Can B vitamins slow brain atrophy and cognitive decline?

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The shrinking brain (60 y old +)

The shrinking brain
• As we age (over 60) the brain shrinks at a rate of ~ 0.5% per year, i.e. ~ 7 mL per year
• Those of us with memory problems – called 'mild cognitive impairment' or 'MCI' – show a faster rate of shrinkage of ~ 1.0% per year
• In patients with Alzheimer's disease, the rate is higher still, at ~ 3% per year
• Progressive atrophy is associated with cognitive decline

Is there anything we can do about it?

Homocysteine and Alzheimer's disease 1998

TOTAL SERUM HOMOCYSTEINE IN SENILE DEMENTIA OF ALZHEIMER TYPE
ANDREW MACDONALD*, GABRIEL DAVIES*, PETER HUTSON*, STEPHEN TAYLOR* AND HENRIK CATTELL*

ORIGINAL CONTRIBUTION

Folate, Vitamin B₁₂, and Serum Total Homocysteine Levels in Confirmed Alzheimer Disease

Robert Clarke, MD; A. David Smith, DPhil; Kim L. John, DPhil; Bridget Rolls, MD
Leaky Salton, RNC; Per M. Ueland, MD

Homocysteine and B vitamins

Odds ratios of Alzheimer's disease

AD path. cases = 76
Controls = 108

OPTIMA 1998
(Arch. Neurol:55:1449)
Hypothesis 1998: raised homocysteine may be one of the causes of Alzheimer's disease

NIH Conference | 2010

Systematic Review: Factors Associated With Risk for and Possible Prevention of Cognitive Decline in Later Life

Homocysteine, B vits: no consistent association with cognitive decline; quality of evidence low

How many studies did they look at? Just seven!

Homocysteine studies by 2008

- 77/84 cross-sectional studies on > 37,000 people showed an association between raised Hcy, or low-normal B vitamins, and cognitive deficit or dementia
- 33/42 prospective studies on > 12,000 people also showed these associations


By 2010, raised homocysteine has been associated in prospective studies with -

- Initiation of cognitive impairment in ageing
- Conversion from cognitive impairment to dementia
- Incidence of dementia and AD in a population
- Increased rate of cognitive decline in AD
- Increased rate of atrophy of the brain

Mid-life homocysteine and Alzheimer's disease 35 years later

Gothenburg women's study

- 1,368 women followed for 35 years
- Blood for tHcy at first visit (mean age 46.8 y)
- Mean tHcy 11.8 mmol/L
- 151 developed dementia, 100 AD
- OR of AD after 35 years for top vs. bottom tertile of tHcy was 2.43 (1.25-4.71)
- Only age and tHcy were associated with increased risk, not cholesterol, BP, education, BMI, smoking, creatinine, folate intake, exercise or B12


Mid-life homocysteine and Alzheimer's disease up to 35y later

Survival free of AD

1st & 2nd tertile

Top tertile tHcy > 12.6

Years since blood sample taken

Zylberstein, Gothenburg women study, 2009

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Baseline homocysteine and shrinkage of the brain over 6 years in controls
95 community elderly (age 77.3) not impaired at baseline

% change in brain volume per year

Quartiles of tHcy at baseline

OPTIMA unpublished, 2009

Serum B12 and change in brain volume
107 community-dwelling elderly, not impaired at baseline

% change in total brain volume per year over 5 years

Baseline vitamin B12 (pmol/L)

OPTIMA, Neurology, 2008

Brain atrophy and B12 status

B12: 535 pmol/L
Atrophy rate 0.28%

B12: 192 pmol/L
Atrophy rate 1.7%

The VITACOG trial
P.I.s AD Smith, H Refsum and R Jacoby

Do B vitamins slow the rate of brain atrophy in those with MCI?

- 270 community-dwelling subjects > 70 years old with mild cognitive impairment (MCI), in Oxford
- Randomised to placebo or to ‘TrioBe Plus’ (0.8 mg folic acid; 0.5 mg B12; 20 mg B6)
- Treated for 2 years
- Volumetric MRI scans at start and end
- Powered to detect a 20% slowing of brain atrophy, using the SIENA protocol

VITACOG recruitment

Assessed for eligibility N = 646
Randomised N = 271
Allocated to vitamin tablets N = 138
Allocated to placebo tablets N = 133
B vitamins, brain atrophy and cognitive decline

The question for VITACOG

Since raised homocysteine and low B12 are associated with an increased rate of shrinkage (atrophy) of the brain, then: Will giving B vitamins to lower the levels of homocysteine slow down the rate of shrinkage of the brain?

VITACOG matrix

Treatment

Plasma homocysteine

Brain shrinkage

Cognition

Effect of B vitamin treatment on plasma homocysteine

Rate of atrophy of the brain

The homocysteine in treated group was 32% lower than in placebo group after 2 years ($P < 0.001$)
B vitamins, brain atrophy and cognitive decline

**Treatment slows the mean rate of brain atrophy**

<table>
<thead>
<tr>
<th>Placebo (n = 83)</th>
<th>Treated (n = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean rate of atrophy (% per y)</td>
<td>Mean rate of atrophy (% per y)</td>
</tr>
<tr>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>1</td>
<td>0.8</td>
</tr>
</tbody>
</table>

30% lower rate

**Slowing of atrophy depends on baseline homocysteine**

<table>
<thead>
<tr>
<th>Quartiles of baseline homocysteine</th>
<th>Rate of atrophy per year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Qt ≤ 9.5, 2nd Qt &gt; 9.5</td>
<td>0.5</td>
</tr>
<tr>
<td>3rd Qt &gt; 13 µmol/L</td>
<td>0.3</td>
</tr>
</tbody>
</table>

53% lower atrophy rate

**Slowing of atrophy is related to the change in homocysteine following treatment**

<table>
<thead>
<tr>
<th>Quartiles of the decrease in homocysteine level upon treatment</th>
<th>Rate of brain atrophy per year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Qt 2nd Qt 3rd Qt 4th Qt</td>
<td>0.5 0.5 0.5 0.5</td>
</tr>
</tbody>
</table>

48% lower atrophy rate in those where the level decreased the most

**What factors determine the final MMSE score after 2 years?**

- MMSE better (partial r)
  - MMSE at 0
  - Age
  - Atrophy rate

**What factors determine the final cognitive test scores after 2 years?**

- The higher the baseline cognitive test score, the better the final score
- The older the person, the worse the final score
- The faster the rate of brain shrinkage, the worse the score

So, rate of atrophy of the brain is a strong determinant of cognition

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B vitamins, brain atrophy and cognitive decline

Effects of B vitamin treatment on cognitive and clinical outcomes

- Episodic memory (HVLT delayed recall)
- Semantic memory (category fluency)
- Executive function (CLOX)
- Global cognition (MMSE)
- Clinical dementia rating (CDR)
- IQCODE

Performance on all the above was better in the B vitamin treated group - unpublished data, VITACOG

Outcomes of the VITACOG trial

- B vitamin treatment slows brain atrophy in Mild Cognitive Impairment by up to 53%
- B vitamin treatment slows cognitive decline
- B vitamin treatment improves clinical outcome

These responses only occurred in subjects with baseline homocysteine levels above ~10

Some possible implications of VITACOG

- MCI is common: prevalence is 16% in those > 70y
- 5 million with MCI in USA; 14 million in Europe
- ~50% of people with MCI develop dementia in 5 y
- Median tHcy in those >60y in USA is 10.1, so many could potentially benefit from treatment
- 14% of >60y have tHcy >13 μmol/L, a level at which treatment slowed rate of atrophy by >50%
- Should those diagnosed with MCI who have high homocysteine be given B vitamins, or must we wait for further trials?