

# Brain Capillaries in Alzheimer's Disease

Perspective

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**Abbreviations:** AD: Alzheimer's disease; BBB: Blood Brain Barrier; EM: Electron microscopy; VaD: Vascular Dementia; VRFs: Vascular risk factors

## Introduction

Alzheimer's disease is the most common cause of irreversible dementia, responsible for two-thirds of all the cases approximately, affecting mostly the presenile and senile age, shaping a tragic profile in the epilogue of the life of the suffering people.

Due to the severity of the disease and the gradually increased frequency of the patient worldwide, associated presumably with the increased aging of the populations, an ongoing research activity is in climax nowadays [1], associated with many legal, social, ethical, humanitarian, philosophical and economic considerations [2].

The clinical manifestations of the disease include gradual memory loss, disorientation, decline of speech fluency, loss of professional skills, behavioral disturbances, personality and emotional changes, learning disability, various neurologic deficits which appear increasingly as the disease advances.

From the neuropathological point of view the disease is characterized by dendritic pathology, loss of synapses and dendritic spines, affecting mostly selective neuronal networks of critical importance for memory and cognition, such as the basal forebrain cholinergic system, the medial temporal regions, the hippocampus and many neocortical association areas [3]. Tau pathology consisted of intracellular accumulation of neurofibrillary tangles of hyperphosphorylated tau protein and accumulation of A $\beta$ -peptide's deposits, defined as neuritic plaques, are the principal neuropathological diagnostic criteria of the disease [4].

The neurotoxic properties of the oligomeric of the A $\beta$ -peptide and tau mediated neurodegeneration are among the main causative factors of impaired synaptic plasticity [5], neuronal loss [6], dendritic alterations [7], and tremendous synaptic loss [8]. The gradual degeneration of the organelles, particularly mitochondria, smooth endoplasmic reticulum and Golgi Apparatus [8], visualized clearly by electron microscopy, emphasizes the importance of the oxidative stress and amyloid toxicity in shaping the fine folds of the etiopathological background, which is plotted many years prior to phenomenological appearance of the disease.

The vascular factor may be an important component of the spectrum of the pathogenesis of AD. First, it is essential that

the concrete and sharp differentiation between AD and VaD has undergone critical reviews the last years, given that mixed findings at autopsy, plead in favor of a vascular component, concerning mostly large vessel, in AD pathology [9], and second, that vascular comorbidity may be present in a substantial number of patients suffered from AD [10,11], and furthermore VRFs, such as cardiovascular diseases [12], hyperhomocysteinemia, diabetes mellitus, obesity and hypertension may contribute in increasing the incidence of AD [13], particularly in advanced ages.

It is of substantial importance the concept that the structural alterations of the brain capillaries, may contribute in the pathology of AD [14], given that the disruption of the BBB [15] may induce exacerbation of AD pathology, by promoting inflammation around the blood capillaries and in the neuropile space diffusely. That phenomenon leads to the hypothesis that a primary vascular damage at the level of brain capillaries may increase the accumulation of A $\beta$ -peptide in the brain in AD [16]. Alternatively, the disruption of the BBB, which is the main physical protection system of the brain, consisted of the tight junctions of the endothelial cells of the blood capillaries [17] and supported by astrocytes and pericytes, may be initiated by the toxic effects of oligomeric A $\beta$ -peptide [18] or by the tau protein [19]. Tau protein may accumulate as puncta in perivascular spaces in sporadic AD [20] and tau alone can initiate breakdown of the BBB, which can recover integrity whenever tau levels are reduced [19]. Dysfunction of the brain capillaries may lead to A $\beta$ -peptide increased accumulation in the brain, since brain hypoxia and hypometabolism are among the modulators of cerebral amyloidogenesis [21].

Studies based on positron emission tomography have revealed regional metabolic decrease in patients suffered from MCI or possible AD [22], which correlates directly with the dementia's rate [23]. In addition, in experimental research, disruption of BBB and dysfunction of the endothelial cells was described in Slit-2 overexpressing transgenic mice [24].

The correlation between AD pathology and vascular

pathology, at the level of brain capillaries and BBB, raises the rational question, whether the efficient treatment of the vascular factor might be beneficial for the patients who suffer from AD [25,26]. It is reasonable that any protection of the brain capillaries at the initial stages of the disease might contribute in the abbreviation of the long chain of pathological alteration, which occur following the disruption of the BBB, which serves as the essential interface between the vascular system and the brain.

From the morphological point of view, silver impregnation techniques revealed a marked tortuosity of the capillaries in the hippocampus and the cerebral cortex in early cases of AD [14]. In addition, the distance between two branch points is longer in capillaries of AD brains, whereas the branch point density as well as the ratio of the branch point density to astrocytic density is substantially decreased in AD in comparison with age matched normal controls [14].

EM revealed, that the most frequent morphological alterations of the brain capillaries in AD consist of thickness, splitting and duplication of the basement membrane, reduction of the length of tight junctions, decrease of the number of tight junctions per vessel length, associated as a rule, with morphological alterations of the mitochondria of the endothelial cells, the pericytes and the perivascular astrocytic processes [14].

The number of the pinocytotic vesicles is substantially increase in the endothelium of the brain capillaries in AD in comparison with age matched normal controls [14]. Endothelial cells play a very important role in the transport systems in the brain, mediating the delivery of glucose and amino-acids to the brain and contributing in the clearance of toxic metabolic factors from the brain to blood [27]. Subsequently, the dysfunction of the endothelial cells and the disruption of the BBB may induce serious impairment in the transport system of the brain [28].

In a substantial number of cases of AD, degeneration of the pericytes is also observed emphasizing even more the importance of the vascular factor [14]. Pericytes share basement membrane with endothelial cells and come in contact with them cell to cell. In the capillaries of the CNS, the ratio between pericytes-to-endothelial cells is higher than in other parts of the body [29]. Pericytes may serve as integrators, coordinators and effectors of blood-brain barrier structure and maintenance, and play a key role in microvascular stability [30,31] capillary density and angiogenesis [32]. It is worth to underline that accelerated pericyte degeneration occur in AD APOE4 carriers [33], the major genetic risk factor of AD, who also may demonstrate vascular permeability changes prior to cognitive decline [34].

The dysfunction of the brain capillaries may result in releasing neurotoxic factors, such as thrombin [35], pro-inflammatory cytokines, nitric oxide and leukocyte adhesion molecules [36,37], and in abnormal regulation of A $\beta$ -peptide homeostasis in the brain, which contribute substantially in the further pathogenetic steps of AD. The impairment of the brain capillaries in structures of the brain, which are crucial for the homeostatic equilibrium of the body, such as the hypothalamic nuclei [38], may induce autonomic dysfunction, which usually occurs in the advanced stages of AD, affecting dramatically the

viability of the patients.

The association of the VRFs with AD, and the frequent pathology of brain capillaries inducing the disruption of the BBB in AD may plead in favor of a focused strategy, aiming at protecting the brain capillaries, avoiding oxidative stress and any alteration of the pericytes and over most protecting the mitochondria, which may be beneficial in the initial stages of AD.

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