METABOLIC SYNDROME, NEUROINFLAMMATION AND COGNITIVE IMPAIRMENT: STATE OF THE ART AND DATA FROM A SECOND LEVEL OUTPATIENT CLINIC IN ITALY

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ALZHEIMER’S DISEASE

35.6 million people worldwide living with dementia in 2010, expected to become 65.7 million in 2030 and 115.4 million in 2050

Alzheimer’s disease (AD) is the most prevalent type of dementia, comprising about 60%–70% of all dementia cases
AMYLOID CASCADE HYPOTHESIS...

...NOT ENOUGH...
• authoptic and imaging studies showed that amyloid deposition, such as neurofibrillary tangles, can be found in cognitively and well-educated normal old subjects.

• therapeutics attempt to clear $A\beta$, although efficient in reducing $A\beta$ load both in animal and human models, didn’t stop or reduce the progression of AD.
NEUROINFLAMMATION

INFLAMMATORY RESPONSE IN THE CENTRAL NERVOUS SYSTEM, DUE TO INJURY; ASTROCITES AND MICROGLIAL CELLS ARE THE MAIN ACTORS IN THE INFLAMMATORY RESPONSE IN THE CNS

Modified from Microglia function in Alzheimer’s disease Egle Solito and Magdalena Sastre
...SELF-PERPETUATING CYCLE OF NEURONAL DAMAGE/DEATH FOLLOWED BY MICROGLIAL ACTIVATION IS COMMONLY REFERRED TO AS REACTIVE MICROGLOSIS AND MAY BE AN UNDERLYING MECHANISM OF THE PROGRESSIVE NATURE OF DIVERSE NEURODEGENERATIVE DISEASES, INCLUDING ALZHEIMER'S DISEASE...

NADPH oxidase as a therapeutic target in Alzheimer’s disease. Michelle L Block
NEUROINFLAMMATION AND NEURODEGENERATION: SUPPORTING EVIDENCE

• up-regulated inflammatory mechanisms co-localize in the same region with high level of AD pathology, absent in the region with low AD susceptibility (e.g., cerebellum)

• microscopical examinations showed that inflammatory mediators are expressed overall closest to the Aβ deposits and neurofibrillary tangles

http://ucmkitazawa.web.fc2.com/mind_project.html
NEUROINFLAMMATION AND NEURODEGENERATION: SUPPORTING EVIDENCE

- subjects withouth dementia but authoptic funding of limbic Aβ and neurofibrillar tangles sufficient to pone diagnosis of AD show a modest elevation of inflammatory markers, greater than non dement subjects but less than AD subjects

  - ultrastructural evidence of inflammatory toxicity in AD brain

  - potential protective effect of the chronic use of Non-Steroidal Anti-Inflammatories
inflammatory mediators by cells local to the insult.

Liver acute phase response and immune cell recruitment from the bone marrow.

The circulating cytokines also communicate with brain centres through the cerebral endothelium, the vagal nerve and the circumventricular organs to effect local cytokine and prostaglandin synthesis and produce sickness behaviours such as fever and reduced locomotor activity. IL and TNF\alpha.
• periodontitis, a clinical condition characterized by chronic periodontal inflammation and systemic release of inflammatory cytokines (Il-1, Il6, TNF)
Insulin resistance, identified by 1 of the following:

- Type 2 diabetes
- Impaired fasting glucose
- Impaired glucose tolerance
- or for those with normal fasting glucose levels (<110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions

Plus any 2 of the following:

- Antihypertensive medication and/or high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic)
- Plasma triglycerides ≥150 mg/dL (≥1.7 mmol/L)
- HDL cholesterol <35 mg/dL (<0.9 mmol/L) in men or <39 mg/dL (1.0 mmol/L) in women
- BMI >30 kg/m² and/or waist:hip ratio >0.9 in men, >0.85 in women
- Urinary albumin excretion rate ≥20 µg/min or albumin:creatinine ratio ≥30 mg/g

*Derived from Alberti et al.7,8
Longitudinal cohort study, counting 1624 Latinos aged 60 and older who participated. Conclusions: Metabolic syndrome and inflammation may both contribute to cognitive decline in older people of diverse backgrounds...the composite measure of metabolic syndrome is a greater risk for cognitive decline than its individual components.

The Metabolic Syndrome, Inflammation, and Risk of Cognitive Decline

A 5-year prospective observational study conducted from 1997 to 2002 at community clinics at 2 sites, for a total of 2632 black and white elders (mean age, 74 years).

Conclusions: metabolic syndrome contributes to cognitive impairment in elders, but primarily in those with high level of inflammation
A total of 2097 participants from a sample of 5632 65–84-year-old subjects from the Italian Longitudinal Study on Aging
Among MCI patients the presence of MetS independently predicted an increased risk of progression to dementia over 3.5 years of follow-up.
High cholesterol and systolic blood pressure were significant predictors of dementia and their risk was additive to that of obesity in this population.

Midlife obesity, high SBP, and high total cholesterol level were all significant risk factors for dementia, each of them increasing the risk around 2 times. Clustering of these vascular risk factors increased the risk of dementia and AD in an additive manner so that persons with all 3 risk factors had around a 6 times higher risk for dementia than persons having no risk factors.
### ALZHEIMER’S OUTPATIENT CLINIC
### LIVORNO HOSPITAL (TUSCANY)

<table>
<thead>
<tr>
<th>subjects (n=127)</th>
<th>female (n=76)</th>
<th>male (n=51)</th>
<th>p (F vs M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>78,2±7,1</td>
<td>78,5±7,1</td>
<td>77,6±7,2</td>
</tr>
<tr>
<td>MMSE</td>
<td>20,6±5,1</td>
<td>20,2±4,9</td>
<td>21,0±5,4</td>
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<tr>
<td>HBP</td>
<td>53,1%</td>
<td>54,2%</td>
<td>51,4%</td>
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<tr>
<td>DM</td>
<td>34,7%</td>
<td>35,6%</td>
<td>33,3%</td>
</tr>
<tr>
<td>IFG</td>
<td>7,9%</td>
<td>10,2%</td>
<td>4,8%</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>79,1%</td>
<td>88,5%</td>
<td>64,7%</td>
</tr>
<tr>
<td>CVI</td>
<td>53,1%</td>
<td>48,8%</td>
<td>57,9%</td>
</tr>
<tr>
<td>CRI</td>
<td>24,0%</td>
<td>48,6%</td>
<td>30,9%</td>
</tr>
<tr>
<td>↑ Inflammation indexes</td>
<td>41,7%</td>
<td>48,6%</td>
<td>30,4%</td>
</tr>
</tbody>
</table>

*With contribution of Cassa di Risparmio di Livorno*
ALZHEIMER’S OUTPATIENT CLINIC
LIVORNO HOSPITAL (TUSCANY)

Mean MMSE score

Quartiles of age

1° <65 n=7
2° 65-75 n=28
3° 75-85 n=66
4° >85 n=26

p=0.02
p=0.05

With contribution of Cassa di Risparmio di Livorno
ALZHEIMER’S OUTPATIENT CLINIC
LIVORNO HOSPITAL (TUSCANY)
PREVALENCE OF CARDIOVASCULAR RISK FACTORS

With contribution of Cassa di Risparmio di Livorno
INTERESTINGLY, ALTHOUGH THE ASSOCIATION BETWEEN PERIPHERAL INFLAMMATION AND COGNITIVE IMPAIRMENT IS GENERALLY RECOGNIZED, RHEUMATOID ARTHRITIS, A TYPICAL SYSTEMIC AUTOIMMUNE DISORDER, SEEMS NEGATIVELY ASSOCIATED TO ALZHEIMER’S DISEASE DEVELOPMENT
On this basis, we propose a translational research project

**Relationship between cognitive function and inflammation in animal models and in patients with morbid obesity, rheumatoid arthritis, osteoarthritis and periodontitis**

to evaluate the effect of peripheral chronic inflammation on neuro-inflammation and cognitive function as well as AD pathophysiology,
GOALS:

Demonstrate that peripheral chronic inflammation, depending on the cytokine pattern, specific for MORBID OBESE, REUMATHOID ARTHRITIS AND PERIODONTITIS PATIENTS, could act at CNS level and favor or prevent negative inflammation and consequent oxidative stress on the ad developing process.

Pisa University Hospital:

• Geriatrics Unit (PI)
• Rheumathology Unit
• Odontostomatholgy Unit
• Neurology Unit
• Endocrinology Unit

Imperial College, London:

Neuro-Imaging Unit, Hammersmith Hospital