

Role of Liver in Alzheimer's Disease

Swatilekha Roy Sarkar¹, Rajib Dutta^{2*}

¹MDS, Consultant Orthodontist, India

²MD, Consultant Neurology, India

***Corresponding Author:** Rajib Dutta, MD, Consultant Neurology, India, Email: rajibdutta@163.com

Abstract: Dementia is a major problem presently of high-income countries and also an increasing concern of low-income nations worldwide. Alzheimer's disease (AD) is the most common progressive neurodegenerative dementing disorder. It is clinically characterized by a preclinical stage, followed by mild cognitive impairment (MCI) due to the progression of the disease into AD dementia. The earliest symptoms of AD include memory problems, disorientation in time and space, and difficulty with calculation, language, concentration and judgment. As the disease evolves, patients may develop severe behavioral abnormalities and may even become psychotic. In the late stages, the sufferers are incapable of self-care and become bed-bound, for years or even decades. It is characterized by the accumulation of amyloid β in the form of extracellular plaques and by intracellular neurofibrillary tangles. Genetic data, autopsy and neuroimaging studies in AD patients show A β plaque deposition precedes cortical tau pathology. Peripheral organs like liver, kidney play important roles in the clearance of brain-derived A β . In this review article we will discuss about the role of liver in pathogenesis of AD.

Keywords: Alzheimer's disease, liver function test, tau pathology, metabolic dysfunction.

1. INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease characterized by the accumulation of extra cellular amyloid β in the form of plaques and the intracellular accumulation of hyperphosphorylated tau proteins as neurofibrillary tangles (NFT), with progressive neuronal loss and cerebral atrophy [1]. The amyloid-cascade hypothesis introduced in 1991 provides an explanation of the pathogenesis of AD [2]. AD typically affects memory initially, but atypical presentations can occur, particularly in younger patients [3]. AD eventually progresses to involve diffuse cortical functions, lead into the inability to manage basic day to day activities. AD also causes a number of psychological and behavioral changes which can cause significant distress to patients, care givers and a big health care burden [4, 5]

Based on Alzheimer's Disease International Federation (ADI), at least 46.8 million people are affected by dementia worldwide, that anticipated to be 74.7 million by 2030 and 131.5 million by 2050 [6]. This disease can be categorized in two forms: early-onset familial Alzheimer disease (EFAD) [7] and Late-onset Alzheimer's disease (LOAD) or non-familial [8]. EFAD is

dominantly inherited but LOAD form is rather a complex or multi factorial disease [9]. The pathogenesis of AD is very complex, though genetic [10] and neuropathological [11], studies suggest that elevations of amyloid β play a central role. However, target interventions intended to prevent amyloid β accumulation did not demonstrate clinical efficacy in preventing or slowing the disease despite having biomarker evidence [12, 13]. Preclinical evidence from AD animal model and patient-derived human induced A β pluripotent stem cell model indicates that tau pathology can progress independent of accumulation of amyloid β , genetic risk factors and other aberrant metabolic pathways [14].

The foundation of amyloid hypothesis was the discovery of autosomal dominant mutations in three genes namely APP, PSEN1 and PSEN2 (the latter two encoding presenilin1 and 2, respectively), that cause pathogenic aggregation of A β peptides into neuritic plaques [15, 16]. Although mutations in APP, PSEN1 and PSEN2 do not occur in sporadic AD, similar neuropathological changes in A β and tau are observed in both familial and sporadic AD [17-20]. Researchers believe pathogenesis of AD includes other mechanisms like microgliosis,

immunoreactivity, oxidative stress and dysregulation of protein homeostasis [2, 21]

Role of liver as a peripheral organ in pathogenesis of AD is not much studied. Peripheral organs are responsible for the clearance of about 40 % of brain-derived A β in APP/PS1 mice [22]. Wang et al has reported previously that shifting the action site from the center to periphery might be safer for the clearance of brain A β as it may decrease the inflammatory process in the brain [23]. It is a well known fact that kidney participates in the peripheral clearance of brain-derived A β [24, 25]. Liver is also an important metabolic organ in periphery, and the role of liver in peripheral A β metabolism is being studied extensively now. Indirect evidences in the past has shown that cirrhosis patients had significantly higher plasma levels of A β and inflammatory factors as compared to healthy adults and plasma A β levels were positively correlated with the hepatic functions [26].

Liver is the main peripheral organ responsible for lipid metabolism. Increasing evidence suggests that abnormal lipid metabolism is associated with increased risk for AD [27]. It is reported that A β binds to ApoE and maybe chaperoned in transport with cholesterol from the brain as a means of toxin clearance [28]. Low-density lipoprotein (LDL) receptor-related protein 1 (LRP1) and its ligand, ApoE, are genetically associated with AD and plasma A β levels [29]. LRP1 is suggested to facilitate A β clearance from the brain across the blood-brain barrier (BBB) [30]. Moreover, it is demonstrated that enhancing the expression of LRP1 in liver aids in peripheral clearance of A β [31]. Insulin is suggested to facilitate the liver mediated peripheral clearance of A β by intracellular translocation of LRP1 to the plasma membrane in hepatocytes [32]. Once efflux from the brain, A β is transported to the liver by high-density lipoprotein (HDL) particles [33]. However there is no direct evidence regarding the role of liver in peripheral A β clearance. It is indicated that a large amount of A β in the blood binds to serum albumin [34].

Patients with Alzheimer disease (AD) display metabolic dysfunction [35]. Clinical studies suggest that impaired signaling, energy metabolism, inflammation, and insulin resistance play a role in AD [36,37]. Metabolic disorders (eg, diabetes, hypertension, obesity, and dyslipidemia) are risk factors for AD and contribute to cortical thinning [38]. Alanine

amino transferase (ALT) and Aspartate amino transferase (AST) are used in general clinical practice to measure liver injury [39, 40] and are factors associated with metabolic diseases [41] known risk factors of AD and cognitive decline [42]. Many researchers think amino transferases are surrogate biomarkers of liver metabolic functioning. Decreased levels of ALT and elevated AST: ALT ratio was observed in patients with AD with poor cognition and reduced brain glucose metabolism. Increased AST: ALT ratio was associated with lower CSF amyloid- β 1-42 levels, greater amyloid- β deposition, and higher CSF p-tau and t-tau levels. Furthermore, it was also observed that decreased levels of ALT were associated with greater amyloid- β deposition and structural atrophy [43]. Altered liver enzymes lead to disturbances in liver-associated metabolites including branched-chain amino acids, ether phosphatidylcholines, and lipids which are altered in AD and may play a role in disease pathophysiologic characteristics [44].

2. DISCUSSION

Disturbed energy metabolism is one of the processes that may explain the observed lower levels of ALT and increased enzyme ratio in individuals with AD and impaired cognition [37]. Brain glucose hypo metabolism is an early feature of AD and cognitive impairment during the prodromal stage [45]. ALT and AST are key enzymes in gluconeogenesis in the liver and production of neurotransmitters required in maintaining synapses [46]. Possible mechanisms may explain altered levels of enzymes in AD. First, reduced ALT levels lead to reduced pyruvate, which is required for glucose production via gluconeogenesis in the liver and glucose is distributed in various body tissues as an energy source [47], thus disturbing energy homeostasis. Second, altered levels of ALT and AST may affect levels of glutamate, an excitatory neurotransmitter of the central nervous system involved in synaptic transmission, which also plays an important role in memory [48].

In the case of low glucose metabolism in the brainless α -ketoglutarate is available via the tricarboxylic acid cycle that favors glutamate catabolism vs glutamate synthesis in reversible reaction (catalyzed by AST and ALT) [49]. Glutamate acts as a neurotransmitter in approximately two-thirds of the synapses in

neocortical and hippocampal pyramidal neurons and thus is involved in memory and cognition via long-term potentiation [50]. Plasma ALT and AST levels were significantly positively correlated with plasma glutamate levels [40]. In older adults, lower serum ALT levels are associated with mortality [51]. Alanine amino transferase decreases with age [52] and may be a sign of hepatic aging. Glutamate levels also decrease with increasing age [53]. Together with the fact that age is the strongest risk factor for AD [54], decreasing levels of ALT with age may also indicate a possible biological link between aging and AD.

Increased AST to ALT ratios are observed in individuals with nonalcoholic fatty liver disease, which is the hepatic manifestation of metabolic syndrome [55]. In the Framingham Heart Study, non-alcoholic fatty liver disease was associated with smaller total cerebral brain volume even after adjustment for multiple cardiovascular risk factors [56]. Liver dysfunction is also associated with the development of disease including cardiovascular disease and insulin resistance through disruptions in glucose and lipid metabolism [57, 58]. Increased alkaline phosphates levels in individuals with AD and an inverse association with cognition [59]. The neuronal form of alkaline phosphatase plays a role in developmental plasticity and activity-dependent cortical functions via contributing in γ -aminobutyric acid metabolism [60], however changes in plasma levels of alkaline phosphatase may occur as a result of central nervous system injury [61].

3. CONCLUSION

Liver plays an important role in peripheral metabolism of amyloid β causing efflux from brain to periphery. Altered liver function markers are associated with AD diagnosis and impaired memory and executive function as well as amyloid- β , tau, and neurodegenerative biomarkers of AD pathophysiological characteristics. The causal pathways are not clear yet. More studies are needed to understand the liver brain axis in longitudinal and model systems in future for complete understanding and gaining deeper knowledge of the pathways.

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