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Periodontal disease's contribution to Alzheimer's disease progression in Down syndrome

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Abstract People with Down syndrome (DS) are at an increased risk for Alzheimer's disease (AD). After 60 years of age, >50% of DS subjects acquire dementia. Nevertheless, the age of onset is highly variable possibly because of both genetic and environmental factors. Genetics cannot be modified, but environmental risk factors present a potentially relevant intervention for DS persons at risk for AD. Among them, inflammation, important in AD of DS type, is potential target. Consistent with this hypothesis, chronic peripheral inflammation and infections may contribute to AD pathogenesis in DS. People with DS have an aggressive form of periodontitis characterized by rapid progression, significant bacterial and inflammatory burden, and an onset as early as 6 years of age. This review offers a hypothetical mechanistic link between periodontitis and AD in the DS population. Because periodontitis is a treatable condition, it may be a readily modifiable risk factor for AD.

Keywords: Down syndrome; Alzheimer's disease; Infection; Inflammation; Dysbiosis; Periodontal disease; Aggressive periodontal disease; Neuroinflammation; Trisomy 21

1. Introduction

Down syndrome (DS) is the most common genetic cause of intellectual disability, and it occurs in approximately 1 to 800 births. The prevalence of DS has increased lately because of increased incidence and longer life expectancy giving rise to an elderly population with DS that is at risk for age-related comorbidities such as Alzheimer's disease (AD). More than 50% of DS subjects acquire dementia after the age of 60. However, the age of dementia onset is highly variable with both genetic and environmental factors contributing to this variability. Thus, modifiable environmental risk factors present a potentially relevant intervention for DS persons at risk for AD. Among them, inflammation is a potential target.

The purpose of this review is to explore the relationship between inflammation, DS, and dementia using knowledge gained from the study of sporadic and familial AD. It has been increasingly recognized that peripheral chronic inflammation and infections through their inflammatory and

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bacterial burden are involved in the pathogenesis of AD [1]. Evidence also exists linking brain inflammation to the AD pathology of DS subjects. However, it remains unknown whether inflammation is downstream of core AD pathology or is even an upstream phenomenon. DS patients are known to have multiple comorbidities throughout their life. They also have an aggressive form of periodontitis characterized by rapid progression, significant bacterial/inflammatory burden, and an onset as early as 6 years of age. This review offers a rationale for examining periodontitis in DS as a possible mechanism contributing to the high risk for AD pathology.

2. Alzheimer's disease

AD is one of the leading causes of dementia afflicting the elderly. The prevalence and incidence of AD increase with age. Eleven percent of people older than 65 and 33% of those >85 have AD.

2.1. Pathological features of AD

AD is a continuous process whose pathology starts years before the onset of dementia. The pathological hallmarks of AD are the presence of senile plaques, neurofibrillary tangles, neuronal and synaptic dysfunction, and neuronal loss. The senile plaques contain extracellular aggregates of amyloid-β (Aβ) peptide and activated glial cells, and reactive astrocytes and inflammatory molecules associate intimately with these plaques. Neurofibrillary tangles comprised phosphorylated tau proteins, and the neuronal loss leads to brain atrophy.

3. Alzheimer's disease in DS

People with DS are at significant risk of developing AD. In fact, according to the new International Working Group Criteria, DS is conceptualized as a form of preclinical AD [2]. Up to 28% of 30-year-old DS subjects develop cognitive impairments but no dementia [3]. After 30, 40, and 60 years of age, increasingly more DS people are diagnosed with dementia reaching prevalence rates of 30%, 55%, and 77%, respectively [3,4].

3.1. Pathological features in DS

The pathological hallmarks of AD, amyloid plaques, and tangles accumulate in the brain of subjects with DS several decades earlier than in the general population with sporadic AD. The earliest amyloid depositions are thought to be diffuse, nonfibrillar, and amorphous plaques, followed by the development of the fibrillar plaques. A review of AD histopathological studies [5] in 398 DS subjects revealed that subjects younger than 10 years old lacked AD plaques and tangles. Then, in teens and in the 20–30 age range, AD pathology affected approximately 7.5% and 16% of brains, respectively. By age 40s, virtually all subjects had AD pathology. The regional distribution of the plaques and tangles in DS subjects resembled that of late-onset sporadic AD [5] although patterns resembling distribution of early-onset AD have also been described.

4. Pathogenesis of Alzheimer's disease

4.1. Role of inflammation

Inflammation is thought to play a significant role [6]. Its role can be primary [7], secondary, or a combination of both. For example, Kristic and Knuesel [7] showed that acute and chronic inflammation were able to induce AD-related pathology and cognitive decline in animal models. In this respect, in a thiamine-deficient model in which chronic inflammation and oxidative stress were early events, there was increased synthesis of Aβ and amyloid plaques [8], and antioxidants reversed the increased production of Aβ. Multiple reviews and animal studies support the concept that pro-inflammatory cytokines and lipopolysaccharide (LPS) are stimulators of Aβ production and tau phosphorylation, and Aβ and tau protein can induce increases in cytokine. However, other studies showed that inflammation could be induced secondarily by the core AD pathological processes related to Aβ cascade or tau-related neurodegeneration.

4.2. Clinical studies

Three lines of clinical evidence support the role of inflammation in AD: increased systemic inflammation, genetic data, and the presence of infectious/inflammatory peripheral conditions. Pro-inflammatory molecules including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor-necrosis factor-β (TNF-β) were associated with and predicted poor cognition, cognitive decline, and dementia 2–25 years later. However, other studies failed to show these cytokines as predictors of cognitive decline. This discrepancy may be explained by the heterogeneous inflammatory responses dependent on timing and individual differences in inflammatory genotypes. For example, we have shown lower cognition in subjects with periodontal inflammation than without [9]. However, among those with periodontal inflammation, cognitive losses were greater in those having IL-1082 AA/AG genotype [10]. Because subjects with IL-10-1082 AA/AG genotype produce less IL-10, an anti-inflammatory cytokine, IL-10-1082 AA/AG genotype qualifies for a pro-inflammatory phenotype. We also found that combination of the plasma TNF-α with antibodies to specific periodontal bacteria (index of bacteria exposure and host response) increased the discriminatory accuracy between normal (NL) and AD subjects [11]. These findings consistent with Holmes [12] show that a) peripheral infectious/inflammations are important in the pathogenesis of AD, and b) perhaps, it is the combination between both peripheral infections/inflammations and the magnitude of the host response, that is critical in understanding the pathophysiology of AD.