

3.84 cm² / 52.5 cm² x 100 = 7.31%
DPVS quantitative measurement

• Intraclass correlation coefficient MGH-Leiden over 14 cases: 0.93 (excellent)
### MGH cohort characteristics

<table>
<thead>
<tr>
<th>(n=63)</th>
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<tbody>
<tr>
<td>Age by MRI, years (mean ± SD)</td>
<td>73.5 ± 8.5</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>29 (46)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>41 (65)</td>
</tr>
<tr>
<td>WM-DPVS degree ≥ 3, n (%)</td>
<td>54 (85)</td>
</tr>
<tr>
<td>BG-DPVS degree ≥ 3, n (%)</td>
<td>43 (70)</td>
</tr>
<tr>
<td>CSO-DPVS area % (median, range)</td>
<td>4.2, 0.7-15.2</td>
</tr>
<tr>
<td>Autopsy study, n (%)</td>
<td>32 (51)</td>
</tr>
<tr>
<td>CAA, n (%)</td>
<td>46 (73)</td>
</tr>
<tr>
<td>CAA without any hemorrhage, n (%)</td>
<td>8 (17.4)</td>
</tr>
<tr>
<td>CAA with only MB, n (%)</td>
<td>17 (36.9)</td>
</tr>
<tr>
<td>CAA with ICH (+/- MB), n (%)</td>
<td>21 (45.7)</td>
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</table>
Sporadic CAA. Visual vs quantitative DPVS assessment

Distribution of CSO-DPVS areas across the cohort

CSO-DPVS area by visual DPVS categories:
Poor discrimination of DPVS burden in the higher range. Clear ceiling effect.
Sporadic CAA. CSO-DPVS and CAA - results

Comparison of CSO-DPVS area between CAA+ and CAA- subjects
(n=63)
Median test  P<0.0001

(Level of significance almost unchanged after adjusting for age, gender, hypertension and BG-DPVS degree)
Sporadic CAA.

**CSO-DPVS area by CAA status/hemorrhage profile**

1=No CAA

2=CAA with no hemorrhage

3=CAA with any hemorrhage

Mann-Whitney test

p = 0.0001

Results remain unchanged after adjusting for age, gender, hypertension and BG-DPVS

1=No CAA

2=CAA with no hemorrhage

3=CAA with only MB

4=CAA with ICH (+/-MB)

Mann-Whitney test

p = 0.0004

Results remain unchanged after adjusting for age, gender, hypertension and BG-DPVS
Leiden cohort characteristics

<table>
<thead>
<tr>
<th>(n=57)</th>
<th>Symptomatic patients</th>
<th>Older controls</th>
<th>Asymptomatic patients</th>
<th>Younger controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>15</td>
<td>17</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Age, years (range)</td>
<td>54.9 (45-63)</td>
<td>57.2 (45-72)</td>
<td>34.3 (20-51)</td>
<td>35.7 (30-44)</td>
</tr>
<tr>
<td>Female sex, n(%)</td>
<td>9(60)</td>
<td>8(47)</td>
<td>9(75)</td>
<td>10(77)</td>
</tr>
</tbody>
</table>
Hereditary CAA. CSO-DPVS analysis by carrier status and presence of symptoms

Symptomatic – old controls:
Mann Whitney without any corrections: p < 0.0001
Linear regression corrected for age, gender, BG-DPVS: p = 0.003

Asymptomatic – young controls:
Mann Whitney without any corrections: p = 0.131
Linear regression corrected for age, gender, BG-DPVS: p = 0.135

If the 2 control groups are collapsed into a single one, highly significant differences remain for symptomatic carriers but the trend observed for asymptomatic carriers gets lost.
Hereditary CAA-examples

Control  Asymptomatic carrier  Symptomatic carrier

Images courtesy of S.van Rooden and M.van Buchem
Conclusions

• We confirmed that CAA is associated with significantly higher burden of WM-DPVS, both in sporadic and hereditary cases.

• High WM-DPVS burden seems to be associated with CAA even in the absence of symptomatic lobar hemorrhages, in the sporadic form (and maybe in the hereditary form).
  – Potential relevance in diagnosis of non-hemorrhagic forms? (similar to A-P WMH)
  – Potential relevance in overall early diagnosis of CAA? – sporadic>hereditary

• Quantitative measurement of WM-DPVS might offer better accuracy than current visual scales in detecting significant differences in burden between CAA and non-CAA subjects.
  – Need for method that relies less on raters’ expertise and decreases workload
  – Whole brain analysis vs. regional analysis
Future steps

- To study if a spatial correlation between PVS dilation and CAA severity exists.  
  Work in progress (collaboration with Utrecht Medical Center)

- To understand the directionality of the WM-DPVS-CAA association.
  - Is PVS dilation a predisposing factor for amyloid stagnation? or
  - Is vascular amyloid deposition directly responsible for PVS dilation?
  Detection and quantification of WM-DPVS and other markers of CAA and small-vessel disease on serial MRI studies in healthy population.
    - Rotterdam, Framingham

- To determine whether ↑WM-DPVS may be risk factor or early marker of CAA.

- To develop a more reliable and fast quantitative method to assess WM-DPVS in the whole brain.
  Assistance from bioinformatics, bioengineers

- To identify methods that can be applied to clinical practice (i.e. presence of WM-DPVS in the temporal or occipital lobe yes/no)
  Focused analysis of WM-DPVS on specific topographies in CAA and non-CAA subjects
Thank you