The role of geriatricians in management of dementia - from the viewpoint of life style modification -

President, Federation of National Public Service Personnel Mutual Aid Associations Toranomon Hospital

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Chair, The Japan Geriatrics Society

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Some about The Japan Geriatrics Society

- The Japan Geriatrics Society (JGS), established in 1959, is only one scientific society in Japan which organizes the research in the field of geriatric medicine, focusing mainly on the research of the diagnosis & treatment of geriatric diseases including dementia, osteoporosis, atherosclerosis, infectious diseases, and geriatric syndrome such as frailty.
- JGS also aims at conducting research toward the construction of better long-term care for the elderly.
- JGS has 6,486 members, mainly medical practitioners and investigators.
- JGS organizes an annual scientific meeting and many educational seminars for practitioners and medical students.
- JGS approves board-certified geriatricians (1,537 all over Japan at present).
- JGS is a member society of The Japan Gerontological Society.

- JGS considers that the role of geriatricians in dementia practice is the management of life style and life style-related diseases including hypertension, diabetes, and dyslipidemia which possibly accelerates the development of not only vascular dementia but also Alzheimer’s disease.
Risk factors for Alzheimer’s Disease

① Unpreventable risk factors
1) Aging
2) Menopause
3) Family history
4) Genetic factors
   - APP gene
   - Presenilin gene1,2
   - Apo E

② Medical risk factors
   - Depression
   - Head trauma
   - Hypothyroidism
   - Hypertension
   - DM
   - Dyslipidemia ….

③ Life style

⇒ Diet, Smoking, Excess intake of alcohol, exercise deficiency ….
What life-style is good for preventing Alzheimer’s disease?

**Diet**

- Rotterdam Study (Holland)
  1. Fish intake \(\geq 18.5\)g/day
  2. Vitamin C, E

**Exercise**

- Canada
  - Regular exercise
    - More than 3 times /week

**Communication**

- Sweden
  - Living with large family

**Intellectual performances**

- USA
  - Reading books, Chess, Music play
# The content of daily foods in AD (Case-control study)

<table>
<thead>
<tr>
<th>Food</th>
<th>AD n=64</th>
<th>Control n=80</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice</td>
<td>261.9 ± 105.8</td>
<td>231.9 ± 94.1</td>
<td>NS</td>
</tr>
<tr>
<td>Potate</td>
<td>16.7 ± 12.2</td>
<td>22.6 ± 16.7</td>
<td>NS</td>
</tr>
<tr>
<td>Sugar</td>
<td>6.1 ± 15.1</td>
<td>5.4 ± 3.8</td>
<td>NS</td>
</tr>
<tr>
<td>Snack</td>
<td>16.1 ± 16.0</td>
<td>16.5 ± 13.4</td>
<td>NS</td>
</tr>
<tr>
<td>Beans</td>
<td>119.5 ± 86.9</td>
<td>127.8 ± 69.2</td>
<td>NS</td>
</tr>
<tr>
<td>Fish</td>
<td>40.5 ± 24.4</td>
<td>58.3 ± 28.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Meat</td>
<td>25.1 ± 15.4</td>
<td>21.0 ± 16.3</td>
<td>0.13</td>
</tr>
<tr>
<td>Egg</td>
<td>16.0 ± 15.4</td>
<td>13.5 ± 11.0</td>
<td>NS</td>
</tr>
<tr>
<td>Milk</td>
<td>77.2 ± 77.8</td>
<td>117.5 ± 99.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Green vegetable</td>
<td>45.7 ± 31.7</td>
<td>68.9 ± 59.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Vegetable</td>
<td>55.9 ± 32.2</td>
<td>70.6 ± 46.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Fruits</td>
<td>78.9 ± 60.1</td>
<td>89.4 ± 54.2</td>
<td>NS</td>
</tr>
<tr>
<td>Fungi</td>
<td>4.4 ± 4.4</td>
<td>7.6 ± 7.7</td>
<td>0.004</td>
</tr>
<tr>
<td>See weeds</td>
<td>6.3 ± 7.3</td>
<td>10.7 ± 8.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Alcohol</td>
<td>65.1 ± 164.4</td>
<td>75.5 ± 177.2</td>
<td>NS</td>
</tr>
<tr>
<td>Soft drink</td>
<td>399.7 ± 320.0</td>
<td>559.8 ± 381.5</td>
<td>NS</td>
</tr>
<tr>
<td>Spice</td>
<td>18.9 ± 23.1</td>
<td>39.4 ± 47.3</td>
<td>NS</td>
</tr>
</tbody>
</table>
Dietary intervention to AD

Adequate calorie intake
Sufficient vitamin & mineral intake
Fatty acids : n-6/n-3 = 3.0

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Fish</td>
<td>60〜90g/day</td>
</tr>
<tr>
<td>Vegetable</td>
<td>100g/day</td>
</tr>
<tr>
<td>Fruits</td>
<td>at least once a day</td>
</tr>
</tbody>
</table>
The effect of dietary modification on MMSE in mild to moderate AD

Diet modified group (n=24)
Control group (n=25)

Cumulative occurrence of all-cause dementia and Alzheimer’s disease when subjects were classified by serum 25(OH)D concentration

The daily steps and cognitive function decline in mild to moderate AD patients

Cognitive function was preserved in AD patients who walk $\geq 5,000$ steps/day.

(Yamada A, Arai H, Kyoto University, unpublished data)
Smoking and Smoking cessation vs. the risk of dementia

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Non-smoker</th>
<th>Ex-smoker</th>
<th>Current Smoker</th>
<th>&lt; 20 /day</th>
<th>&gt; 20 /day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&lt;Total dementia&gt;</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-, sex-, survey year-matched OR</td>
<td>1.0</td>
<td>1.4 (0.6-2.8)</td>
<td>2.2 (1.1-4.4)</td>
<td>2.1 (1.1-4.3)</td>
<td>2.6 (0.9-7.3)</td>
</tr>
<tr>
<td>Multivariable OR</td>
<td>1.0</td>
<td>1.5 (0.7-3.3)</td>
<td>2.3 (1.1-4.7)</td>
<td>2.2 (1.1-4.7)</td>
<td>2.7 (0.9-8.2)</td>
</tr>
<tr>
<td><strong>&lt;Dementia with history of stroke&gt;</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-, sex-, survey year-matched OR</td>
<td>1.0</td>
<td>1.4 (0.4-4.5)</td>
<td>2.4 (0.8-7.1)</td>
<td>2.4 (0.8-7.2)</td>
<td>2.5 (0.5-11.9)</td>
</tr>
<tr>
<td>Multivariable OR</td>
<td>1.0</td>
<td>1.7 (0.5-5.9)</td>
<td>2.4 (0.8-7.7)</td>
<td>2.4 (0.7-7.9)</td>
<td>2.5 (0.4-14.4)</td>
</tr>
<tr>
<td><strong>&lt;Dementia without history of stroke&gt;</strong></td>
<td></td>
<td></td>
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<td>2.0 (0.8-4.9)</td>
<td>2.6 (0.6-11.1)</td>
</tr>
<tr>
<td>Multivariable OR</td>
<td>1.0</td>
<td>1.5 (0.6-4.3)</td>
<td>2.3 (0.9-6.0)</td>
<td>2.2 (0.8-5.9)</td>
<td>3.0 (0.7-13.8)</td>
</tr>
</tbody>
</table>

(Adjusted for body mass index, alcohol use, serum total cholesterol, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, atrial fibrillation and ST-T abnormality)

AD and life style-related diseases

Well-known risk factors for atherosclerosis...

Hypertension  have been reported to be risk factors also for AD
Diabetes
Dyslipidemia
Obesity
Smoking

Also, treatment of life style-related diseases has been reported to decrease the incidence of AD.
The incidence of AD in Syst–Eur Trial

Possibility: Treatment of life style-related disease reduces the risk of AD. Diabetes, HT.....

- Intention-to-treat analysis
  - Placebo: 7.7
  - Nitrendipine: 3.8
  - Reduction: -50% (~76~0%) *P=0.05*

- Per-protocol analysis
  - Placebo: 6.8
  - Nitrendipine: 2.7
  - Reduction: -80% (~83~2%) *P=0.03*

*(Staessen JA, et al., 1997)*
The effect of anti-hypertensive treatment on the occurrence of dementia

−Meta-analysis−

(Peters R., et al., 2008)

<table>
<thead>
<tr>
<th>Study</th>
<th>Active(N/n)</th>
<th>Placebo(N/n)</th>
<th>HR(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROGRESS RR</td>
<td>3051/193</td>
<td>3054/217</td>
<td>0.89 (0.74-1.07)</td>
</tr>
<tr>
<td>Syst-Eur RR</td>
<td>1238/11</td>
<td>1180/21</td>
<td>0.50 (0.25-1.02)</td>
</tr>
<tr>
<td>SHEP RR</td>
<td>2365/37</td>
<td>2371/44</td>
<td>0.84 (0.55-1.30)</td>
</tr>
<tr>
<td>HYVET RR</td>
<td>1687/126</td>
<td>1649/137</td>
<td>0.90 (0.71-1.13)</td>
</tr>
</tbody>
</table>

Combined (random) 0.87 (0.76-1.00)

Cochran Q=2.409, p=0.491
Test for overall effect; p=0.045

N=total participants, n=number with dementia
Co-culture system (size; 0.4μm micro pore)

PC12

SA-β-gal-positive cells (%)

AICD (µg) 0 1 3

HUVEC

PC12

SIRT1

PAI-1

p53

AICD

HUVFEC (RT-PCR mRNA)

MCP-1 Relative expression

IL-8 Relative expression

AICD 0 1 3

AICD 0 1 3

TNF-alpha Relative expression

IL-6 Relative expression

AICD 0 1 3
Vascular Neuron

IL-6, IL-1α, IL-1β, IL-24
IL-8, GROα, β, γ, CXCL20, CCL3
MMP3, MMP14
BMP2, PAI-1, PAI-2 et al

Longevity gene SIRT1

SASP (Senescence-associated secretory phenotype)

1. Progression or inhibition of tumor
2. Induction of inflammation
3. Progression of Cellular Senescence

Hypothesis: Vascular senescence/damage promotes neuronal senescence/damage by secretion of inflammatory cytokines
Messages from JGS

- Life style modification is important for the prevention of both vascular and Alzheimer’s types of dementia.

- Although evidence is not concrete, life style-related diseases, especially diabetes and hypertension, should be well treated for the prevention of both types of dementia.

- The basic research on the mechanism underlying the effect of life style modification or treatment of life style-related diseases may provide a new preventive and therapeutic approach for AD.
The perspective of dementia practice from the geriatric point of view

1. Seamless coordination:
   ◯ Prevention → diagnosis & treatment at early stage → care

2. Insight from whole body to brain
   ◯ Control of vascular risk factors

3. Insight from brain to whole body
   ◯ Treatment and care for geriatric syndrome including aspiration pneumonia, osteoporosis and frailty
   ◯ Treatment and care of complicated diseases in demented patients

4. Coordination: Geriatricians – Neurologists - Psychiatrists

5. Coordination: Medical - Care & Social welfare
Thank you very much for your attention

New Toranomon Hospital
(completed 2018)

Toranomon Hospital
since 1958