Reconsidering the role of vascular disease in Alzheimer’s disease pathogenesis

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Disclosure

• Consultant and Scientific Advisory Board: Keystone Heart, LLC
• Consultant and Scientific Advisory Board: ProPhase, LLC

Disclosure

• I have either too many slides or too few slides.
• I am biased.
Agenda

- Facts and figures
- Current hypothetical pathogenic models of AD?
  - Support
  - Caveats
- Epidemiological evidence linking vascular factors to AD.
- What are the possible mechanisms linking vascular disease to AD?
- Is there a special role of white matter damage in AD?
  - Why might white matter be particularly vulnerable and underlie cognitive aging?
  - Is there a special role of white matter disease in cognitive aging and AD?
- Summary/conclusions
Amyloid cascade hypothesis

Changes in Aβ metabolism
- Increase in total Aβ
- Increase in the Aβ/APP ratio
- Reduced degradation
- Gliogenesis of Aβ and diffuse plaque deposits
- Surface effects of soluble oligomers on synapse function
- Abnormal distribution of tau and aberrant tau phosphorylation and dephosphorylation
- Oligomerization of tau
- Propagation and neuronal dysfunction leading to cell death
- Dementia with plaque and tangle pathology

AD: the Zeitgeist


Diagnosing based on putative etiology

Sperling et al., 2010; Albert et al., 2010; McKhann et al., 2010
Evidence for pathology

- Amyloid plaques and neurofibrillary tangles have been observed in the brains of AD patients since the beginning.
- Over 18,000 articles on the association between beta amyloid and AD.
- Autosomal dominant forms of AD and Down's are associated with genetic mutations that either encode APP or alter AB generation (PS1 and PS2).
- Mouse models that overproduce beta amyloid sort of look like dementia.
- Removal of amyloid from AD mice improves their symptoms.
- CSF measures of tau and postmortem measures of neurofibrillary tangle burden correlate moderately with severity of cognitive symptoms.

Evidence for ordering

- Some cross-sectional evidence that biomarker change in beta amyloid precedes biomarker change in tau.
- Beta amyloid changes appear early, but not in a “dose-dependent” fashion.
But does Aβ cause AD?

- Genetic mutations that cause amyloid overproduction produce an early-onset syndrome similar to AD, but is it the same as the much more typical “sporadic” or “late-onset” form of the disease?
- Amyloid plaques do not initially form close to where we see the earliest damage in AD (frontal lobe vs. hippocampus/entorhinal cortex)
- No “dose effect” of beta amyloid
- So many unsymptomatic older adults have huge amounts of amyloid in their brains
- Very old people (90s-100s) can develop dementia similar to the one seen in younger adults with AD, but have very few plaques at autopsy
- Some have argued that it is the soluble forms of beta amyloid (oligomers) that are more toxic, but the amount needed to produce a toxic effect is physiologically unlikely
- Transgenic mouse models of beta amyloid do not produce tangles
- All beta amyloid reducing trials have failed or are harmful to patients

Caveats: pathological features

- ~30% of non-demented older adults have significant amyloid deposition detected with PET or at autopsy without any apparent cognitive impairment
- “Both Phase 3 programs await numerous further analyses. For example, the ApoE4 non-carrier bapineuzumab trial, startlingly, turned out to have included 36.1 percent of participants who were amyloid-negative on PIB PET. Was this a technical error with PET or a clinical misdiagnosis?”
- Tau-related changes can be non-specific markers of neuronal damage and frequently occur before or in the absence of beta amyloid
- Individual risk: Given a specific biomarker profile, we still don’t know what the risk of AD is in a given period of time for a single individual

Caveats: Other factors?

- Diabetes (Luchsinger et al., 2001; Ott et al., 1999; Poli et al., 2002)
- Insulin resistance (Craft, 2005)
- High blood pressure and hypertension (Kloog et al., 1996)
- Atrial fibrillation (Ott et al., 1997)
- Hypercholesterolemia (Khajetti et al., 2003)
- Midlife central obesity (Whitmer et al., 2008)
- Presumably, increase risk for AD is due to proximal vascular damage in the brain
- Cumulative vascular burden may put the brain’s white matter at particular risk of injury
Vascular risk factors: Metabolic syndrome, diabetes, and obesity

**METABOLIC SYNDROME**
- Central obesity
- Dyslipidemia (↑TG and/or ↑HDL-C)
- High blood pressure
- Diabetes or pre-diabetes (↑ fasting glucose)

Vascular risk factors: Hypercholesterolemia

- Serum cholesterol levels have been shown to be higher in middle age among individuals who develop AD in the Seven Countries Study (Finland) and WHICAP.
- Cholesterol levels tend to decrease close to incidence.
- Prevalence of AD among older adults taking statins is 60%-70% lower than those not taking statins.

Vascular risk factors: Hypertension

- Framingham: high blood pressure and chronicity of hypertension in 1702 55-88 year-olds inversely related to attention and memory.
- Midlife HTN predicted impairment on MMSE and Trails 20 years later in 999 Swedish men (OR 1.45).
- Midlife HTN associated with 2.5-fold increase in risk for AD in 1,449 Swedes age 65-79.
- Epi studies in Japan, Hawaii, China, Canada, etc. have had similar observations.
- Barnes & Yaffe estimated that 5% (1.7 million) of the current 34 mill. AD cases are attributable to midlife HTN. A reduction of 35% BP would result in 400,000 fewer cases of AD.
Several studies have shown a link between diabetes and AD.

Risk of developing clinical AD in the Rotterdam study was 2X higher among individuals with diabetes than among those without.

According to Barnes and Yaffe, 2% of cases of AD in the world is attributable to diabetes; a 10% lower prevalence of diabetes would lead to 81,000 fewer cases of AD.

Vascular Disease
- Additive
- Synergistic
- Relationship is epiphenomenological

- Second, independent hit
- May interact with, reflect, cause, or be caused by "1st" AD pathology
- Other factors may precipitate both AD and vascular disease.
Why might vascular risk and AD be linked?

- If we define Alzheimer’s disease only by plaques and tangles, then the question is whether vascular disease is independent of plaques and tangles or somehow promotes plaques and/or tangles (or results from them).
- If we define Alzheimer’s disease as a mixed pathology disorder, then does it matter if the pathologies are independent of each other?
- Indeed, cerebrovascular disease occurs in patients with clinical AD more often than it does not.

**Additive**

- Vascular risk factors are risk factors for small and large cerebrovascular disease.
Why might vascular risk and AD be linked?

Additive

Small and large cerebrovascular disease increase the risk for clinical AD and (or?) the clinical expression of the disease.

Mixed brain pathologies account for most dementia cases in community-dwelling older persons

ARTICLES

Jiko A. Akidula, MD
Pediatrics, MGH, Boston, MA
Westmoreland K, MD
David B. Reimer, MD
Cerebrovascular disease and dementia: an additively collaborative relationship in genetic-risk groups

ABSTRACT

Objective To assess the impact of hypertension on brain anatomy and function in community-dwelling older persons, we studied a cohort of patients with and without hypertension.

Methods We enrolled 60 patients with hypertension and 40 patients without hypertension. Patients were evaluated with a comprehensive battery of behavioral, cognitive, and neuroimaging tests. The results were then compared with those of healthy older adults.

RESULTS We found that patients with hypertension had lower scores on all cognitive measures compared with healthy older adults.

Conclusions Hypertension is associated with a greater risk of Alzheimer disease and dementia, regardless of age and sex. This finding has important implications for the development of strategies to prevent cognitive decline in older adults.
Why might vascular risk and AD be linked?

Additive

Vascular and amyloid pathologies are independent predictors of cognitive decline in normal elderly

- Additive not synergistic effect
- Vascular and AD markers not related to each other
- Vascular disease contributed EQUALLY to cognitive decline as AD pathology

Second, independent hit

Vascular Disease

Additive

Synergistic

Relationship is epi-phenomenological

May interact with, reflect, cause, or be caused by AD pathology

Other factors may precipitate both AD and vascular disease
Why might vascular risk and AD be linked?

Synergistic

Little to some evidence from autopsy studies

- Diabetes associated with infarcts but not with NPs or NFTs (Peila et al., 2002)
- In BLSA, quantitative measures of atherosclerosis in the aorta, heart, and intracranial vessels not associated with AD pathology (Dolan et al., 2010)
- CF. Other groups have shown a modest relationship between atherosclerosis and AD pathology (Roher et al., 2004; Beeri et al., 2006)

Chui et al., 2012

Why might vascular risk and AD be linked?

Synergistic

Microcirculation

- Neurovascular unit (capillary)
- Endothelial cells and pericytes form the BBB (ion channels, permeability, and transporters)
- These cells regulate multiple neurovascular functions

Sagare, Bell, & Zlokovic, 2012

Why might vascular risk and AD be linked?

Synergistic

- A. In the arteries, dyregulated CBF in early stages of AD is associated with diminished A-beta clearance by smooth muscle cells. Later stags, CAA causes microbleeds.
- B. In the capillaries, BBB dysfunction leads to diminished A-beta clearance and accumulation of toxic bi-products (AB). P-tau accumulates in response to injury or AB toxicity. Increased microglia activation and other inflammatory processes in response.

Zlokovic, 2011
Three non-mutually exclusive paths

- Blood brain barrier breakdown
- Hypoperfusion and hypoxemia
- Endothelial neurotoxic and inflammatory processes

Zlokovic 2011

BBB breakdown

- Typically leads to accumulation of various molecules in the brain
  - Serum proteins can cause edema and suppression of capillary flow
  - Increased RBCs deposits other toxic products like iron, which generate neurotoxic reactive oxygen species (ROS)

Zlokovic 2011

BBB breakdown

Blood-Brain Barrier Breakdown in the Aging Human Hippocampus

Montagne et al., 2015
BBB breakdown

Montagne et al., 2015

BBB breakdown vs. CBV (parenthetical)

Enhancing dentate gyrus function with dietary flavanols improves cognition in older adults

Brickman et al., 2014
Hypoperfusion and hypoxemia

- CBF is regulated locally (neurovascular coupling)
- Hypoperfusion can affect protein synthesis and ATP synthesis
- Reduced CBF occurs in older adults at risk for AD before onset of cognitive symptoms or measurable neurodegenerative changes
- Hypoperfusion causes oligomerization of beta amyloid in animal models
- Ischemia leads to accumulation of hyperphosphorylated tau
- Hypoxemia causes mitochondria to release factors that mediate oxidative damage to the endothelium

Zlokovic 2011
Endothelial neurotoxic and inflammation

• Microvessels in AD brains secrete multiple inflammatory mediators
• Cause or effect?

Is there a special role of white matter damage in cognitive aging and AD?

White matter

• Emerging literature suggests that lifespan development changes in white matter properties may mediate much of the cognitive change we see with age
• Takes up a large proportion of the brain, but has been understudied.
• Plays an important role in cognition across various stages of development and neuropsychological disorders.
White matter

- White matter is white because of myelin.
- 80% lipid fat and 20% protein
- Increases the speed at which electrical impulses propagate along the axon, facilitating fast and efficient neural transmission.
- Damage to myelin can have obvious consequences to neural transmission, affecting basic perceptual, motoric, and cognitive processes.

Measuring various aspects of WM with MRI

- Macrostructure
- Microstructure
- Pathology

- REMEMBER: MRI scans do not provide a photograph of the brain; they provide reconstructed representations of tissue types that roughly reflect various aspects of the underlying tissue. Diffusion tensor measures, for example, may reflect myelination, density of the fibers, and gross organization of fibers.
Measuring various aspects of WM with MRI

- T1 anatomical
- Diffusion Tensor
- FLAIR

- Recent advances in acquisition and analysis of structural neuroimaging allow for greater visualization of normal and abnormal white matter.

Why might white matter be particularly vulnerable?

- Vascular supply throughout the brain is not uniform.
- WM is perfused mostly by delicate arterioles that are quite vulnerable to damage or pathology.

Why might white matter be particularly vulnerable?

- Anderson VC et al. (2011). Cardiovasc Psychiatry Neurol
Why might white matter be particularly vulnerable?

**BBB breakdown**
- Arterioles/capillaries in WM are particularly delicate and leaky
- Astrocytes form tight junctions with the capillaries (BBB)
- Damage to the capillaries and/or astrocytes can make vessels more leaky, allowing toxic materials to enter and reducing blood flow, nutrient delivery, and the ability to clear toxic material, increasing risk of neuronal damage
- Damage can be caused by a variety of factors that accumulate across the lifespan (HTN, inflammation, mechanical injury, oxidative stress, etc) and/or by frank pathology (AB)

**Lack of myelin repair**
1. Age-related vascular injury leads to oxidative damage
2. Vascular injury promotes oligodendrocyte progenitor cell expansion but cell intrinsic changes block differentiation
3. Astroglisis contributes to inhibition of OPC differentiation
4. Failure to repair myelin damage leads to conduction deficits that contribute to cognitive decline

**Tortuous arterioles**
- Grey matter
- White matter

*Kohama SG et al., 2012. AGE.*
*Brown WR et al., 2002, J Neurol Sci.*
Why might white matter be particularly vulnerable?

Pathology accumulation

Brown WR et al., 2000, Ann NY Acad Sci

Why might white matter be particularly vulnerable?

String vessels

Brown WR & Thore CR, 2011, Neuropathology & Applied Neurobiology

Why might white matter be particularly vulnerable?

Wallerian degeneration

http://neuropathology-web.org/chapter12/chapter12Neuropathy.html
Why might white matter be particularly vulnerable?

Microembolic lesions

Brown WR et al., 1996; Echocardiography

Caveats: Other factors?

- Diabetes (Luchsinger et al., 2001; Ott et al., 1999; Peila et al., 2002)
- Insulin resistance (Craft, 2005)
- High blood pressure and hypertension (Skoog et al., 1999)
- Atrial fibrillation (Ott et al., 1997)
- Hypercholesterolemia (Kivipelto et al., 2002)
- Midlife central obesity (Whitmer et al., 2008)

Presumably, increase risk for AD is due to proximal vascular damage in the brain.

Cumulative vascular burden may put the brain’s white matter at particular risk of injury.

White matter hyperintensities

www.graphicshunt.com
WMH what we know

• White matter hyperintensities are bad.
• White matter hyperintensities are not good.
• Most older adults have some degree of WM change (normal vs. healthy?)
• Overall burden accounts for a lot of variance in cognitive performance in normal aging, esp working memory and executive functioning (Raz et al)
• If you have white matter hyperintensities now, you used to not have them.
• In the context of aging, once you have them, they tend get worse. They rarely get better.
• WMH burden (severity) is a measurable reflection of brain pathology, whereas many other MRI markers may reflect pathology or may reflect lifelong individual differences

Pathology

Non-ischemic, demyelination secondary to ependymal gliosis, WM rarefaction

Ischemic in nature, perivascular reduction in lining, rarefaction of myelin, fiber loss, arteriosclerosis, etc. Pathogenic mechanisms?

• Most consider WMH to reflect rarefaction of white matter secondary to small-vessel occlusive disease

WMH risk factors

• Age, stroke, diastolic blood pressure, diuretic use, internal carotid artery thickness (Monstoli Kronmal et al., 1994)
• HTN, elevated cholesterol, myocardial infarction, carotid atherosclerosis (de Leeuw et al., 2000, Rotterdam)
• Prior h/o HTN, being African American (accounted for mostly by HTN) (Liao et al., 1996, 1997, ARIC)
• Association between middle life systolic BP and later life WMH volume (DeCarli et al., 1999, NHLBI twin study)
• Carotid artery atherosclerosis (Romero et al., 2009, FHS)
Overall questions

• Are white matter hyperintensities, “normal aging” pathology, involved with the pathogenesis and/or clinical presentation of AD?
• Do WMH help explain what we see in the trajectories of cognitive aging above and beyond (or interacting with) putative AD biomarkers?
• Can we leverage neuroimaging to identify targets for group or personalized intervention, prevention, or maintenance strategies?

Quantification: Scheltens Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Overall (4–16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occipital</td>
<td>3</td>
</tr>
<tr>
<td>Frontal</td>
<td>3</td>
</tr>
<tr>
<td>Temporal</td>
<td>3</td>
</tr>
<tr>
<td>Overall WMH (0–9)</td>
<td>9</td>
</tr>
<tr>
<td>Periventricular HYPERTENSITIES</td>
<td>2</td>
</tr>
<tr>
<td>Grade</td>
<td>Overall (4–16)</td>
</tr>
<tr>
<td>Occipital</td>
<td>3</td>
</tr>
<tr>
<td>Frontal</td>
<td>3</td>
</tr>
<tr>
<td>Temporal</td>
<td>3</td>
</tr>
<tr>
<td>Overall WMH (0–9)</td>
<td>9</td>
</tr>
<tr>
<td>Grade</td>
<td>Overall (4–16)</td>
</tr>
<tr>
<td>Occipital</td>
<td>3</td>
</tr>
<tr>
<td>Frontal</td>
<td>3</td>
</tr>
<tr>
<td>Temporal</td>
<td>3</td>
</tr>
<tr>
<td>Overall WMH (0–9)</td>
<td>9</td>
</tr>
</tbody>
</table>

Courtesy of P. Scheltens
Washington Heights Inwood Columbia Aging Program

WHICAP

- N = 2125 in 1992
- Added 2174 in 1999 to total 2801
- Age 65 and older
- Spanish or English speaking
- Seen in home at 18 – 24 month intervals
- Based on neuropsychological test battery, medical & functional interview

WHICAP imaging sample

- 769 imaged

Brickman, Schuff, et al., 2008, Arch Neurol
### WHICAP imaging sample

<table>
<thead>
<tr>
<th></th>
<th>AGE</th>
<th>EDUCATION</th>
<th>VASCULAR (P: HTN, DM, CAD, stroke)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAUCASIANS (n = 203)</td>
<td>80.25</td>
<td>13.73</td>
<td>1.29</td>
</tr>
<tr>
<td>AFRICAN AMERICANS (n = 243)</td>
<td>79.71</td>
<td>12.31</td>
<td>1.92</td>
</tr>
<tr>
<td>HISPANICS (n = 256)</td>
<td>80.27</td>
<td>6.86</td>
<td>1.96</td>
</tr>
<tr>
<td>TOTAL SAMPLE (N nondemented = 717) (N AD = 52)</td>
<td>80.07</td>
<td>10.73</td>
<td>1.69</td>
</tr>
</tbody>
</table>

Brickman, Schupf et al., 2008, Arch Neurol

### Quantification of WMH

- Standard T2-weighted FLAIR images.
- WMH volume calculated with intensity-driven algorithm.

Brickman, Muraskin, & Zimmerman, 2009, Dialogues Clin Neurosci; Brickman et al. 2011, Psychiatry Research
Quantification of WMH

Brickman, Muraskin, & Zimmerman 2009; Brickman et al. 2011

MCI

- Neuropsychological battery:
  - Memory
  - Language
  - Processing speed/Executive function
  - Visuospatial abilities

- Cognitively normal (n=508)
- Amnestic MCI (n=97): Impairment in memory function
- Non-amnestic MCI (n=74): Impairment in non-memory domains
- Alzheimer’s disease (n=52)

Luchsinger, Brickman, et al., 2009, Neurology

MCI

Luchsinger, Brickman, et al., 2009, Neurology
Regional specificity

MCI: Regional specificity

AD: Regional specificity

Brickman, et al., 2011
Replication: AAG

[Graph showing WMH volume across different lobes for NC, MCI, and AD groups.]

Mesar et al., 2012, JINS

Replication: DeCarli et al.

[Images showing brain scans for High MMSE and Low MMSE groups.]

Yoshita M et al., 2006, Neurology

Replication: DeCarli et al.

[Images showing brain scans for NC, MCI, and AD groups.]

Yoshita M et al., 2006, Neurology

See also: Scheltens et al., 1992; Kalaria, 2000; Rezek et al., 1987
Regional specificity: predicting aMCI (x-sectional)

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parietal lobe WMH volume</td>
<td>0.195</td>
<td>0.020</td>
</tr>
<tr>
<td>Hippocampus volume</td>
<td>-0.080</td>
<td>0.672</td>
</tr>
<tr>
<td>Age</td>
<td>0.040</td>
<td>0.058</td>
</tr>
</tbody>
</table>

Results from logistic regression analysis predicting aMCI vs. NC. Additional covariates: sex, TCV (both non-significant).

Future decline

- 2005-2007
  - MRI (n=717 non-demented)
  - Clinical work-up
  - Biomarkers
  - ETC

- 2008-2010
  - Clinical follow-up (n=503)

Non-demented
- n=457
- AD n=46

Repeat AD
- n=35

AD n=32
Regional specificity: predicting AD (future decline)

<table>
<thead>
<tr>
<th>Regional WMH</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.075</td>
<td>0.032</td>
</tr>
<tr>
<td>Frontal WMH</td>
<td>0.949</td>
<td>0.424</td>
</tr>
<tr>
<td>Temporal WMH</td>
<td>1.116</td>
<td>0.903</td>
</tr>
<tr>
<td>Parietal WMH</td>
<td>1.197</td>
<td>0.049</td>
</tr>
<tr>
<td>Occipital WMH</td>
<td>0.221</td>
<td>0.156</td>
</tr>
<tr>
<td>Hippocampal volume</td>
<td>0.302</td>
<td>0.701</td>
</tr>
</tbody>
</table>

Controlling for APOE e4, education*, sex, ethnicity

Brickman, et al., 2012

Predicting future decline

WMH predicts cognitive decline

Brickman, et al., 2008, Arch Neurol; Tosto et al., 2014
Longitudinal analysis with latent difference scores

- Do individuals who “convert” from ‘normal’ to AD have a selective increase in parietal lobe WMH over time?
- Rather than calculating difference scores in raw data, latent difference scores define a latent variable as the portion of the time 2 value that is not identical to the initial value and models
- We modeled the latent change in parietal lobe WMH vs. all other WMH as a function of incident AD status, controlling for baseline values, change scores of hippocampus volume, and relevant demographic covariates.

Brickman et al., 2014

Latent Difference Score model

Do individuals with incident AD have a selective increase in parietal lobe WMH over time?

Latent Difference Score model

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>SE</th>
<th>Z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in parietal WMH</td>
<td>0.39</td>
<td>0.16</td>
<td>2.40</td>
<td>0.02</td>
</tr>
<tr>
<td>Change in all other WMH</td>
<td>0.03</td>
<td>0.09</td>
<td>0.39</td>
<td>0.70</td>
</tr>
<tr>
<td>Change in hipp volume</td>
<td>0.70</td>
<td>0.18</td>
<td>-3.83</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age</td>
<td>0.05</td>
<td>0.03</td>
<td>1.66</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Covariates: baseline WMH and hipp, age, education, ethnicity, sex, total cranial volume APOE
Why would WMH and AD be linked?

- WMH
  - Second independent hit
  - Pathology is heterogeneous (as fx of location)
  - Relationship is epi-phenomenological
  - May interact with, reflect, cause, or be caused by "1" AD pathology
  - Other factors may precipitate both AD and WMH

- Autoregulation
- Vascular risk factors
- Amyloid imaging
- Postmortem work
- Genetic risk factors

Perfusion: Vascular disease history

- No Vascular Disease History
- Vascular Disease History
Perfusion: Autoregulatory dysfunction

• Cerebrovascular disease via hypoperfusion and oxidative stress may modulate neuronal overproduction of beta amyloid
  • Beta amyloid may exert detrimental effects on cerebrovascular function
  • AD amyloid mice have reduced CBF, endothelium-dependent vasodilation is impaired, and vasoconstrictor responses are impaired.
  • Never shown in humans....
  Claassen & Zing, 2011

Perfusion: Autoregulatory dysfunction

• Autoregulatory dysfunction could promote small vessel disease, which in turn can promote the deposition or inhibit the clearance of amyloid pathology
  • Alternatively, it is possible that amyloid pathology itself leads to vascular disease, via vessel deposition of beta amyloid pathology (i.e., cerebral amyloid angiopathy), and subsequently result in autoregulatory dysfunction
  • Transgenic amyloid mice have severely impaired autoregulation prior to deposition of amyloid pathology
  • In humans, the relationship between autoregulatory dysfunction and AD has not been shown definitively.
Perfusion: Blood pressure and WMH

<table>
<thead>
<tr>
<th>Mean mean BP</th>
<th>SD (variance in blood pressure over time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LO LO</td>
<td>LO, Hi</td>
</tr>
<tr>
<td>Hi, Lo</td>
<td>Hi, Hi</td>
</tr>
</tbody>
</table>

Brickman, Reitz et al., 2010, Arch Neurol

Perfusion: Blood pressure and WMH

Log WMH ration volume

-4.9  -4.8  -4.7  -4.6  -4.5
Lo Mean mean BP, Lo SD  Lo Mean, Hi SD  Hi Mean, Lo SD  Hi Mean, Hi SD

Controlling for age, sex, treated

Brickman, Reitz et al., 2010, Arch Neurol

Perfusion: ASL

Brickman, Zarko et al., 2008
Perfusion: ASL

Perfusion: Autoregulatory dysfunction

WMH x AD pathology

Cerebral Amyloid Angiopathy

Brickman, Zahra et al., 2009

Brickman et al., under review

Brown WR et al., 2000, Ann NY Acad Sci
Heterogeneous pathology: CAA

Cerebral Amyloid Angiopathy

More parietal lobe WMH in people with 2+ microbleeds

Meier et al., 2012 (INS)

Heterogeneous pathology: CAA

Cerebral Amyloid Angiopathy

2+ microbleeds, worse memory, due to WMH?

Heterogeneous pathology: Amyloid

PIB negative PIB positive

Amyloid imaging

Provenzano et al., 2013
Why might vascular risk and AD be linked?

- Additive
- Synergistic
- Other factors may precipitate both AD and vascular disease

Vascular Disease

Second, independent hit

May interact with, reflect, cause, or be caused by AD pathology

Relationship is phenomembal
AD: the Zeitgeist


DIAN Study

The NEW ENGLAND JOURNAL of MEDICINE

Clinical and Biomarker Changes in Dominantly Inherited Alzheimer’s Disease

DIAN Study

A  Global Rates of Brain Atrophy

B  Rate of Atrophy Rate Estimation

C  APOE E4 Allele Effects

D  Hypothetical Pathway

E  Changes in Metabolites in the Posterior

F  P301L Operations in the Posterior
DIAN Study: WMH

UNPUBLISHED DATA

Neuroimaging-guided histopathological examination of WMH

- CAA
- Myelin density
- Fibrosis/denudation
- Soluble Aβ
- Oligodendrocyte progenitor cells
- Relation with plaques and tangles
- Inflammatory markers (cytokines, microglia act.)
- Etc.

NC vs. AD
Summary

• Vascular risk factors certainly increase risk for AD and they do so at least additively.
• Some viable mechanisms that might suggest causal or interactive effects.
• Brain white matter is particularly vulnerable to injury in later life.
• White matter injury appears to play a specialized role in AD symptoms onset or pathogenesis.

Summary

• Does white matter damage play a particularly specific role in Alzheimer’s disease?
  • At least additive
  • Possibly interactive
  • Does it matter?
  • Is it a semantic question?

Is there a role for WMH/vascular disease in disease conceptualization?

• What is normal/healthy and what is not normal/healthy?
• Who are we including in our studies and how is that impacting our conclusions and definitions?
• Are we defining disease by a preconceived notion of the biology of that disease rather than focusing on a behavior and trying to understand the factors that lead to that behavior?
• Diseases like AD occur in the context of (normal?) aging and normal aging sometimes occurs in the context of disease.
Mixed pathology: norm not exception

- Lest we forget, AD has always been a "mixed" pathology (plaques and tangles)

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