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Rheumatoid Arthritis and Alzheimer Disease: Possible Cellular and Molecular Links

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Abstract

Alzheimer disease (AD) is the most common form of dementia of the old population over 85 years. AD pathogenesis is multifactorial and several findings support the neuroinflammatory pathogenetic hypothesis. There is an inverse relationship between AD and Rheumatoid arthritis (RA) due to different factors. Among them, NSAIDs use acting both on amyloid formation and COX enzymes has been supposed to play a protective role on AD risk. Moreover, new insights on colony stimulating factors (GM-CSF, M-CSF and G-CSF) pathways in immune cells differentiation suggested a possible cellular link between AR and the AD onset.

Alzheimer disease (AD) is the most common form of dementia, accounts for 50-60% of all dementia cases. It interests about 20-40% of the old population over 85 years and is characterized by cognitive dysfunction as memory loss, language difficulties, visuospatial deficits, impairment in judgment and decision-making, deficit in higher and subsequently in basic daily activities, behavioral disturbances and psychiatric alterations. The classical AD pathologic hallmarks are senile plaques made by extracellular amyloid beta (Aβ) deposition and neurofibrillary tangles made of hyperphosphorylated Tau proteins [1].

The pathogenesis of AD is multifactorial and neuroinflammation seems to play an important role. Although histopathological analysis did not demonstrate leukocyte infiltration in AD brain, several findings support the "neuroinflammatory hypothesis" such as the presence of anti-neuronal antibodies in AD brain [2], circulating anti-A antibodies in serum of AD patients, higher levels of peptidylarginine-deiminasis (PAD) and citrullinated proteins such as vimentin in hippocampal extracts from AD patients [3], polymorphism in inflammatory genes (as IL-1α, IL-1β, IL-6, TNFα, α1-anti-chimotrypsin, α2-macroglobulin) enhancing the risk of developing AD [4-7], complement proteins colocalizing in senile plaques and neurofibrillary tangles, elevation of several inflammatory mediators (as IL-6, chemokines, acute phase proteins) in serum [8] and in affected brain area of AD patients [9] as well as the increased count of mononuclear phagocytes and their products (IFN-γ, TNF-α and IL-1) able to trigger the production of Aβ in neuronal and extraneuronal cells [10,11]. In this way it seems that the innate immunity is chronically activated while the adaptive immunity declines together with the Th2 response [10]. Moreover Aβ deposition may activate microglia through receptors for advanced glycation end products (RAGE) and cause cellular stress and inflammatory factors release by binding RAGE on neurons [12]. However it remains unclear if the inflammatory stimulus may cause AD or it is only a concurrent epiphenomenon secondary to the Aβ deposition [1].

It is pretty well known the inverse relationship between AD and Rheumatoid Arthritis (RA), since 1990, when McGeer described a reduced prevalence of AD through post-mortem study in long-using NSAIDs RA patients [13]. This is biologically of great interest given that RA is a chronic inflammatory disease that per se when poorly controlled can give rise to systemic amyloidosis. Previously, Jenkinson et al. [14] described a decreased RA incidence among AD patients compared to healthy controls. Moreover Myllykangas-Luosujarvi and colleagues [15] found that AD brain hallmarks occurs four times less often in RA patients compared to healthy subjects. To date, many epidemiological studies have been performed suggesting controversial data about the prolonged use of NSAIDs and their possible protective effect, reducing AD risk. A meta-analysis of 17 epidemiologic studies concluded that RA and NSAIDs are protective factors for AD onset [16]. Moreover, Stricker et al. [17] prospectively analysed almost 7000 healthy subjects older then 55 years using NSAIDs (approximately 83% using diclofenac, ibuprofen and naproxen) for joint symptoms (about 3.4% for RA) and followed for 6.8 years showing that long-term use of NSAIDs (more than 24 months of cumulative use) protects against AD. This finding was confirmed through a systematic review of prospective and non-prospective studies published from 1960 to 2003 that concluded that NSAIDs exposure was associated with decreased risk of AD disease [18]. In contrast to these data the ADAPT trial (Alzheimer Disease Anti-inflammatory Prevention Trial) that randomized 2528 elderly (2% with RA history) healthy person with family history of AD to receive naproxen or celecoxib or placebo did not show a significant decrease of AD risk [19].

Nevertheless, except for a small-size 6-months clinical trial reporting the positive effect of indomethacin on individuals with mild to moderate AD [20], many clinical trials demonstrated no benefits of NSAIDs on cognitive performance in symptomatic AD patients. A multicenter, randomized, double–blind, controlled trial on 351 mild-to-moderate AD patients randomized to receive naproxen, rofecoxib or placebo did not show any significant beneficial effect of NSAIDs on AD progression [21]. Similar results derived from a randomized controlled trial using indomethacin versus placebo in 51 mild-to-moderate AD patients [22]. Thus the anti-inflammatory approach is really effective eventually only in primary prevention of AD, not in treatment of AD.

Recently a Cochrane meta-analysis has been carried out, including 14 RCTs showing that nor NSAIDs, aspirin or steroids have significant beneficial effect in the treatment of AD [23].

Taking into account that different NSAIDs have different capacity in crossing the brain-blood-barrier because of their lipophilicity, part of the beneficial effects of NSAIDs on reducing the risk and delaying

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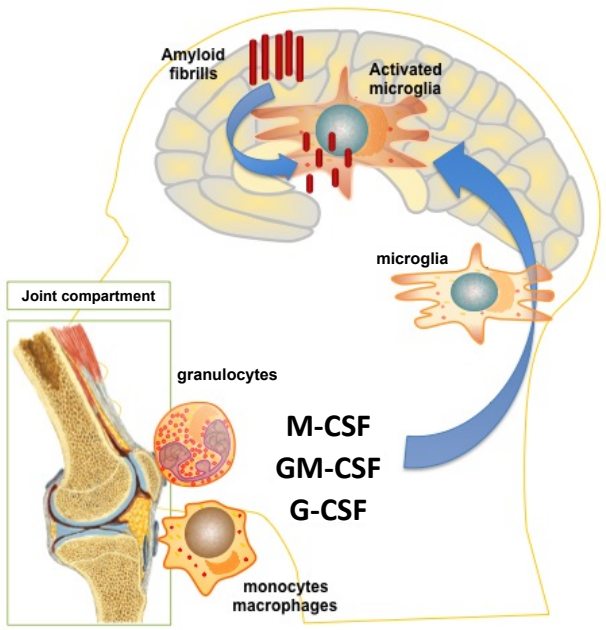

GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; **M-CSF:** Macrophage Colony-Stimulating Factor; **G-CSF**: Granulocyte Colony-Stimulating Factor.

Figure 1: Rheumatoid arthritis and Alzheimer disease: possible cellular and molecular links.

the onset of AD may be explained by their common anti-inflammatory effect through COX enzymes inhibition. It has been proposed that COX-1 should be a preferential target being up-regulated in microglia [24] (probably COX-2 plays a minor role being involved only at the later stage of AD animal models) [25]. NSAIDs also modulate the activation of inflammatory microglia binding PPAR-γ and consequently reducing cytokine production [26].

New insights are emerging about a direct anti-amyloidogenic effect of NSAIDs *in vitro* and in animal models. NSAIDs, in particular ibuprofen and flurbiprofen, could act in a COX-independent manner shifting the βAPP metabolism toward shorter, more soluble and less fibrillogenic form of Aβ peptides, interfering with the γ [27] and β-secretases activities. Electron microscopy and fluorescence spectroscopy used to examine the effects of NSAIDs on β-amyloid fibrils demonstrated an inhibition of Aβ fibrils formation in a dose-depend manner as follows (ibuprofen > sulindac > meclofenamic acid > aspirin ~ ketoprofen > flurbiprofen ~ diclofenac > naproxen ~ indomethacin) [28]. In AD mice ibuprofen was able to reduce the number and the total area of β-amyloid deposits. It has also been shown that NSAIDs could interfere with Aβ aggregation inducing the expression of amyloid-binding protein such as transthyretin (TTR) that prevents Aβ aggregation [29] and enhances the transfer of Aβ from plasma to the central nervous system (CNS) across choroid plexus [30].

It has also been studied, just in animal and *in vitro* models, the potential role on AD pathogenesis of DMARDs (Disease-Modifying Antirheumatic Drugs), commonly used in RA treatment. Among them, CyclosporinA (CsA), preventing mitochondrial-membrane damage, seems to attenuate both the β-amyloid and Tau proteins induced neuronal apoptosis [31] and the oxidative stress [32]. CsA also seems to prevent APP overexpression and amyloidogenic peptides overproduction [33] but conversely it has been described to enhance Tau phosphorylation. Phosphatase calcineurin, that is a specific target for CsA, is known to be upregulated in AD models inducing astrogliosis and neuroinflammation [34]. Few evidences are available on Methotrexate (MTX): the folate deficiency, induced by MTX, increases levels of phosphorylated Tau [35]. Morover, Sulphasalazine, blocks NMDA-toxicity and prevents the Aβ-peptides induced calcium currents enhancement that leads to cell death through NF-κB inhibition [36]. There are no data about the effects of Leflunomide on AD. TNF-α inhibitors represent a powerful therapeutic tool for RA. In CNS TNF-α, secreted by microglia, is over-produced in AD brain where it has been demonstrated to play a major role in neuroinflammation-mediated cell death. It increases production of the precursor necessary for amyloid plaques and neurifibrillary tangles formation [37] and affects synaptic physiology acting as a gliotransmitter [38,39]. Unfortunately TNF-α blockers are unable to cross the blood-brain barrier; however in a 6 months study on 12 mild-to-moderate AD patients, perispinal administration of Etanercept rapidly improved cognitive function [40].

Based on these findings, it is fair to suppose a possible tight intrinsic link in RA pathogenesis able to explain itself the protective effect of RA against AD. So far, different research hypotheses have been developed. GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor), a molecule over-expressed in RA was demonstrated to induce dendritic cells, macrophages and granulocytes, innate cells having the ability to differentiate into specializing cells such us microglia. Furthermore GM-CSF and RA dysregulated leukocytes are able to the cross blood-barrier but lymphocytic infiltrates have never been described in AD patients brain. This lack of inflammatory infiltrates suggests that RA protective effect on AD development is likely dependent on the innate immunity. Potter et al. showed that both intracerebral and subcutaneous injection of GM-CSF in AD mice reduced amyloid load within hippocampal and entorinal cortex, improving cognitive functions associated with the microglia density increase. They argued that GM-CSF could acts on bone-marrow derived microglia transforming it in a really "amyloid-clearing factory", enhancing its ability to bind and remove amyloid deposition. Moreover because of the physiological GM-CSF-receptor expression on hippocampal stem cells, GM-CSF could increase neuronal growth and synaptic differentiation of fibers involved in neuronal circuit, critical for short-term memory [41]. Similar results have been previously shown for M-CSF (Macrophage Colony-Stimulating Factor) [42] and G-CSF (Granulocyte Colony-Stimulating Factor) [43]. One of the last insights derived from AD mice model with collagen induced arthritis (CIA) showed reduced levels of soluble and insoluble amyloid beta (Aβ) peptides and amyloid plaque formation in the cortex and hippocampus, associated to the increased blood brain barrier disruption and CD45-positive microglia/macrophages transfer [44].

Recently, Estus et al. studied the possible disruption of RA crucial genes in AD performing a case control analysis to evaluate the RA and AD risks. They found that only one of 17 RA-associated single nucleotide polymorphisms (SNPs), the rs2837960_G, was significantly associated with AD. Surprisingly this SNP was associated with increased risk of both RA and AD, in individuals younger than 80 years. In particular, the rs2837960_G SNP modulates gene expression of BACE2, in human brain, which express β-secretase activity [45].

In conclusion, the relation between RA and AD should be thought considering multiple cellular (microglia) and molecular (colony-stimulating factors) factors. Among them, microglia could represent the biological link to justify the reduced incidence of AD in RA patients due to their proactivated status leading to a better tissue clearance of

the Aβ amyloids. However, more extensive investigations are needed to prove this challenging hypothesis.

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