Prevention of cognitive decline and improvement of innate immunity in patients with mild cognitive impairment by omega-3 fatty acid and anti-oxidant supplementation

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**Background:** Preventive therapy of mild cognitive impairment (MCI) patients is based on repairing the innate immunity centered on macrophages. Therapeutic antibodies are helpless in repairing innate immunity. The macrophages of MCI patients are deregulated to either inflammatory M1 or pro-resolution M2 type, but macrophages of all AD and MCI patients are defective in phagocytosis and degradation of amyloid-beta1-42 (Abeta). Cellular defects of macrophages include defective migration, subcellular transport, and propensity to apoptosis from fibrillary Abeta related to transcriptional, genetic, epigenetic, and metabolomic mechanisms in individual patients. Exogenous Abeta increases inflammation in peripheral blood mononuclear cells (PBMCs) of patients in comparison to controls. The lipid modulator from docosahexaenoic acid (DHA) called resolin D1 (RvD1) and the hormonal form of vitamin D3 termed 1,25dihydroxyvitamin D3 (1,25D3) promote Aβ1-42 phagocytosis and regulate inflammatory genes in macrophages and PBMCs. Omega-3 fatty acids DHA and EPA are precursors of the lipid modulators resolvins, protectins and maresins that resolve inflammation.

**Methods:** Prospective study of 18 MCI patients (up to 2 years) supplemented with omega-3 antioxidant drink “Smartfish” (Oslo, Norway), which is stabilized against oxidative degradation by botanical additives (pomegranate, chookberry and transresveratrol; curcumin in select patients) and vitamin D3; Flow cytometric test of Abeta phagocytosis (mean fluorescence intensity (MFI) units; mRNA testing by PCR; M1M2 testing of macrophages using anti-CD54, anti-CD80, anti-CD163, anti-CD206 (M1M2 ratio = CD54+CD80/CD163+CD206); Minimental state examination (MMSE); RvD1 (pg/ml) EIA assay.

**Results:** MCI patients were separated according to the initial M1M2 ratio into non-inflammatory (M1M2 ratio <1) and inflammatory (M1M2 ratio >1) patients. On nutritional supplementation by the Smartfish drink, MMSE (Mean (M) ~26) was maintained in non-inflammatory but decreased in inflammatory patients. MFI increased in both groups. The M1M2 ratio increased in the non-inflammatory patients to 2.7 and marginally increased in inflammatory patients to 3.55. Transcription of inflammatory genes increased in the non-inflammatory patients and was not changed in the inflammatory patients.

<table>
<thead>
<tr>
<th>Category</th>
<th>duration (months)</th>
<th>MMSE initial</th>
<th>MMSE final</th>
<th>MFI initial</th>
<th>MFI final</th>
<th>M1M2 initial</th>
<th>M1M2 final</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Noninflammatory (n=6)</td>
<td>M=14.8</td>
<td>M=25.83</td>
<td>26.00</td>
<td>496.68</td>
<td>1272.17</td>
<td>0.79</td>
<td>2.70</td>
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<td></td>
<td>S.D.1.84</td>
<td>4.43</td>
<td></td>
<td>321.28</td>
<td>408.30</td>
<td>0.31</td>
<td>0.91</td>
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<tr>
<td>B. Inflammatory    (n=5)</td>
<td>M=10</td>
<td>M=27.00</td>
<td>26.20</td>
<td>584.60</td>
<td>1943.40</td>
<td>3.40</td>
<td>3.55</td>
</tr>
<tr>
<td></td>
<td>S.D.4.24</td>
<td>5.93</td>
<td></td>
<td>389.29</td>
<td>869.53</td>
<td>0.98</td>
<td>1.65</td>
</tr>
</tbody>
</table>

**Conclusions:** Nutritional supplementation of MCI patients by omega-3 and antioxidants maintained or improved cognition in Apo E3/E3 genotype patients but failed in 3 of 6 Apo E3E4 genotype patients. The supplementation improved Abeta phagocytosis and regulated macrophage type to M1/M2 pro-phagocytic, mildly inflammatory type in both groups. Therefore, omega-3/ antioxidant supplementation is beneficial in individual MCI patients who are observed and treated in a personalized fashion. Large studies of MCI patients fail due to heterogeneity of patients and lack of effective therapy of innate immunity.