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Featured Article

Microvascular changes in Down syndrome with Alzheimer-type pathology: Insights into a potential vascular mechanism for Down syndrome and Alzheimer's disease

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Abstract

Introduction: The mechanism triggering degeneration in Alzheimer's disease (AD) remains uncertain. Therapeutic failure following β amyloid (Aβ) removal casts doubt on amyloid neurotoxicity per se as the primary cause of AD. Impaired microvascular function has been suggested as an alternative etiology. People with Down syndrome (DS) develop Alzheimer pathology, but whether microvascular impairment also occurs in DS (as in AD) is unknown.

Methods: We examined brain microvasculature in five DS subjects with AD-type histopathology, seven AD cases, and seven controls without AD-type pathology. We counted microvessels in five anatomic regions and assessed endothelial integrity by CD31 staining intensity.

Results: Microvascular numbers and endothelial integrity were significantly diminished in DS brains compared with controls and were similar to AD brains.

Discussion: People with DS and trisomy 21 produce a large amount of Aβ. If Alzheimer pathology occurred in DS without microvascular loss or endothelial impairment, a direct neurotoxic Aβ mechanism would be supported and microvascular impairment rejected. The observation of microvascular impairment in DS with Alzheimer changes fails to reject the microvascular hypothesis and provides some support for this potential mechanism of injury.

Keywords: Down syndrome; Alzheimer's disease; Microvascular/endothelial impairment; Amyloid; Notch-1; Presenilin; Angiogenesis

1. Introduction

In 1948 Jervis [1] reported the clinical changes of "senility," with characteristic postmortem findings of Alzheimer's disease (AD), in three persons with Down syndrome (DS), 37 to 47 years of age. He suggested that premature senile dementia in DS, "…may offer some clue with regard to the problem of pathologic aging of the brain…suggesting lines of future research." Typical neuropathological changes of AD have been found subsequently in nearly all brains of individuals with DS by the age of 40 years [2], with gross atrophy of brain, neuronal losses, and the presence of neuritic plaques and neurofibrillary tangles (NFTs). Clinical dementia develops 10 to 30 years [3] later and is not documented in all DS subjects [4], partly due to the difficulty of recognizing dementia in individuals with severe mental retardation, partly to the variable delay before dementia develops after the initial pathological changes.

The similarity between the neuropathology of DS and AD led to a search for the genetic cause of familial AD (FAD) on

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chromosome 21, the site of trisomy in DS. The first gene mutation causing dominantly inherited FAD was discovered on chromosome 21 in 1989 [5] and was recognized to affect the gene for amyloid precursor protein (APP) [6]. This observation and subsequent findings of mutations of presenilin 1 and 2 causing early-onset, dominantly inherited FAD have been considered to support the "amyloid hypothesis of AD," and the view that AD and the dementia occurring in DS are caused by an excess of neurotoxic β amyloid (Aβ).

Over the quarter century since the first gene for FAD was identified, increasing doubts have been raised regarding the presumed role of Aβ neurotoxicity in the pathogenesis of AD [1], and particularly of late-onset sporadic AD (LOSAD). The most critical issues include the lack of relation between the amount of Aβ in the AD brain and dementia severity; the fact that many cognitively normal elderly people have extensive cerebral Aβ accumulation without cognitive impairment; and the repeated failures of drugs that remove Aβ to improve or stabilize the dementia of AD. Alternatively, it has been suggested that the accumulation of Aβ-containing plaques and NFTs is associated with a process by which loss of neurons and synapses occurs with age but that these pathological changes are secondary "downstream" effects rather than the primary cause of the process [7]. The precise mechanism(s) by which the neuronal and synaptic losses, and the associated accumulation of Aβ, occur has thus remained uncertain.

Advancing age is the most consistent risk factor related to the development of LOSAD: the incidence of AD is 20 to 30 times greater at the age of 85 years than at 65 years [8]. This likely reflects the increased vulnerability of the aging brain, rather than a specific etiology of AD [9]. Vascular risk factors, including hypertension in midlife, diabetes, dyslipidemia, and cardiac disease, have been consistently associated with the development of AD [10]. Neuropathological studies have shown microvascular changes in AD, including fewer microvessels in the cerebral cortex, narrowed capillaries and small arterioles, loss of the endothelial lining, and "string vessels" and corkscrew vessels [11–13]. These are not manifestations of amyloid angiopathy (AA), which commonly occurs in AD, but are a distinct process. As these changes may cause a decrease in cerebral blood flow, which can compromise brain tissue, the decline of trophic factors produced by the vascular endothelium [14] may also cause neural degeneration and cerebral atrophy.

The relation of this microvascular endothelial impairment to the pathological and clinical mechanisms of AD/dementia suggests a potential explanation. Insights may be found both in age-related changes and in the effects of DS, both of which show pathological and clinical similarities to AD. We hypothesize that failure of angiogenesis in elderly people with vulnerable brains is an important mechanism leading to LOSAD.

Presenilin, best known for its γ secretase function in splitting Aβ from the post-β-secretase cleavage fragment of APP, is also necessary for the cleavage of Notch-1. This produces the active Notch intracellular domain, which is involved in normal angiogenesis, together with VEGF, delta-like ligand, Hes and Hey. APP and Notch-1 compete for cleavage by presenilin, however; so the more APP that is split, the less Notch-1 is converted to the functioning Notch intracellular domain. The balance of presenilin cleavage of Notch versus APP can be shifted in several ways:

1) With advancing age, the amount of Notch split by presenilin decreases [15], more APP is then cleaved by presenilin, and more Aβ will accumulate. This mechanism most likely occurs in elderly individuals.
2) If more APP is produced, it can preempt the function of presenilin: less Notch is cleaved by presenilin, and more Aβ is secreted from APP. This may occur in DS, where duplication of the APP gene due to chromosome 21 trisomy increases the amount of APP produced [16].

In both cases, competitively decreased Notch cleavage would cause impaired angiogenesis, and be marked by the accumulation of increased Aβ.

If this mechanism is responsible for premature AD-like pathology in DS, we predicted that the brains of middle-aged patients with DS should show, besides hallmark Aβ/neuritic plaques and NFTs, *a diminished microvascular pattern* as is seen in AD, although this has not (to our knowledge) been reported in DS. If, despite the characteristic AD senile plaques and NFTs, the DS microvasculature *remains intact* (i.e., is neither attenuated nor denuded of endothelium), we would reject a primary vascular hypothesis for the occurrence of AD-type pathology in DS.

In this study, we attempted to resolve this question by performing a semi-quantitative postmortem analysis of the microvasculature in a small number of brains from people with DS in comparison to a group of AD and nondemented elderly control subjects.

2. Materials and methods

This study was reviewed by the University of Massachusetts IRB and did not require review or exemption because it involved only de-identified data from deceased individuals. Q4

2.1. Postmortem specimens

2.1.1. Down syndrome

Paraffin-imbedded 5-micron sections from five subjects with DS, mounted on glass slides, were obtained from the Brain Bank at the Massachusetts Alzheimer's Disease Research Center, provided by Dr. Matthew P. Frosch and Ms. Karlotta Fitch. Sections of superior frontal lobe, middle temporal lobe, hippocampus, cerebellum, and basal ganglia (striatum) from five patients with DS, aged 58, 59, 59, 60, and 62 years, were available; all had Alzheimer-type