Journal of the Neurological Sciences 323 (2012) 25–32

Contents lists available at SciVerse ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Vascular factors and epigenetic modifications in the pathogenesis of Alzheimer's disease

Jerzy Leszek [a], Marta Sochocka [b,*], Kazimierz Gąsiorowski [c]

[a] Wroclaw Medical University, Department of Psychiatry, 10 Pasteur Str., 50-367 Wroclaw, Poland
[b] Laboratory of Virology, Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, 12 R. Weigla Str., 53-114 Wroclaw, Poland
[c] Wroclaw Medical University, Department of Basic Medical Sciences, Faculty of Pharmacy, 14 Kochanowskiego Str., 51-601 Wroclaw, Poland

ARTICLE INFO

Article history:
Received 11 January 2012
Received in revised form 4 September 2012
Accepted 10 September 2012
Available online 29 September 2012

Keywords:
Vascular factors
Oxidative stress
Free radicals
Brain hypoperfusion
Cerebral ischemia
Epigenetic modifications

ABSTRACT

Alzheimer's disease (AD) is a debilitating illness with no known cure. Nowadays accumulating evidence suggested that the vascular endothelium and chronic hypoperfusion may play important role in pathobiology of AD. The vascular endothelium which regulates the passage of macromolecules and circulating cells from blood to tissue, is a major target of oxidative stress, playing a critical role in the pathophysiology of vascular diseases. Since the vascular endothelium, neurons and glia are all able to synthesize, store and release reactive oxygen species (ROS) and vascular active substances in response to certain stimuli, their contribution to the pathophysiology of AD can be very important. New evidence indicates that continuous formation of free ROS induces cellular damage and decreases antioxidant defenses. Specifically, oxidative stress increases vascular endothelial permeability and promotes leukocyte adhesion. We summarize the reports that sporadic, late-onset of AD results from vascular etiology. Recently an involvement of epigenetic alterations in the etiology of AD is also intensively investigated. Gaining a more complete understanding of the essential components and underlying mechanisms involved in epigenetic regulation could lead to novel treatments for a number of neurological and psychiatric conditions.

Contents

1. Introduction

1.1. Epidemiological findings

On November 3, 1906 Alois Alzheimer presented to the Meeting of the Psychiatrics the neuropathological and clinical features of Auguste D., who had died of a senility illness at age of 55. The disease was given his eponym by his senior colleague E. Kraepelin. The description initiated the slow separation between Alzheimer's disease (AD) and other causes of presenile dementia [1]. AD is a complex, slowly progressive neurodegenerative disorder of the brain and is the most common form of dementia. Nowadays a century of clinic-pathological, biochemical, molecular, and pharmacological studies have carried out on AD, the disease continues to affect millions of people all over the world.

* Corresponding author. Tel.: +48 71 370 99 24; fax: +48 71 337 21 71.
E-mail address: mars@iitd.pan.wroc.pl (M. Sochocka).

0022-510X/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jns.2012.09.010

Alzheimer's disease (AD) is the most frequent cause of dementia (50–70%), followed by vascular dementia (30–40%), and mixed dementia (15–20%). These prevalent forms of age-related neurodegeneration represent a major problem of health in developed countries with more than 25 million people affected and probably more than 75 million people at risk during the next 20–25 years worldwide [2]. Progressive cognitive decline is often accompanied by affective, behavioral disturbances, also termed neuropsychiatric symptoms [3]. In AD, depression and apathy are the most common at the mild stage; agitation, aggressiveness, delusions and hallucinations are commonly associated with the moderate stage; patients with severe AD often exhibit agitation, anxiety, abnormal motor behavior and day–night reversal. The duration of the clinically silent stage may be longer than 10 years [1].

In former times, AD was regarded as a rare pre-senile disorder. At present, AD shows an increase in incidence and prevalence with increasing age [4]. The annual treatment costs of AD in the USA are estimated at about more than 200 billion dollars [5]. The costs increase with the severity of the disease, from approximately 18,500 dollars per patient with mild AD per year to more than 36,000 per patient with severe AD per year.

2. Current brief discussion of different pathogenic hypotheses for AD

Several factors have been implicated in the pathogenesis of AD. However, up to now, there is no definite conclusion addressing the principal pathogenic agents [6]. Mutations in the amyloid precursor protein (APP) that lead to increased production of amyloid beta peptide (Aβ) are associated with the early-onset, familial forms of AD.

AD is regarded as a disorder of neural input modulation caused by degeneration of four modulatory amine transmitter (MAT) systems, namely the serotoninergic, the noradrenergic, the histaminergic, and the cholinergic. MATs modulate cognitive processing including arousal, attention, and synaptic plasticity in learning and memory. Presumably, the MAT receptor (or a group of receptors) initiates a pathogenic cascade in the AD brain. Neurotoxicity of Aβ peptides, derived from APP cleavage through such a way, includes disturbance in calcium homeostasis. Chronic over-excitation in brain metabolism is conceived to result in Ca-dependent cellular excitoxicity. Aβ-induced dysregulation results in reactive oxygen species production. However, main role is played by the endogenous ion transport through Ca^{++}, K^{+}, and activity of ATPase Na^{+}/K^{+} [7].

Neuronal losses occurring in the normal aging and AD-associated neurodegenerative processes are, ostensibly, the result of classical caspase-dependent apoptosis (programmed cell death-PCD). Apoptosis-inducing factor (AIF) is a mitochondrial oxidoreductase originally identified for its role in caspase-independent PCD. In the study of AIF levels in frontal and temporal cortices of normal subjects of various ages and in subjects with AD, it was shown that all three AIF isoforms increased significantly with age in both cortical areas. AIF expression levels in the cortex (but not hippocampus) were lower in AD compared to age-matched controls. This is consistent with the role of AIF as a free radical scavenger representing an adaptive cellular response to compensate for the steady increase in oxidative stress occurring with age [8,9].

The cell cycle hypothesis for the pathogenesis of AD focuses on the suggestion that neurons in the adult nervous system are able to re-enter the cell division cycle (from G0 to G1) before the G1/S transmission point. In AD the G1/S control mechanisms fail. Neurons can replicate their DNA and progress into the late G2 phase of the cycle. Cellular mechanisms activated in the G2 phase of the cycle drive the formation of neurofibrillary tangles and amyloid plaques in apoptosis incompetent neurons. Some findings also imply that the AD-related G1S regulatory failure is probably due to genomic variation of cyclins, cyclin-dependent kinases and respective inhibitors (CDKIs) involved in the regulation of the G1S transition [10]. Such a "re-entry" phenotype results in cytoskeletal changes as protein tau phosphorylation, alterations in mitochondrial activity and DNA replication. Recently, an interesting the two-hit hypothesis was described, which implicate that both oxidative stress and aberrant stimuli can independently initiate disease pathogenesis and progression. It is suggested that amyloidβ protein precursor (APP) and presenilins share a common function in cell cycle control, which may be key to this hypothesis since neurons bearing these mutations may enter a mitotic steady state, depleting their compensatory potential, which renders them more vulnerable to additional insults [11].

3. Stroke and Alzheimer's disease

According to literature 64% of persons with stroke have some degree of cognitive impairment and up to a third have dementia [12]. It is worth to mention that strokes damage areas exhibit pathological precursors of Alzheimer's [13]. Another similarity between stroke and AD is inflammation, a dominant force in neurodegenerative properties of stroke and AD. The interaction between small strokes and AD during "brain at risk stage" (preceding clinical stroke and dementia) may suggest targets for therapy. Now a growing body of evidence suggests that, far from being diseases that develop independently of each other, stroke and AD can overlap and speed up sings of dementia [14,15].

Recent studies have shown that a history of stroke can increase AD prevalence by about 2-fold among elderly patients [16]. The risk is highest when stroke is concomitant with atherosclerotic vascular risk factors [17,18]. Patients with stroke or cerebral infarction also show a diminished cognitive performance and greater severity of clinical dementia [19–21]. It has been hypothesized that there may be a synergism between AD and stroke pathogenic mechanisms [22–24]. Death of brain cells due to stroke or head injury could increase levels of amyloid beta protein. Expression of APP is increased following of cerebral ischemia [25]. Increased APP levels provide increased substrates for the formation of neurotoxic Aβ via beta and gamma secretase cleavage. In fact, Aβ production has been shown to increase following both mild and severe ischemia [26]. Cerebral ischemia and amyloid may synergize to produce AD and vascular changes in the brain. Furthermore, an angiogenesis hypothesis has been proposed, which links the two pathophysiological processes [27,28]. However, in a recently published neuropathological study, cerebral infarctions were shown to independently contribute to the likelihood of dementia but did not interact with AD pathology to increase the likelihood of dementia beyond their additive effect [29]. Knowledge of how stroke can progress to AD should provide a better understanding of the physiopathology characteristics of AD and also develop more precise targeted therapies in preventing, controlling or reversing this dementia.

4. Vascular risk factors and Alzheimer's disease

Accumulating evidence from epidemiological and clinical studies suggests that vascular risk factors may be involved in the pathogenesis of Alzheimer's disease [30–43]. Quantification of atherosclerotic lesions in the circle of Willis and large leptomeningeal vessels revealed a correlation with clinical diagnosis for Alzheimer's disease and neuropathology [44–46]. Sadowski et al. hypothesized that AD pathology is the complex end result of a slowly-evolving vascular disease and parenchymal lesions [47]. At present, four risk factors (diabetes, hypertension, heart disease, and current smoking) are associated with a higher risk of AD [48–53]. Although the precise contribution of vascular disturbances to the pathogenesis of AD is still unclear, various biochemical and neuropathological data strengthen the view that cerebrovascular deficiencies such as reduced blood supply to the brain and disrupted microvascular integrity in brain parenchyma play a direct or intermediate role in the chain of events ending with dementia syndrome. In this aspect, vascular endothelium, neurons and glia are very important because they are able to synthesize, store and release reactive oxygen species (ROS) and vasoactive substances in response to certain stimuli, especially those by chronic hypoxia/hypoperfusion [54–57]. According to the two-hit vascular hypothesis of AD, vascular hit factors (hit one)