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Review article

The impact of obesity on neurodegenerative diseases

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ABSTRACT

Neurodegenerative diseases are a growing health concern. The increasing incidences of these disorders have a great impact on the patients' quality of life. Although the mechanisms of neurodegenerative diseases are still far from being clarified, several studies look for new discoveries about their pathophysiology and prevention. Furthermore, evidence has shown a strong correlation between obesity and the development of Alzheimer's disease (AD) and Parkinson's disease (PD). Metabolic changes caused by overweight are related to damage to the central nervous system (CNS), which can lead to neural death, either by apoptosis or cell necrosis, as well as alter the synaptic plasticity of the neuron. This review aims to show the association between neurodegenerative diseases, focusing on AD and PD, and metabolic alterations.

Contents

1. Introduction

Besides being associated with comorbidities, recent studies have shown that obesity is also closely linked to the increase of neurodegenerative diseases [1,2]. The prevalence of obesity has increased globally in a worrisome way, and ranks as the fifth leading cause of death worldwide [3,4].

With the increase in life expectancy, the incidence of neurodegenerative diseases is expected to grow, as age is a determining risk factor for these diseases [5,6]. Specifically, Alzheimer's disease (AD) and Parkinson's disease (PD) are related to metabolic changes and obesity [1,7]. Knowing the risk factors for AD and DP, the most common types of neurodegenerative diseases, may help prevent and treat them [8,9].

Overweight and obesity are characterized as risk factors for the development of AD and PD, because obese patients are at risk for developing type 2 diabetes mellitus (DM2), which is also closely related to neurodegenerative diseases [10,11]. Another explanation for this fact is that there is a relationship between obesity and insulin resistance, which plays a fundamental role in developing dementia [8]. Elevated

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levels of proinflammatory cytokines increase inflammation, which, in turn, causes a cognitive deficit [6,11].

2. Methodology

This is a review study. We carried out a bibliographic searching in the databases of the Virtual Health Library (LILACS, MEDLINE, SciELO) and PUBMED, from March through October 2016. Articles published between 1998 and 2016 were included in the review. The descriptors used were the following: obesity, neurodegenerative diseases, Alzheimer's disease, and Parkinson's disease.

3. Obesity

Obesity has become a serious public health problem worldwide, and its prevalence in increasing both in developed and developing countries [12–14]. Obesity has a multifactorial origin and is associated with the development of other comorbidities, such as hypertension, dyslipidemia, DM2, coronary artery disease, cerebrovascular accident, respiratory disorders, some types of cancer, as well as depression and poor quality of life [4,15].

The etiology of obesity encompasses the positive energy imbalance, that is, when the daily ingested calories surpass the caloric burn, there is excessive storage of triacylglycerol in cells that form the adipose tissue, termed adipocytes [16,17]. The finding that obesity and metabolic disorder are associated with chronic low-grade inflammation has fundamentally changed the view of the underlying causes and progression of obesity, and metabolic syndrome. It is now known that an inflammatory response is activated early in the adipose expansion and during chronic obesity, permanently diverting the immune system to a proinflammatory phenotype, and thus begins to delineate the reciprocal influence of obesity and inflammation [18].

The increase in dietary intake is associated with the increase in reactive oxygen species (ROS) and the activity reduction of antioxidant enzymes, inducing increased oxidative stress, which plays an important role in obesity-related metabolic alterations [19,20]. Mitochondria, one of the main generators of ROS and free radicals, play a central role in energy homeostasis through the production of adenosine triphosphate (ATP) from dietary substrates (carbohydrates, fats and proteins) [21]. Because of the dysfunction in the ATP production, the cells may not perform their functions adequately, thereby, establishing a correlation between obesity and cognitive impairment [20].

Obesity can be characterized as a condition that affects cognition through different mechanisms [22]. Although the effects are initially observed in peripheral systems and organs, excessive nutrition can cause abnormalities in the hypothalamus [23,24], through insensitivity to insulin and leptin hormones, which are involved in the regulation of energy balance [25,26], as well as atrophy in the hippocampus [27], and damage in the cerebral frontal cortex [28].

4. Neurodegeneration

Neurodegenerative diseases are multifactorial debilitating disorders, consisting of an interaction between environmental factors and genetic predisposition [29]. A clear classification of neurodegeneration may be based on the presence of abnormal protein components that accumulate in the brain, leading to neuronal loss [30]. Dementia is characterized as a major cause of cognitive function impairment [31], and AD and PD are the most common neurodegenerative disorders, as described below.

5. Alzheimer's disease

AD was first described in 1906 by a German neuropathologist named Alois Alzheimer. In his first report, Alzheimer observed behavioral changes, delusions and memory loss, among other cognitive deficits [32]. It is a progressive and fatal neurodegenerative alteration, causing loss of intellectual functions [33].

AD is the most common cause of dementia (60–70% of cases), and numbers are increasingly alarming [34]. Epidemiological data have reported nearly 44 million patients diagnosed with AD or a related dementia [35]. The global cost is estimated at US$ 605 billion [35]. It is estimated that the total number of people with dementia will be almost 75.6 million by 2030, tripling to 135.5 million by 2050 [34].

The disease is defined as a chronic neurodegenerative disorder, characterized by the pathological accumulation of beta-amyloid peptides (Aβ) and the presence of the TAU protein. Aβ peptides are natural products of metabolism, and in patients with AD, they are in an abnormal state, with accumulation and deposition of these peptides in amyloid plaques [36]. Another protein associated with AD is TAU, which is hyperphosphorylated in the disease and gives rise to paired helical filaments that integrate neurofibrillary tangles [37].

Although the Aβ and TAU proteins play an important role in the development of AD, other neurodegenerative mechanisms have been proposed and are associated with the disease [38], such as genetic and environmental causes, mitochondrial dysfunction, oxidative damage, proinflammatory responses, energy metabolism failures, and dysfunctions in various neurotransmission systems [39–41]. These factors may interact in a vicious circle, involving inflammatory response, oxidative stress, and increased toxicity, through the release of proinflammatory cytokines and a decrease in the activity of anti-inflammatory cytokines, which leads to neuronal dysfunction and finally to cell death (Fig. 1) [41].

Genetic causes are strongly associated with the disease, and some genes are considered the main risk factors for the development of AD, including the following: amyloid precursor protein (APP), presenilin 1 (PSEN1), presenilin 2 (PSEN2), and apolipoprotein E (ApoE) [42,43]. The apoE gene is the most susceptible to developing late-onset AD [44].

There is a deficiency in the processes of energy generation at the mitochondria level in AD, strictly associated to a deficiency of complex I of the mitochondrial respiratory chain, and a lipid metabolism dysregulation. Since mitochondria are responsible for producing about 90% of ATP in the cellular respiration, mitochondrial dysfunction characterizes the reduction of ATP synthesis and ROS generation, which are the basis for oxidative stress [45].

Oxidative stress has been identified as one of the major factors in the AD pathogenesis, and contributes to the Aβ formation, which is known as the disease triggering mechanism [46]. Studies have reported that the interaction between oxidative stress and neuroinflammation leads to Aβ formation [47,48].

Many cytokines have been implicated in the AD pathophysiology and in the immune reaction involving proinflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [49], which contribute to the disease progression [50]. In addition to the increase in proinflammatory cytokines, there is a decrease in the activity of anti-inflammatory cytokines, such as interleukin-4 (IL-4), interleukin-10 (IL-10) and interleukin-13 (IL-13) [51], which serve to reduce inflammation [52].

Among the neurotransmission systems, the progressive loss of cholinergic neurons is also part of the disease pathophysiology, which leads to the appearance of behavioral problems, and changes in memory and learning [53]. Studies suggest that a cholinergic dysfunction in AD is a result of decreased acetylcholine release (the main neurotransmitter of the cholinergic system), as well as alterations in both the amount of muscarinic receptors in various brain regions and intracellular signaling induced by these receptors [54].

AD is characterized by hippocampus and cerebral cortex atrophy, with primary involvement of the fronto-temporal association cortex [38]. According to recent proposals, three clinical phases of pre-symptomatic AD may be defined as follows: (I) presymptomatic stage, which may last for several years or decades until excess production and accumulation of Aβ in the brain reaches a critical level that triggers