White matter hyperintensities in Alzheimer’s disease

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Outline

• Contribution of WMH to AD
• Angiotensin converting enzyme gene to AD by WMH
• Management of white matter lesion in AD, acetylcholinesterase inhibitors; cilostazole
White Matter Lesion Load Is Associated With Resting State Functional MRI Activity and Amyloid PET but not FDG in Mild Cognitive Impairment and Early Alzheimer's Disease Patients

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Significance of WMH in AD

Late Onset Alzheimer’s disease

• Increased total volume of ante-mortem WMH increased odds for having autopsy-confirmed Alzheimer’s disease neuropathology.

• High fiber tract WMH burden is associated with reduced functional connect in connected areas, could be the effects of amyloid pathology on neuronal network function.

• Promote tau pathology and exacerbate the effects of tau on clinical status independent of beta-amyloid

Familiar Alzheimer’s disease

• Total WMH volume was increased in mutation carriers compared with non-carriers, up to 20 years prior to expected symptoms onset, after controlling for microbleed status.

J Alzheimers Dis. 2018; 63: 1347–1360. PLOS ONE. https://doi.org/10.1371/journal.pone.0195838, 2018

Alzheimers Dement. 2017; 13; 225–235
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• **Angiotensin converting enzyme gene** to AD by WMH
• Management of white matter lesion in AD, acetylcholinesterase inhibitors; cilostazole
White matter lesion in AD

ACE gene and protein to AD & WMH
Vascular? Amyloid path?
The predominant pattern of progression is lesion growth at the sites of preexisting lesions rather than occurrence of new abnormalities.
A. Caps abutting upon the frontal horns of the lateral ventricles.
B. Gross overview of ventricle, subventricular zone and partly pale white matter

C. Multiple punctate white matter hyperintensities
D. Enlarged cell-free perivascular spaces in the presence of vessel wall hyalinosis.
E. Early confluent and confluent white matter lesions in the deep and periventricular white matter
F. Patchy myelin loss with some cystic lacunar lesions representing areas of more severe tissue damage

Large Meta-Analysis Establishes the ACE Insertion-Deletion Polymorphism as a Marker of Alzheimer’s Disease

In East Asians, D/D homozygote is less likely to be associated with having AD.

ACE-I/I homozygote corresponds to lower plasma ACE protein level. These findings signal the importance of ACE indel polymorphisms to their corresponding protein levels and to AD.
ACE protein and activity in post-mortem CSF of AD

Disparity between the level and activity of ACE in the CSF.

In AD, ACE levels were significantly lower in AD and advanced disease stage.

The activity of AD was higher than control, insignificantly

• 403 patients clinically diagnosed with AD, ACE I/D genotyped
• Cerebral white matter rating was rated by ARWMC
• ACE I/I may be less likely to develop WMCs, especially in female.
• Low ACE level to less cardiovascular events to WMH.
3 years longitudinal examinations for ACE I/D to clinical course. 177 AD patients; MMSE, CASI, NPI, CDR-SB annually tested. ACE I/I genotype had a more rapid deterioration, particularly those patients without hypertension.
In total, 278 patients with sporadic AD were enrolled in this study. The mean age of the patients was $76.6 \pm 7.4$ years, and 166 patients had hypertension. Over 3 years longitudinally following up, baseline severe WMH will worsen clinical outcome only in AD with hypertension, not without hypertension.
ACE to WMH or beta-amyloid

ACE I/I → Low clearness of beta-amyloid → having and worsening AD

AD&HTN+ → WMH → AD worsening
Subgroup of AD by HTN, WMH & ACE genotype (n=12)

- ACE I/I  HTN (+) WMH (Severe: Fazekas’ scale: 2&3)
- ACE I/I  HTN (-) WMH (Severe: Fazekas’ scale: 2&3)
- ACE I/D HTN(-) WMH
- ACE I/D
  -
  -
  -
- ACE D/D HTN(-) WMH (Minor: Fazekas’s scale: 0&1)
1. I form fragment upregulated the transcriptional activity of ACE promoter by approximately 70% but that the D form fragment did not.
2. Alu sequence in human ACE gene possesses a regulatory function on the ACE promoter activity in neuron.
3. Alu sequence is not merely a "junk" DNA in human ACE gene.
We found lisinopril increased the ACE promoter activity of I-form vector by 17.2%, but contrarily reduced that of D-form vector by 16.8%, compared with respective control without lisinopril treating.
Systolic Hypertension in Europe (SYST-EUR)

- Double-blind placebo-controlled trial
- > 2000 participants for 2 years
- Included a side project that examined the incidence of dementia
- Treatment of older patients with hypertension treated with a ACE-I (enalapril) and others.
- Reduced risk for both vascular dementia and Alzheimer’s disease.

Perindopril Protection Against Recurrent Stroke Study (PROGRESS)

• Randomised, double-blind, placebo-controlled trial following up for 4 years
• >6000 patients with a previous stroke or ischemic attack.
• Treated with perindopril with/without indapamide.
• Dementia and cognitive decline were reduced in the treatment group.

~Arch Intern Med 2003; 163: 1069–75.~
Khachaturian et al with > 3000 participants
adjusted for age, sex, education, number of APOE ε4 alleles, cholesterol, diabetes, myocardial infarction, and stroke

• Increased protection from Alzheimer’s disease (AD) with the use of antihypertensive medication as a whole.
• Both β blockers and diuretics had the lowest associated risk for incidence of AD
• ACE inhibitors increased incidence of AD

Role of ACE to WMH in AD

• ACE I/I, lower ACE protein level, less WMH, less capability of degrading beta-amyloid, risk factor of having AD and developing overt AD, enhancing ACE gene activity could be a wish to treat AD
• Severe WMH in AD with hypertension, more prone to vascular contribution, control vascular risk.
• Treating HTN with ACE-inhibitor (ACE-I) in AD subjects could be based on ACE I/D genotype.
• Using ACE-I to enhance I allele can increase the activity of ACE protein
• Treatment for hypertension in AD patients could be individualized in relation to ACE I/D
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Cilostazol with 3 Arrows: triple effects toward dementia

Frontiers in Aging Neuroscience 2014. doi: 10.3389/fnagi.2014.00290
Animal model:

- Cilostazol administration on the increase BBB permeability following bilateral common carotid artery occlusion.
- Improve cerebral white matter rarefaction, glial activation and gait disturbance
Cilostazole to AD and other dementia: 5 year longitudinal study


Excluding:
1. Age < 40 years old or age > 90 years old (N=508,291)
2. Patient diagnosed all cause dementia before index date (N=4,656)
3. Demographic data incomplete (N=737)
4. Cilostazol cohort usage cumulative days < 3 months (N=2,635)

Study population selected from Jan 1, 2004 to Dec 31, 2009.

(Matching with propensity score for 1:3)

Comparison cohort (N=6861)
586 events (8.5%)

Cilostazol cohort (N=2287)
109 events (4.8%)

Neurotherapeutics. 2017 Feb 13. doi: 10.1007/s13311-017-0512-4
Hazard Ratio of all-cause dementia by use and dosage of cilostazole

Neurotherapeutics. 2017 Feb 13. doi: 10.1007/s13311-017-0512-4
Conclusion

1. Patients using cilostazol had a significantly decreased risk of incident dementia compared with patients not using the drug.
2. Cilostazol use was found to have a dose-dependent association with reduced rate of dementia emergence.
3. The effect of cilostazol use on lowering dementia was significantly among having cerebral vascular disease, male, and age greater than 65 y/o.
Participants & Methods
Case: Clinically diagnosed AD with Peripheral artery occlusive disease (PAOD) with either side ABI ≤0.9, treating with donepezil 5 mg/QD with cilostazol 50 mg/BID.
Control: clinically diagnosed AD without PAOD with both side ABI >0.9, treating with Aricept 5 mg/ QD.
Measurements: Annual psychometric: CASI, MMSE, CDR, NPI
Cognitive outcome of cilostazol as an add-on therapy for patients with Alzheimer’s disease

**Conclusion:** Cilostazol may reduce the decline of cognitive function in AD patients applied as an add-on therapy.
AChEIs users had **lower incidence of ischemic stroke** (HR:0.508; 95% CI, 0.434–0.594; P < 0.001).

2. There was **no significant difference in all-cause mortality** between AChEIs users and nonusers.
Follow-up duration, numbers, and incidence rate of ischemic stroke among dementia patients using and not using acetylcholinesterase inhibitors

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Patients using AChEIs (n = 5182)</th>
<th>Patients not using AChEIs (n = 5182)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total follow-up person-years</td>
<td>26,077.03</td>
<td>26,122.93</td>
</tr>
<tr>
<td>Mean follow-up time (y)</td>
<td>5.03</td>
<td>5.04</td>
</tr>
<tr>
<td>No. of ischemic stroke</td>
<td>418</td>
<td>629</td>
</tr>
<tr>
<td>Incidence rate per 10,000 person-years (95% CI)</td>
<td>160.3 (145.5–176.2)</td>
<td>240.8 (222.5–260.2)</td>
</tr>
</tbody>
</table>

Hazard ratio for ischemic stroke among acetylcholinesterase inhibitors users and nonusers in dementia cohort

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Hazard ratio</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.655</td>
<td>0.579–0.742</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.508</td>
<td>0.434–0.594</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.947</td>
<td>0.875–1.024</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.996</td>
<td>0.872–1.137</td>
</tr>
</tbody>
</table>
Cumulative incidences of ischemic stroke of dementia

HRs of ischemic stroke to the use of acetylcholinesterase inhibitors

<table>
<thead>
<tr>
<th></th>
<th>No. of patients with ischemic stroke</th>
<th>Incidence rate (95% CI)</th>
<th>Crude HR (95% CI)</th>
<th>P-value</th>
<th>Adjusted HR (95% CI)</th>
<th>P-value</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AChEIs use duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonuser (&lt;28 cDDD)</td>
<td>646</td>
<td>235.4 (217.7–254.2)</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>User (28–365 cDDD)</td>
<td>227</td>
<td>195.9 (171.7–222.7)</td>
<td>0.757 (0.621–0.921)</td>
<td>0.006</td>
<td>0.646 (0.567–0.736)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>User (&gt;365 cDDD)</td>
<td>174</td>
<td>132.1 (113.6–152.9)</td>
<td>0.517 (0.416–0.641)</td>
<td>&lt;0.001</td>
<td>0.587 (0.512–0.672)</td>
<td>&lt;0.001</td>
<td></td>
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</table>
Rivastigmine may provide better benefits in cognitive function for AD patients with more advanced WMCs
Patients with WMC in the frontal area and basal ganglia had significant decreases in their therapeutic response to donepezil.

The location of WMC might be associated with the therapeutic response in patient with Alzheimer’s disease.
Thank you for your attention

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