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Cerebrovascular contributions to aging and Alzheimer's disease in Down syndrome☆

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Abstract

Down syndrome (DS) is a common cause of intellectual disability and is also associated with early age of onset of Alzheimer's disease (AD). Due to an extra copy of chromosome 21, most adults over 40 years old with DS have beta-amyloid plaques as a result of overexpression of the amyloid precursor protein. Cerebrovascular pathology may also be a significant contributor to neuropathology observed in the brains of adults with DS. This review describes the features of cardiovascular dysfunction and cerebrovascular pathology in DS that may be modifiable risk factors and thus targets for interventions. We will describe cerebrovascular pathology, the role of comorbidities, imaging studies indicating vascular pathology and the possible consequences. It is clear that our understanding of aging and AD in people with DS will benefit from further studies to determine the role that cerebrovascular dysfunction contributes to cognitive health.

Keywords

Beta-amyloid; Cerebral amyloid angiopathy; Hypertension; Hypotension; Microhemorrhages; Moyamoya; Sleep apnea; Stroke

1. Cerebrovascular disease and Alzheimer's disease

Vascular contribution to cognitive impairment and dementia (VCID) is widely considered to be the second most common cause of dementia after Alzheimer's disease (AD), accounting for 20–30% of cases [54]. In addition, VCID occurs as a co-morbidity with other common dementias including AD and is estimated to be co-morbid in as many as 40–50% of AD

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cases [12,46,50]. The most obvious, acute cause of VCID is a stroke. Dementia symptoms such as confusion, disorientation and trouble understanding speech can occur following a major stroke. However, most VCID cases are those that have a more-subtle pathophysiology. These pathophysiologies can include multiple small strokes, chronic cerebral hypoperfusion, cerebrovascular occlusions, cerebral microhemorrhages, and cerebral amyloid angiopathy (CAA) [54]. While VCID is clearly a significant cause of dementia, VCID remains understudied relative to other causes of dementia such as AD and frontotemporal dementia (FTD). This is in part due to a lack of in vitro or in vivo models and a lack of a single gene target or abnormal pathology [44].

Vascular factors are increasingly being recognized as a critical comorbidity that not only accelerates the age of onset of dementia but also can lead to a faster progression of the disease. White matter hyperintensities (WMH) can serve as a “second hit” necessary for clinical signs of dementia particularly when significant Aβ is present in the brain [76]. In addition, recent evidence from the Rotterdam Scan Study strongly suggests a link between white matter (WM) integrity (measured by fractional anisotropy — FA; lower FA is poorer WM integrity) and the number of cerebral microbleeds in older nondemented individuals over the age of 60 years old [3]; individuals with higher numbers of microbleeds had lower FA. Interestingly, previous studies show that ex vivo imaging of autopsy brain indicates an overlap between FA and WM lesions that reflect vascular deficits [6]. WMH, typically prominent in periventricular regions, lead to reduced FA [16].

Studies in mouse models of VCID suggest a critical role of inflammatory processes in the neurodegeneration and progression of the cerebrovascular pathology. Mouse models of CAA show a distinct inflammatory signature compared to animal models of parenchymal amyloid deposition [104]. Further, the hyperhomocysteinemia model of VCID that develops primarily impaired cerebral blood flow, microhemorrhages and WMH indicates a critical role for pro-inflammatory responses in the brain contributing to the progression and severity of cerebrovascular pathologies, as well as cognitive impairment [92]. Further support for a causal link between neuroinflammatory responses and WM integrity loss comes from a study of the permanent bilateral carotid artery occlusion rat model [29]. In this model significant microglial activation correlated with loss of myelin basic protein and oligodendrocyte density.

2. Down syndrome, aging and Alzheimer's disease

DS or trisomy 21 is one of the most common causes of intellectual disability. Improved medical care in DS has led to a significant lifespan extension (median life span is now estimated to be 60 years) and enhanced quality of life [9,33] but also has increased AD risk. Dementia incidence and prevalence increase substantially after 50 years old [85]. However, there is a subset of aged DS individuals who do not develop dementia at any age [38,39,85,112]. The reasons for a subset of older people with DS not developing dementia are as yet unknown and may be complex. A simple explanation may be that these individuals may have died before developing dementia. However, the underlying genetic cause for DS may also provide an explanation. For example, in a case study of a person with partial trisomy 21 (disomic for the amyloid precursor protein) lived into her 70s without dementia

[75]. There may be other people who have a DS phenotype without genetic confirmation of trisomy 21 that may be in this group, including those with mosaicism. It may also be that lifestyle factors or other genes on chromosome 21 can be protective in some people with DS. These observations strongly suggest the need to follow larger groups of older adults with DS to clearly establish factors associated with a lack of development of dementia despite significant AD pathology. Mild cognitive impairment (MCI), a precursor to dementia in sporadic AD is of limited applicability to DS (at this time) and continues to be an important area to develop [48]. Virtually all DS adults have sufficient neuropathology for a diagnosis of AD by 40 years old [57,106,107], including senile plaques (SP-beta-amyloid (Aβ) protein) and neurofibrillary tangles (hyperphosphorylated tau protein). Aβ is derived from the β-amyloid precursor protein (APP), the gene for which is on chromosome 21 and overexpressed in DS [81]. Aβ accumulation in diffuse plaques does not appear to be consistently observed until after the age of 30 years old [57]. However, several interesting studies show significant diffuse plaque accumulation in much younger individuals such as the work by Lemere and colleagues and Leverenz and Raskind [51,53]. In particular, work by Lemere's group strongly suggests that more studies of younger individuals are necessary as the presence of diffuse plaques in children may as yet be underappreciated. Between the ages of 30 and 40 years old, neurofibrillary tangle and Aβ plaque neuropathology accumulate until they reach levels sufficient for a pathological diagnosis of AD [106]. Thus, there is a preclinical phase in DS when AD pathology accumulates (30–40 years) but dementia diagnosis may be delayed by up to a decade if not longer [49].

3. Cardiac abnormalities in Down syndrome

Reports of cardiac abnormalities in DS have shown a prevalence of 33% to 48% (cf. [30,87]) in children with DS with atrioventricular septal and ventricular septal defects appearing as the most common congenital heart defects. In a review of the heart and vascular system in DS, Vis and colleagues [100] described increased frequency of congenital heart defects along with factors associated with heart disease such as hypothyroidism, lipid levels, reduced homocysteine levels, decreased atherosclerosis and their association with chromosome 21 overexpression. Clearly, as noted by Vis and colleagues, DS affects both structure and function of the heart and vasculature; the resulting impact on the central nervous system has yet to be fully delineated. Several of these vascular risks are discussed below.

4. Cerebrovascular pathology in Down syndrome

Although cardiovascular disease (CVD) is a key contributor to sporadic AD, it has been virtually unexplored in DS. DS represents a unique opportunity to study the cerebrovascular features of aging and AD in a setting of more limited systemic vascular risk factors such as atherosclerosis, hypertension and hyperhomocysteinemia (as will be discussed later).

Adults with DS exhibit significant cerebral amyloid angiopathy (CAA), which is the term commonly used to define the deposition of amyloid in the walls of medium- and small-sized leptomeningeal and cortical arteries, arterioles and, less frequently, capillaries and veins. CAA can lead to micro- and macro-hemorrhages [99]. CAA is consistently observed in older

individuals with DS over the age of 55 years old [7,40,49] (Fig. 1A, B) and also contains post-translationally modi-fied Aβ [31]. CAA in DS may be associated with extensive cerebrovascular hemorrhages or stroke [7,22,42,60,62,69] in some studies but not in others [40,49]. In our autopsy studies, we find a significant number of microhemorrhages in the DS brain (Fig. 1C). Aβ40 (typically associated with CAA — Fig. 1B) rises exponentially with age in the brain [15] and plasma [83] of people with DS and appears preferentially in the occipital cortex (Fig. 1D) but other areas are affected. Interestingly, there are no systematic studies in DS brain to evaluate the distribution of CAA with age, which could be accomplished by MR studies or by autopsy. With increased CAA and Aβ1-40 in DS, interestingly, VCID (or multi-infarct dementia as it was termed then) per se is rare with only one case report in the literature of a 55-year old woman with DS [19].

5. Comorbidities associated with cerebrovascular disease or protection in DS

5.1. Atherosclerosis

In a previous study of 70 adults with DS ranging in age from 40 to 66 years old, blood pressure was lower and atheroma (accumulation of degenerative material in the tunica intima (inner layer) of artery walls) was absent compared to similarly aged adults without DS [66]. Other studies also report much lower frequency of atheroma [13,109]. Although less frequent in DS, atherosclerosis has been observed in two middle aged adults who had strokes [73] but it tends to be milder in adults with DS [110]. Indeed, death from atherosclerosis in adults with DS in a Swedish population was rare but may be more frequent than previously thought [26]. Possible mechanisms by which people with DS are protected from atherosclerosis may include reduced heart-type fatty acid binding protein, which is typically correlated with age-associated atherosclerosis in the non-DS population [98] as well as reduced brassicasterol (a plant sterol implicated with atheroprotective properties, which interestingly is reduced in DS plasma) [94] and C-reactive protein [34]. However, many serum proteins associated with increased atherosclerosis are also observed in DS including elevated triglycerides and total body fat [23,70].

Interestingly, chromosome 21 contains the cystathionine-beta-synthase gene that converts homocysteine to cysteine [1], suggesting lower homocysteine levels in DS [74], which is in turn thought to be associated with decreased coronary heart disease [11]. The observation of lower homocysteine in children with DS [74] suggests this may be protective, however, in a small study of older adults, higher levels were observed [55]. This interesting divergence suggests that homocysteine may be modified with age in people with DS.

5.2. Hypertension/hypotension

Lower blood pressure in children [79] and adults with DS [23, 24] has been consistently reported. Further, blood pressure does not rise with age in DS as it does in the general population [63]. Indeed, in one report, hypotension is a feature of aging and dementia in people with DS and hypertensive drugs were less likely to be prescribed [4]. In this large retrospective study, the incidence of hypertension was 0.58/100 person years and hypotension was 0.15/100 person years over the age of 30 years old. The overexpression of

cystathionine β-synthase on chromosome 21 may be an underlying factor for these observations.

5.3. Moyamoya disease

Moyamoya is a chronic occlusive cerebrovascular disorder [93] of the carotid arteries and/or the arteries of the circle of Willis that can cause ischemic strokes in children with DS and hemorrhagic strokes in adults [8,20,21,68,71,73]. It is thought that moyamoya disease is more frequent in children with DS [32]. Further, there is up to a 26 fold greater prevalence of DS in patients with moyamoya [45]. The first report of moyamoya in DS was in 1977 by Schrager and colleagues where a child developed acute hemiplegia, cortical blindness, and a right paraventricular frontal infarct [82]. Subsequently, several case reports of moyamoya in children with DS were described [73,96]; in a study of 41 patients with DS, 4 had moyamoya [73]. Possible mechanisms underlying the higher frequency of moyamoya in DS may be linked to autoimmunity [52] or to genes on chromosome 21 associated with arterial physiology for example, superoxide dismutase 1, interferon gamma receptor, and cystathionine β-synthase [20].

5.4. Obesity/diabetes

Children and adults with DS show a higher frequency of being overweight or obese [18,61,67,78,80,89,97] with up to 60% of individuals being overweight. For example, in a study of 1600 Dutch children with DS, 25% of these healthy children were overweight with numbers reaching as high as 40% overweight or obese up to 18 years old [97]. This may be, in part, related to higher prevalence of hypothyroidism in addition to increased levels of circulating leptin [56]. Interestingly, postmenopausal obese women with DS perform significantly better on a test of verbal memory (but not other cognitive tests) than non-obese women with DS [72]. While this finding may be related to body mass index associated estrogen levels being higher, no differences were seen for serum estradiol levels between groups based on obesity and the association between estrogen levels and memory scores did not suggest a large effect size (R^2 from .053 to .073). However, estrogen receptor variants (ESR1 polymorphisms) contribute a 2 to 3-fold increase in AD risk in women with DS [84,111] suggesting that the associations between memory, obesity, and estrogen levels in DS are likely complex and would not support the use of estrogen replacement to reduce AD risk in DS. Finally, obesity may suggest an increased propensity to develop type II diabetes in DS. There are few reports describing type II diabetes in DS however it could be lower than in the general population [27].

5.5. Sleep apnea

Given the higher prevalence of obesity in DS along with orofacial an-atomical variations (cf. [77]), it is not surprising that the frequency of obstructive sleep apnea is also high. The incidence of obstructive sleep apnea (OSA) in children 2 to 4 years old with DS is 57% based on polysomnography alone in one study [86]. Further OSA increased to 80% when the criterion also included an arousal index that was elevated in 61% of the children who were evaluated. Of note, Shott and colleagues did not find an association between OSA and body mass index (BMI) or presence of cardiovascular disease in their sample. In contrast, Trois and colleagues studied individuals with DS between the ages of 17 and 56 years old [95].

They reported that 94% of their sample had OSA of varying levels of severity with 69% in the severe range based on their apnea–hypopnea index. More importantly, they did not find an association between OSA and age but showed a correlation between BMI and apnea–hypopnea index.

The implications for the brain in OSA are well known in the general population and include elevated risk for dementia [10,108] and CVD (stroke, transient ischemic attack, small vessel disease, silent cerebral infarction), and are hypothesized to contribute to gray and white matter losses (cf., [14,17,47]). Durgan and Bryan [25] in a relatively recent review of the impact of OSA on CVD implicate multiple mechanisms such as inflammation, endothelial dysfunction, and oxidative stress. Given the prevalence of OSA in DS, it is possible that in addition to the impact of the genetic aspects of this disorder, OSA could readily contribute to VCID as well as AD as these individuals age.

6. Imaging studies in DS suggesting CVD

A key contributor to sporadic AD, the role of CVD, has been virtually unexplored in DS. As mentioned previously, the CVD contribution to AD is increasingly being recognized as a critical comorbidity that accelerates the age of onset of dementia and also leads to a faster progression of the disease [2,5,28,41]. Estimates of a mixed etiology of AD with CVD range from 5.7 to 45% in autopsy cases from the general population [43]. CVD can serve as a “second hit” necessary for clinical signs of dementia particularly when significant Aβ is present in the brain [76]. Several studies are underway that are evaluating the presence of cerebrovascular pathology in aging adults with DS by imaging approaches and in the coming years, more information will become available (e.g. Fig. 1D).

7. Consequences of CVD in DS — neuroinflammation

The rationale for interest in neuroinflammation stems from observations regarding decreased WM integrity and preliminary magnetic resonance (MR) imaging data showing CVD. Each of these pathologies can be caused by, or lead to, neuroinflammation. Interestingly, although neuroinflammation is widely accepted as a critical mediator in sporadic AD, little is known about the aging DS brain (recently reviewed in [101, 103]). Early studies by Dr. Griffin's and Lemere's group demonstrated some intriguing findings suggesting increased pro-inflammatory responses in the DS brain including increased IL-1b expression in the DS brain and increased complement activation [35–37,65,88,103]. This is particularly surprising given that chromosome 21 contains genes that are involved in pro- and anti-inflammatory processes [101].

Data from our current study support the systematic study of neuroinflammation in DS [105]. To explore the spectrum of neuroinflammatory responses, several laboratories have used markers associated with distinct macrophage phenotypes (reviewed in [102]). The macrophage nomenclature of M1, M2a, M2b and M2c has been used in the assessment of this neuroinflammatory spectrum [58]. M1 responses are the typical pro-inflammatory responses one expects to see with an immune stimulus such as lipopolysaccharide and interferon-gamma (IFNg). The M1 response is characterized by high IL-12, low IL-10, and high IL-1b, TNFa and I-6. The M2a response is associated stimulation by IL-4 or IL-13 and

is characterized by the expression of high IL-12, arginase-1, chitinase-like proteins and IL-1 receptor antagonist. The primary role of this phenotype in the periphery is wound repair and matrix deposition. The M2b response is stimulated by the presence of immune complexes and the activation of the Fcg receptor signaling pathways. This response is characterized by high IL-10, low IL-12, and moderately high IL-1b, TNFa and IL-6. The exact functional consequence of this phenotype, beyond stimulating phagocytosis, is relatively unknown [59,64]. The M2c response is stimulated by IL-10 and is characterized by increased expression of TGFb1. The role of this phenotype is to actively downregulate potential M1 responses.

Using the M1–M2 spectrum of markers, we recently showed that DS brains, especially those with AD pathology, are characterized by the presence of a high M2b response. We have not previously found that human AD brains, even at the severe stages, show any M2b responses. In a previously published study of human autopsy tissue from early and late stage AD, we found expression of M1 and M2a associated markers, but not M2b [91,102]. This indicates to us that the DS brain has a different inflammatory response relative to sporadic AD. Based on our understanding of the M2b phenotype, and its dependence on stimulation by immune complexes [90], we hypothesize that the presence of this phenotype in the DS brain suggests a broad dysfunction of the blood–brain barrier (BBB) allowing significant leakage of IgG into the brain parenchyma generating sufficient immune complexes to promote this M2b response. Future studies will explore the potential for this mechanism and the dependence of the M2b response on cerebrovascular degeneration. The long term implications of this unique NI profile in individuals with DS are as yet unknown, but most likely will affect cognition, CVD, and WM integrity.

8. Summary and future studies

DS represents a unique opportunity to study the cerebrovascular features of aging and AD in a setting of more limited systemic vascular risk factors. Thus, adults with DS represent an important cohort to study CVD co-morbidities because of their unique characteristics: atheroma-free model and lower blood pressure but with significant CAA. Given that many of the co-morbidities associated with cerebrovascular dysfunction may be modifiable, it will be critical to determine if these may be targets for intervention that benefit this highly vulnerable group of adults. Thus, future studies that include biomarkers of cerebrovascular dysfunction as outcome measures will be important to consider in the design of longitudinal observational studies and clinical trials.

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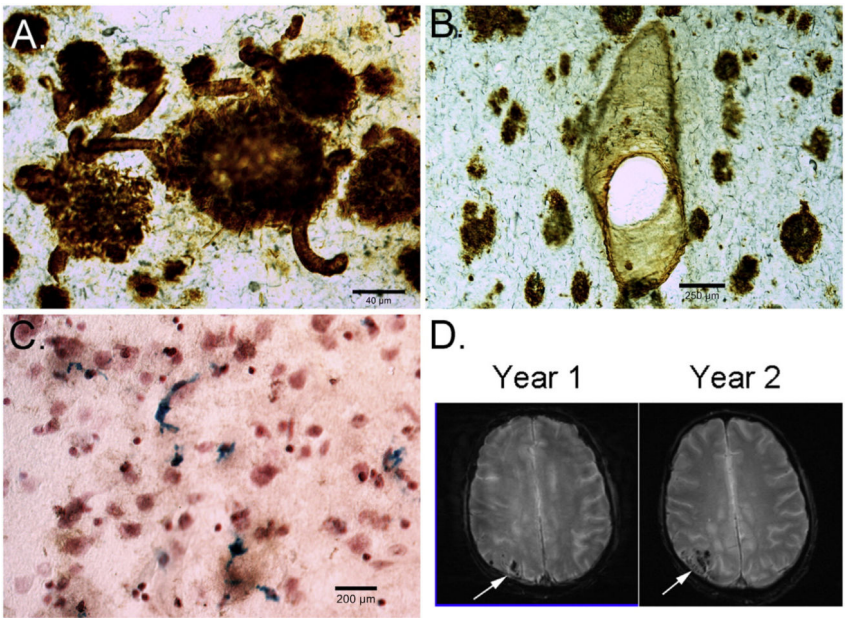

Fig. 1.

Cerebrovascular neuropathology in DS. (A) Beta-amyloid 1-42 immunostaining of the frontal cortex in 67-year old adult with DS and AD shows plaques and significant CAA in multiple small vessels (arrows). (B) Beta-amyloid 1-40 shows a different pattern with fewer plaques being labeled with CAA appearing more prominent, particularly in vessels (arrows). (C) Prussian blue staining of a 58-year old with DS and AD shows significant numbers of microhemorrhages (blue). T2* weighted MR images in a 60-year old male with DS, who is currently nondemented over a 2-year time interval, shows significant CAA in the occipital cortex that is progressively getting worse (white arrows) (images courtesy of Dr. David Powell, University of Kentucky).