Physician Guide to Understanding the Role of Inflammation in the Loss of Cognitive Function or the Development of Dementia in Older Persons

1. Overview on Neuro-inflammation
Primary care physicians may be queried by older patients about the wisdom of taking anti-inflammatory medications to reduce the risk of dementia (1). Several lines of evidence suggest that abnormal inflammatory processes may contribute to cognitive decline and the pathogenesis of dementia (1). Some epidemiological studies suggest that individuals with long-term consumption of anti-inflammatory medications were less likely to develop dementia; however, meta analytic review does not support this linkage (2), (3). A second line of evidence suggests a relationship between elevated serum levels of inflammatory markers such as C-reactive protein or interleukin 6 and increased risk for cognitive decline. Subsequent evidence demonstrates neurochemical and microscopic brain abnormalities that support inflammatory damage in Alzheimer’s disease.

2. The relationship of inflammatory markers and cognitive decline
Multiple longitudinal studies have examined the relationship between circulating immunological markers and the risk for cognitive decline in elders. C-reactive protein is a nonspecific inflammatory marker associated with a variety of cardiovascular risk factors. Individuals with metabolic syndrome demonstrate elevated levels of C-reactive protein that correlate to severity of cardiovascular disease. Isolated elevation of C-reactive protein is associated with increased risk for cognitive decline (See Table 1). Likewise, elevated markers for interleukin 6 and alpha 1 chymotrypsin are also associated with cognitive decline in later life. Data is not consistent in all studies; however, the general trend indicates that elevated markers for systemic inflammation predict elevated risk for cognitive decline (8).

Table 1

<table>
<thead>
<tr>
<th>#</th>
<th>n</th>
<th>a</th>
<th>t</th>
<th>Finding</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>540</td>
<td>&gt;65</td>
<td>CS</td>
<td>Chronic low grade inflammation may ▲ age-related cognitive decline</td>
<td>4</td>
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<tr>
<td>2</td>
<td>3031</td>
<td>&gt;65</td>
<td>CS</td>
<td>Markers for IL6 and CRP may predict ▼ cognitive function</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>1284</td>
<td>&gt;62</td>
<td>3yrs</td>
<td>Alpha 1 – antichymotrypsin is associated with cognitive decline but not IL6 or CRP</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>799</td>
<td>&gt;70</td>
<td>7yrs</td>
<td>IL6 may predict ▼ cognitive function</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>290</td>
<td>55+</td>
<td>3yrs</td>
<td>IL6 ▲ risk in African-Caribbeans</td>
<td>28</td>
</tr>
</tbody>
</table>

n = study size  a = age  IL6 = interleukin 6  CRP = C-reactive protein  CS = cross-sectional
3. Animal models for brain inflammation
Rodents that are genetically altered to produce excessive amounts of \( \text{A\beta} \) amyloid in their brain may exhibit a diminished amyloid load after pretreatment with anti-inflammatory medications, as well as diminished inflammatory markers such as IL6 (9), (10). Conversely, excessive amounts of glucocorticoids in aged macaque monkeys are related to increased levels of \( \beta \) amyloid in comparison to levels of \( \beta \) 40 and this over-production of toxic amyloid may be mediated through alterations of the insulin degrading enzyme (11). Chronic administration of Ibuprofen reduces the density of amyloid plaque pathology in the mouse model of Alzheimer’s disease (10). Molecular biological studies from rodent models suggest that NSAIDs directly alter the amyloid pathway by reducing \( \text{A\beta} \) peptide levels; however, this effect does not appear dependent on cyclooxygenase (COX) activity (12).

4. Neuropathology and Inflammation
Inflammatory cells may be an integral part of the damage associated with senile plaques and amyloid deposits. The role of inflammation in neurofibrillary pathology is less well understood. Microglial cells are intrinsic brain inflammatory cells that may be activated by glycation of the APOE protein (7), (13). The limited pathological data on the density of senile plaque and tangles counts suggest no difference between brains of persons who took NSAIDs and those who took no anti-inflammatory medication; even in medicated persons with better cognitive function (14).

5. Potential Pharmacological Interventions to reduce Inflammatory Processes
Damage produced by inflammation in the brain might be reduced by multiple methods including: 1) reduction of the severity of metabolic syndrome, and 2) use of non-steroidal anti-inflammatories. Long-term, low dose use of NSAIDs may protect against cognitive decline (15), (16), (17). The overall efficacy of these medications is undetermined. Long-term use of NSAIDs carries significant risks for gastrointestinal bleeding (18), especially during acute initiation of the medication. Long-term use of COX 2 inhibitors may produce significant risk for cardiovascular complications (19). The long-term use of these medications as an anti-Alzheimer protectant is not proven (20); in fact, there is no proven method to reduce possible brain damage produced by pathological immune responses in the older human.

Understanding the efficacy of anti-inflammatory medication is limited by the absence of double-blind placebo controlled trials (21). The suggestion that NSAIDs may act independently of cyclooxygenase (COX) inhibition may explain poor results produced by clinical trials for naproxen, celecoxib and rofecoxib in clinical trials (1). The conventional wisdom suggests that Ibuprofen may provide the safest, most cost-effective intervention for individuals required to take anti-inflammatories (3).

6. The Role of the Metabolic Syndrome in Producing Inflammation
The metabolic syndrome will increase levels of inflammatory markers such as CRP in older persons. The metabolic syndrome and increased inflammatory markers are independent risk factors for cognitive loss. Management of the metabolic syndrome may reduce some component of the inflammatory response (24), (25), (26). CLICK HERE FOR MORE INFORMATION – 2513.91

Genes that control proteins involved with inflammatory response may be altered in AD. Other future pharmacologic interventions may target the production of these inflammatory proteins (29), (30).
7. Clinical Recommendations to Reduce Inflammatory-Mediated Brain Damage

The risk-benefit ratio weighs against recommending non-steroidal anti-inflammatory medication to reduce the risk for dementia in older persons. Clinicians can advise patients about two possible methods of reducing the risk for dementia produced by an abnormal systemic inflammatory response. First, passive measures such as reduction of risk factors for metabolic syndrome may provide secondary effects through reduction of risk for excessive production of inflammatory responses. A second direct anti-inflammatory effect may be mediated through the use of Ibuprofen or aspirin. Low dose aspirin may also be protective for declining memory in individuals 75 years in age and older -- a mechanism that maybe mediated by its anti-platelet effect (15), (16), (17). The chronic use of non-steroidal anti-inflammatories may also delay the onset of other neurodegenerative diseases such as Parkinson’s disease (23). Patients who use NSAIDs for other medical problems, such as arthritis, may enjoy a slight cognitive benefit from this medication (27) if used chronically (22).

Other immunological interventions to reduce amyloid burden have produced inconsistent results. Active immunization against Aβ amyloid has not been shown to be effective in persons with Alzheimer’s disease. Prophylactic vaccination in at-risk individuals may be attempted when safe, effective vaccines are developed.

Recommendations to Primary Care Physicians

1. Encourage treatment of the metabolic syndrome to reduce the risk of abnormal systemic inflammatory responses.
2. Chronic use of NSAIDs for other indications may slightly reduce the risk for dementia.
3. Chronic NSAID use carries significant risk for toxicity.
4. Discourage the use of anti-inflammatory medications to reduce the risk for dementia.
References

10. van Groen T, Kadish I. Transgenic AD model mice, effects of potential anti-AD treatments on inflammation and pathology.


