A closer look into down syndrome: Unlocking the mystery of alzheimer’s disease

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Abstract

Down syndrome and Alzheimer’s disease share the same neuropathological hallmarks. Down syndrome individuals have an extra whole or part of chromosome 21. Exploring the molecular and cellular events governed by the genes on chromosome 21 gives the opportunity to find avenues for prevention or cure of Alzheimer’s disease in both Down syndrome and the general population.

Introduction

Alzheimer’s disease (AD), the most common type of dementia, was first defined by Alois Alzheimer, a German psychiatrist, and neuropathologist in 1906 [1]. The worldwide prevalence of dementia is fifty million, and this number is expected to reach 75 million in 2030 if no cure is found [2]. Furthermore, it is the second leading cause of death in Australia [3]. To date, the challenge of finding a cure for Alzheimer’s disease continues a century after its discovery following the failure of clinical trials.

AD begins with changes in neuropathology in the hippocampus and as the disease progresses, spread to the cortex. Short term memory loss is one of the earliest signs, followed by long-term memory loss, confusion and mood swings. The later signs include anterograde amnesia, depression, irritability, language problems and memory retrieval deficits in explicit memory. Ultimately, patients are severely demented, lose ambulation and are reduced to a behavioural repertoire consisting of a few basic reflexes [4,5].

One avenue in searching for a cure is the connection between Down syndrome (DS) and AD. All Down syndrome individuals develop the neuropathology of AD at an early age but not all develop the clinical symptoms [6]; and the factors involved are not known. DS and AD share the same neuropathology. By the age of 40, DS individuals have developed neuropathology akin to AD [7], which includes β-amyloid (Aβ) plaques, tau-containing neurofibrillary tangles (NFT) [8], inflammation [9], basal forebrain cholinergic neuron (BFCN) degeneration [10], microglial degeneration [11], oxidative damage [12] and the presence of enlarged early endosomes [13].

Down syndrome is full or partial trisomy of chromosome 21 (Homo sapiens autosome 21 (HSA21)), and is the most common intellectual disability with prevalence of 1 in 700 live births [14]. It was first described by Dr John Langdon Haydon Down in 1862 [15] who had a grandson with DS. In 1959, DS was classified as a chromosomal abnormality by Jerome Lejeune, a French doctor who detected 47 chromosomes instead of the normal 46 chromosomes in each cell [16]. More than 95% of DS individuals have an extra whole chromosome 21 which is the result of non-disjunction at maternal meiosis [17], and the risk of having a DS child due to this non-disjunction at meiosis rises with the maternal age [18]. Chromosome 21 is the shortest human autosome and contains 1-1.5% of the human genome [19]. There are a vast number of characteristics associated with the extra dosage of genes in people with DS [20] such as abnormal craniofacial morphogenesis, deficits in learning and memory, degeneration of basal forebrain cholinergic neurons, premature aging, Alzheimer’s disease neuropathology, decreased hippocampal and cerebellar volume, slow growth and development, haematological and immunological disorders and male sterility [21].

People with DS have a much lighter brain compared with people in the general population. The adult DS brain typically weighs about 1000g verses about 1350g in the non-DS population [22]. The DS brain has a smaller cerebellum, hippocampus, and frontal and temporal cortices [23,24]. Although at birth, DS individuals have brains with normal anatomy and morphology, during infancy the brain starts to fail normal development [25]. During the first year of life, the dendrites stop growing; as DS individuals age, the length and thickness of dendritic spines are reduced [25]. The neurons show signs of atrophy, and microglia and astrocytes are more prominent, and there is delayed myelination of oligodendroglocytes [26]. In addition, there is an imbalance of cellular density within the grey matter [27]. In a recently published longitudinal study by Pujol and colleagues (2018), it was shown that the changes in DS brain volume was consistent with well-known anatomical changes in Alzheimer’s disease including the cortical thinning at the early stages [28] and during clinical progression [29] of Alzheimer’s disease. Pujol, et al. [30] also stated that their results exhibited DS hippocampal volume degeneration similar to the AD brain.

It has been suggested that endosomal defects in the brains of both DS and AD may contribute to pathological processes. Furthermore,
enlarged early endosomes, the initial neuropathological alteration known in the sporadic AD, were not observed in healthy aging brains [13]. Early endosomes were distinctly enlarged in DS neurons as early as 28 weeks of gestation [13] and in Ts65Dn, a mouse model of DS [31]. Through endocytosis, neurons achieve the rapid vesicle recycling necessary for maintaining neurotransmission, but endocytosis is also the process used by neurons and other cell types to take up macromolecules from the extracellular environment. Indeed, early endosomes are the sites of internalisation of APP and apolipoprotein E, as well as the site of Aβ peptide generation and is believed that all contribute to the development of the AD [32]. Moreover, defective neuronal growth factor signalling due to disturbances in endocytosis could be an early event in the manifestation of the AD [33] which can lead to the formation of amyloid plaques, hyperphosphorylated tau and NFTs and BFCN degeneration [34]. As mentioned, in DS, enlarged endosomes are present as early as 28 weeks of pregnancy in neurons [13], which leads to diffuse Aβ plaque deposition apparent at around 12 years of age, and is followed by mature Aβ plaques when the DS individuals are in their 30's [35].

Conti, et al. [36] demonstrated that mitochondrial gene expressions are altered in the DS. Interestingly, both AD and DS share mitochondrial dysfunction [37,38]. It has been shown that mitochondrial dysfunction facilitates or initiates molecular cascades of AD-like pathology [39]. In DS, mitochondrial dysfunction may also contribute to increased levels of oxidative stress leading to AD-neuropathology. Mitochondria are crucial for the regulation of reactive oxygen species (ROS) levels and the production of ATP in neurons [40]. Embryonic DS neurons have reduced levels of mitochondrial activity [38], and DS foetal tissue has decreased mitochondrial DNA (mtDNA) content [41]. Oxidative stress is a well-known cause of the mitochondrial apoptotic pathway [42] and DS foetal neurons display features associated with initiation of the mitochondrial death pathway [43]. Simón, et al. [44] using a mouse model of APP overexpression showed that mitochondrial dysfunction is a result of APP overexpression although there was no sign of plaques in their brain. Indeed, Amyloid Precursor Protein (APP) gene that located on chromosome 21 is required for the manifestation of the AD [45], but not all the DS individual with APP exhibit the clinical symptoms [6]. This evidence demonstrates that there are other genes/factors involved.

Oxidative damage is a common pathway in manifestation of AD in DS and the general population. It is caused by overexpression of APP [46] and Superoxide dismutase-1 (SOD-1) [47,48] in DS. SOD-1 is also located on chromosome 21 and over-expressed in DS. The SOD-1 over-expression increases the ratio of SOD-1 to catalase and Glutathione Peroxidase (GPs) leading to higher production of hydrogen peroxide (H₂O₂) and inducing oxidative stress [47,48]. Studies have shown that in addition to SOD-1 and APP, other genes located to chromosome 21, such as S100β [49,50], and Ets-2 [51] contribute to premature neuronal death and the development of AD.

Oxidative damage also includes the damage that the lipid peroxidation by-products such as 4-hydroxy-2-neonal (HNE) induce [52]. HNE, the most toxic by-product of lipid peroxidation, could interact with proteins and modifies them irreversibly impairing their function [53]. It can activate autophagy-lysosomal activity [54] and consequently the caspase-3 and cell death pathway [55]. Telomerase activity which stabilises DNA is downregulated by HNE [56]. It would be of interest to investigate what would trigger oxidative damage in AD brain of the general population.

Collectively, these are intriguing evidence that indicates looking closer into Down syndrome might have critical answers for Alzheimer's disease not only for Down syndrome but also the general population. The functional genomic study of chromosome 21 and development of the various cellular and mouse models have all offered an astonishing chance to examine the molecular events of genome dose imbalance. Studies of DS could deliver a wealth of knowledge beyond the well-known features of intellectual disability and dysmorphic characteristics. Understanding the molecular mechanism that leads to the phenotypes of AD in the DS could open the doors to limitless therapeutic options and unlock the mystery of Alzheimer's disease.

References
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