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Review

The blood brain barrier in Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is the most common form of dementia, affecting millions of people worldwide. One of the prominent causative factors of AD pathogenesis is cerebral vascular dysfunction, which results in diminished cerebral perfusion. Moreover, due to the loss of the protective function of the blood-brain barrier (BBB), impaired clearance of excess neurotoxic amyloid beta (Aβ) occurs, causing vascular perturbation and diminished cognitive functioning. The relationship between the prevalence of AD and vascular risk factors is complex and not fully understood. In this review we illustrate the vascular risk factors, their effects on BBB function and their contributions to the onset of AD. Additionally, we discuss the underlying factors that may lead to altered neurovascular function and/or cerebral hypoperfusion in AD.

Contents

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia affecting millions of individuals worldwide. Moreover, it is an economically burdensome disease raising global concern on public health (World Alzheimer Report 2015). AD is a neurodegenerative disease characterized by declining episodic memory followed by long-term memory loss, personality and behavioral changes, eventually leading to overall cognitive decline [61]. AD is a multifactorial disease with no single cause known but several modifiable or non-modifiable risk factors such as age, female gender, family history, and vascular risk factors including hypertension, are associated with the development and progression of the disease [51].

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The likelihood of developing AD increases exponentially with age, approximately doubling every 5 years after [65] [100]. The epsilon four allele of the apolipoprotein E (APOE) gene is the strongest genetic risk factor for the development of late onset AD [101] [48]. Along with genetic risk factors, cerebrovascular risk factors also play a significant role in both the development as well as the progression of the disease [4] [43]. Beside genetic and cerebrovascular risk factors, environmental and lifestyle were also found to be partly responsible for disease cause and progression [25] [98]

Pathologically, AD causes significant structural and functional damage of the central nervous system (CNS). At a cellular level, AD is characterized by a progressive dysfunction and eventually loss of neurons, causing higher cognitive decline [85] [86]. Neuronal damage in AD is related to the deposition of extracellular amyloid β (Aβ) protein both within and outside of neurons as well as the presence of hyperphosphorylated tau (p-tau) or tangles. Accumulation of Aβ causes microglial and astrocytic activation as an inflammatory response towards plaque clearance [46], causing further damage of surrounding neurons and neurites. In addition, neurofibrillary tangles (NFT: aggregates of hyper-phosphorylated tau), which normally play a role in intracellular functioning, now inhibit normal axonal transport and eventually lead to neuronal death [86] [100]. Neuritic plaques and neurofibrillary tangles are commonly accompanied by Aβ deposition at the brain vasculature, a process also known as cerebral amyloid angiopathy (CAA) [71]. This aggregation can lead to brain dysfunction and additional Aβ accumulation in the parenchyma triggers cognitive decline, ultimately resulting in memory loss.

During life, the diagnosis is based on clinical criteria/symptoms. The diagnostic work-up usually includes medical history, physical and neurological testing, neuropsychological evaluation, and neuroimaging using magnetic resonance imaging (MRI) or computed tomography (CT). In addition, the novel diagnostic criteria support the use of biomarkers based on cerebrospinal fluid (CSF) [117] and amyloid positron emission tomography (PET) to attribute the clinical syndrome with a high/middle or low probability to underlying Alzheimer pathophysiology [74] [109]. One of the initial steps in understanding disease development is to unravel the critical events prior to neuronal death. The so-called 2-hit vascular hypothesis poses that Aβ is not the central niche but it is still clearly implicated in disease progression. The hypothesis describes a substantial relation between the vascular mediated pathology and neurodegeneration caused by Aβ. The key pathways include the breakdown of the BBB [106] [138] and cerebral hypoperfusion. Breakdown of the BBB can induce inflammation, which leads to increased secretion of angiogenic molecules [87], reduced amyloid clearance [120] [136] increased accumulation of Aβ, and the formation of pathological vessels, which are fenestrated and leaky [125]. Accumulating evidence suggests that changes in the peripheral and cerebral vasculature can cause altered blood flow into the brain thereby increasing the risk of developing AD [95] [103] [135]. Additionally, the coexistence of mixed vascular disorders with AD and occurrence of brain microvascular dysfunction and/or degeneration also strengthens the vascular hypothesis [21] [111]. The relationship between the prevalence of AD and vascular risk factors is complex and intricate and it is more than a pathological overlap, as was the previous notion. Therefore, this review explores this convoluted relationship by examining risk factors that affect the neurovasculature leading to altered endothelial activity and cerebral neo-angiogenesis in AD. In addition, this study also aims to identify platforms for early diagnostics and therapeutic interventions.

2. The blood-brain barrier

The vasculature of the brain comprises the blood-brain barrier (BBB), which is a protective barrier that maintains optimal neuronal functioning. The BBB is a cellular barrier that not only shields the CNS from the circulation by restraining the entry of neurotoxic compounds, but also dynamically regulates blood flow to meet the neuronal demands [1]. Specialized endothelial cells, line the wall of the brain capillaries and create a basic cellular barricade by expressing adherence junction and tight junction proteins that limit paracellular flow of water, ions, and large molecules into the brain [115]. Pericytes envelop the brain endothelial cells at irregular intervals on the abluminal side and contribute to the function of the barrier properties of the BBB [8] [20] [119]. The brain endothelial cells and pericytes are ensheathed by the basal lamina and are further supported by astrocytes, which wrap their end feet around the brain capillaries [2]. Together, these different cell types closely interact with each other and create a highly dynamic BBB, therefore also termed the neurovascular unit (NVU) [1] [44].

The BBB not only provides a stable and optimal environment for neuronal functioning by separating the blood from the brain but also by expressing a series of specific transporters and ion channels that maintain the ion balance for proper functioning of the synapses. Proper performance of the BBB is critical to maintain brain homeostasis and failure to do so may lead to neurological disorders [105]. Imaging studies have revealed a dysfunctional BBB at multiple levels in AD [33]. Using MRI in a subpopulation of AD patients, so-called microbleeds can be observed, which is indicative for damaged cerebral vasculature [37] [65]. In addition, functional studies using PET demonstrated reduced function of the brain endothelial efflux transporter P-glycoprotein in AD patients [126] which is thought to be involved in amyloid clearance from the brain [130]. Moreover, post-mortem studies also showed the disruption of ATP-binding cassette (ABC) transporters [19] and an altered tight junction expression at the BBB [18]. These results, together with other BBB alterations such as vasospasm, failed auto-regulation of cerebral blood flow and increased coagulation [114], show a dysregulation of the BBB in AD. However, although cerebrovascular diseases and a dysfunctional BBB can exist together, it is still unclear what is the cause or consequence [76] [128] [138].

3. Vascular risk factors affecting blood-brain barrier function

The disruption of the BBB is an important cause of further cellular damage in many neurological diseases [88]. In this section, we will discuss vascular risk factors that affect BBB integrity and are a predisposition for developing AD .

3.1. Atherosclerosis

The occurrence of atherosclerosis increases the risk of AD and other types of dementia. Atherosclerosis in carotid arteries, especially plaques in the intimal medial thickness region of the carotid artery is linked to accelerated cognitive decline [129]. In addition, high plasma cholesterol levels may also induce the production of Aβ by hippocampal neurons, which may lead to neurodegeneration [36]. Vice versa, Aβ may change cholesterol metabolism thereby enhancing the risk of neurodegeneration and AD [70]. Atherosclerotic changes in the blood vessels of the heart, peripheral, and cerebral arteries cause ischemic damage thereby introducing a series of events, including ionic imbalances, oxidative stress, and inflammation. These events may lead to increased BBB permeability and degeneration [108] (which further affects the development of dementia, as seen in the Leiden 85 plus study, a unique cohort of old people followed for survival and cause of death [121]. To surmise, the cerebrovasculatur dysfunction can lead to impaired oxygen and nutrients delivery in brain predisposing it to neuronal death, or the neurodegeneration in certain brain regions leads to deregulation in cerebrovasculatur function [66], although which one is the initial event it's still a question of debate.

3.2. Hypoxia / Ischemia

Atherosclerotic plaques are also considered a prime factor for the development of ischemic stroke in many sporadic AD patients [104]. Vice versa, a strong association between the occurrence of a stroke and the