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Aging in Down syndrome and the Development of Alzheimer's disease Neuropathology

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Abstract

Chromosome 21, triplicated in Down Syndrome, contains several genes that are thought to play a critical role in the development of AD neuropathology. The overexpression of the gene for the amyloid precursor protein (APP), on chromosome 21, leads to early onset beta-amyloid (Aβ) plaques in DS. In addition to Aβ accumulation, middle-aged individuals with DS develop neurofibrillary tangles, cerebrovascular pathology, white matter pathology, oxidative damage, neuroinflammation and neuron loss. There is also evidence of potential compensatory responses in DS that benefit the brain and delay the onset of dementia after there is sufficient neuropathology for a diagnosis of AD. This review describes some of the existing literature and also highlights gaps in our knowledge regarding AD neuropathology in DS. It will be critical in the future to develop networked brain banks with standardized collection procedures to fully characterize the regional and temporal pathological events associated with aging in DS. As more information is acquired regarding AD evolution in DS, there will be opportunities to develop interventions that are age-appropriate to delay AD in DS.

Keywords

beta-amyloid; neurofibrillary tangles; neuroinflammation; oxidative damage; posttranslational modifications; senile plaques; trisomy 21; vascular pathology; white matter damage

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Background

Down syndrome (DS) was initially described by J. Langdon Down in 1866 [1]. In 1959, Lejeune identified DS as a trisomy of chromosome 21 [2]. DS or Trisomy 21, is one of the most common causes of intellectual disability (ID) and recent national prevalence estimates suggest that 1 in every 691 babies in the USA is born with DS leading to ~6,000 annual DS births (www.ndss.org). DS is associated with characteristic physical features, deficits in the immune and endocrine systems and delayed cognitive development [3, 4].

Improvements in medical care, education, and support for children and adults with DS, have led to significant extensions in lifespan and enhanced quality of life [5, 6]. As a consequence, up to age 35 years, mortality rates are comparable in adults with DS to individuals with intellectual disability from other causes [7]. However, after age 35, mortality rates double every 6.4 years in DS as compared to every 9.6 years for people without DS [7]. The average lifespan of DS individuals has approximately doubled over the past 30 years to 55-60 years of age (www.ndss.org; [8, 9]). One of the consequences of aging in people with DS is increasing accumulation of Alzheimer's disease (AD) neuropathology primarily due to overexpression of the APP gene on chromosome 21.

APP Processing and Down syndrome

Aβ is produced from a longer precursor protein, APP, which is present in triplicate in DS [10, 11]. It is interesting to note that when APP is overexpressed, there is a parallel increase in the release of sAPPα, which in turn can activate microglia and induce IL-1β and lead to additional increases in APP [12]. This in turn may explain why there are observations of a greater than 1.5 fold increase in APP as a result of trisomy 21 [10]. Aβ is produced by sequential cleavage of APP by β-secretase and subsequently by γ-secretase [13, 14]. β-secretase has been identified as beta-site APP cleaving enzyme or BACE1 [15]. In DS, however, β-secretase activity has variably been shown to increase with age [16] or shows modest increases in protein level [17], whereas other studies report little change suggesting that APP overexpression may be the primary driver of Aβ plaque accumulation [18, 19].

BACE2 can also cleave APP at the β-secretase site [20] Interestingly, the gene for BACE-2, which shares significant homology with BACE1, is also located on chromosome 21 in the DS obligate region and may contribute to increased Aβ production. Developmentally, BACE-2 RNA levels are significantly higher in DS fetal tissue relative to controls [21]. In addition, in cultured fibroblasts from adults with DS, BACE-2 mRNA (i.e. protein expression) was 2.6 fold higher than normal controls. Increased levels of BACE-2 may also contribute to aging in DS. In 13 individuals with DS ranging in age from 27 weeks to 37 years, frontal cortex BACE-2 immunoreactivity was observed only in neurons of adults with DS and AD. BACE-2 immunoreactivity was not observed in younger individuals [22]. However, several studies comparing DS brain to similarly aged control brains do not find higher levels of BACE2 protein [18, 23]. Similarly, no differences in DS as compared to controls was observed for BACE2 in the intracellular compartment [21]. It is possible that despite increased RNA for BACE2 in DS, there may be posttranscriptional regulatory

mechanisms that lead to normal levels of BACE 2 or that increase the degradation of this enzyme [19].

Soluble Aβ oligomers in DS

Once Aβ is cleaved from APP it may first appear in soluble form either within neurons or in the extracellular space. Changes in the levels of soluble Aβ measured biochemically and from peripheral samples may allow for early detection of APP processing abnormalities in DS [24]. Higher levels of soluble Aβ are observed in DS fetal tissue than in tissue from controls [25]. Specific soluble forms of Aβ include different conformations of the peptide such as oligomers, protofibrils and Aβ-derived diffusible ligands (ADDLs)[26, 27]. Soluble species of Aβ may accumulate prior to extracellular Aβin DS and may be more important than extracellular Aβ in causing neuronal dysfunction (reviewed in [24]). Despite the fact that extensive extracellular Aβ accumulation is a feature of AD in both the general population and DS, inconsistent associations between Aβ and dementia severity have been reported [28]. The hypothesis that brain amyloid is the cause of dementia in sporadic AD has also been questioned [29]. Transgenic mice overexpressing mutant human APP show signs of cognitive dysfunction prior to the accumulation of insoluble and extracellular Aβ[30], suggesting that earlier more soluble forms of Aβ may be important [31]. Aβ oligomers may be critically important in causing neuronal dysfunction prior to overt neuron loss [32]. Thus, there has been a shift to study earlier and possibly more toxic species of Aβ. Both biochemical and immunohistochemical experiments reveal significant amounts of oligomeric Aβ in the AD brain [33-36]. Oligomeric Aβ may play a critical role in causing neuron dysfunction during both development and aging in DS and is a key area requiring further study and has yet to be fully characterized in DS brain.

Intracellular Aβ in DS

Although a large amount of Aβ exists in a soluble form, insoluble deposits also begin to progressively form over time. However, the subcellular location for these events is less well understood, particularly in DS. Gyure et al (2001) report intracellular Aβ1-40 but not Aβ1-42 [37]. In contrast, other studies report intracellular Aβ1-42 but not Aβ1-40 [38, 39], which in one study was clearly distinguished from intracellular APP immunoreactivity [38]. A report by Hirayama et al. found neither Aβ1-40 nor Aβ1-42 but observed intracellular Aβ1-43 [40]. Each length of Aβ has different properties with Aβ1-40 more rapidly degraded within lysosomes than the longer, more toxic Aβ1-42/43 [41, 42]. The reasons for observations of different length Aβ species in intracellular deposits in each study may be due in part to technical differences.

However when all the observations of these different reports are combined they provide evidence for APP processing into heterogeneous fragments. One hypothesis specifically describes a “solid phase” pathway for Aβ production from APP where nonspecific proteolytic cleavage leads to heterogeneous Aβ (including Aβ1-40/42/43). A key component of this hypothesis is that APP processing occurs within the endosomal/lysosomal system [43]. It is interesting to note that studies of intracellular Aβ in DS all report a possible endosomal/lysosomal location.

A common observation in the majority of the studies of intracellular Aβ in DS is the early age of onset; both infants and children with DS accumulate intracellular Aβ. In addition, intracellular Aβ is consistently observed prior to the accumulation of extracellular Aβ deposits [38], which parallels reports in transgenic mouse models of AD [44, 45]. These findings suggest that prior to extracellular Aβ deposition there is an accumulation of intracellular Aβ within neurons in DS at a much earlier age than in the general population. Thus, intracellular Aβ accumulation may be important for development and occurs prior to and contributes to age-associated extracellular Aβ deposition. The accumulation of neuronal Aβ may be associated with caspase cleavage products leading to increased apoptosis [46], which in turn may partially account for observed brain atrophy and neuronal loss.

Aβ Plaques

While people with DS have an age-dependent increased risk for developing dementia, virtually all adults with DS over 40 years of age have sufficient neuritic plaques and neurofibrillary tangles for a neuropathologically based diagnosis of AD [47-49]. Senile plaques contain the β-amyloid (Aβ) peptide that is derived from a longer precursor protein, β-amyloid precursor protein (APP), the gene for which is on chromosome 21. The most common form of DS, trisomy 21, leads to the overexpression of APP [10]. Thus, many neurobiological studies in aged DS cases have focused primarily on APP processing and the temporal events in Aβ pathogenesis [24] based upon the general hypothesis that Aβ is thought to be a causative factor in AD pathogenesis and that overexpression of APP may lead to the elevated levels of Aβ in DS [50-52].

Cerebral Aβ deposition occurs decades earlier in DS compared to aged control and AD brain [10]. Extracellular Aβ accumulation in diffuse plaques appears to consistently deposit after the age of 30 years [47], although widespread diffuse Aβ42 plaques have also been observed in brain sections from DS individuals in their teens and 20's [53](Figure 1, 2A). It is also apparent that diffuse plaques precede neuritic plaques with age in the cortex. In DS, Aβ42 diffuse plaques precede fibrillar senile plaques containing dystrophic neurites and the formation of neurofibrillary tangles, and Aβ42 plaques are more prevalent than Aβ40 plaques at all ages [53, 54]. Interestingly, diffuse Aβ42 is deposited in DS cerebellum and striatum in the third decade of life, but fibrillar plaques are rarely observed in these brain areas in older DS brain [55], suggesting regional effects on plaque maturation. Overall, senile plaques progress in the same brain regions and cortical layers as in AD, however, plaque density is higher in DS brain [56]. In addition, the presence of an Apo E ε4 allele doubles the cerebral amyloid plaque burden and shortens life span in DS [57]. Apo E protein, a possible chaperone for Aβ deposition, is detected early in plaques in DS brain [53].

Between the ages of 30 and 40 years, neuropathology rapidly accumulates until it reaches levels sufficient for a diagnosis of AD in DS by 40 years [49]. In fact, there is an exponential rise in AD pathology, and specifically Aβ measured biochemically after the age of 40 years [16], suggesting an acceleration phase to disease development. There are reports of younger individuals with AD pathology, including plaques and tangles, although typically, not of sufficient extent for a neuropathology diagnosis of the disease [53, 58, 59]. The source of

extracellular Aβ is thought to be mainly neuronal and in autopsy studies of younger individuals with DS shows that as young as 3 years, intracellular Aβ can be observed[38, 60]. Intracellular Aβ is localized to endosomes, intracellular organelles responsible for degrading and turning over proteins within cells [60, 61].

Post-translationally Modified Aβ

Over time, extracellular Aβ with the N-terminus starting at Asp 1 in DS can be post-translationally modified by isomerization [62], racemization [63] and oxidation [64]. In addition, an N-terminally truncated form of Aβ is generated by degradation of the first 2 amino acids followed by cyclization of the newly formed N-terminus by glutaminyl cyclase, resulting in degradation-resistant, highly toxic aggregates of pyroglutamate-3 Aβ that deposit into plaques and blood vessel walls in AD and DS brain [53, 65-67]. Mehta and colleagues recently reported increased levels of pyroglutamate-3 Aβ in plasma of older DS people compared to non-DS people with and without developmental disabilities [68]. Pyroglutamate-11 Aβ, a minor species, is also detected in some plaque cores and vascular amyloid in DS brain [69, 70]. Unmodified Aβ11-40/42 is also elevated in DS brain, possibly due to the overexpression of BACE 2, a gene encoded on chromosome 21 [70]. In addition, the APP P3 peptide starting at the non-amyloidogenic α-secretase site (Aβ17leu) can be observed readily in DS brain extracts [71] and cerebellar plaques [72]. These modifications may reflect mechanisms of Aβ production and could potentially serve as possible chronobiological age markers for individual deposits and Alzheimer's disease progression.

Cerebrovascular Aβ Pathology in DS

A key contributor to sporadic AD, the role of cerebrovascular disease (CVD) has been virtually unexplored in DS. 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 [73]. Estimates of a mixed etiology of AD with CVD range from 5.7-45% in autopsy cases from the general population [74]. CVD can serve as a “second hit” necessary for clinical signs of dementia, particularly when significant Aβ is present in the brain [75]. In addition, evidence from Rotterdam Scan Study suggests a link between WM integrity and the number of cerebral microbleeds in older nondemented individuals (>60 years)[76]): individuals with higher numbers of microbleeds had lower FA. Thus, CVD may be a second major contributor to cognitive decline and WM integrity, with each potentially being additive [77, 78].

DS represents a unique opportunity to study the cerebrovascular features of aging and AD in a setting of more limited systemic vascular risk factors. In a previous study of 70 adults with DS ranging in age from 40-66 years, there was an absence of atheroma and lower blood pressure than similarly aged adults without DS [79]. Lower blood pressure appears to consistently occur in younger adults with DS between 13-42 years [80]. Other studies also report much lower frequency of atheroma [81, 82]. Cerebral amyloid angiopathy (CAA) is the common term used to define the deposition of amyloid in the walls of medium- and small-size leptomeningeal and cortical arteries, arterioles and, less frequently, capillaries and veins. CAA can lead to micro and macro hemorrhages [83]. CAA is consistently observed in

older individuals with DS (>55 yrs - [84-86] and also contains post-translationally modified Aβ [67]. Interestingly, there are reports of CAA in DS that is associated with extensive hemorrhages [86-90] in some studies but not in others [84, 85]. Brain Aβ40 (typically associated with CAA – Figure 2B) rises exponentially with age in DS [36]. 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 cerebral amyloid angiopathy (CAA).

There are currently no systematic reports of CVD as a function of aging, cognition, dementia or WM integrity in DS. It is known, based upon autopsy studies, that there should be significant WMH, CAA and CVD that could be captured and quantified by the appropriate MR imaging protocols. In terms of designing future clinical trials, characterizing the age of onset and extent of CVD in adults with DS will be critical given that CVD is mediated to large extent by lifestyle factors that are amenable to intervention. Individuals with hypertension, high cholesterol, obesity, type II diabetes, show a higher risk of CVD (reviewed in: [91]).

Enzymes involved with Aβ Degradation and Clearance in the Brain

Once Aβ begins to accumulate either in soluble or insoluble form, several enzymes in the brain may be involved with subsequent degradation and clearance. These Aβ clearing enzymes include insulin degrading enzyme (IDE), neprilysin, and tissue plasminogen activator [92-94]. In DS, two components leading to increased production of Aβ are present in triplicate and include APP and BACE2. However, despite life-long overexpression of these two proteins, full blown AD neuropathology is not consistently observed until after age 40 years. Thus, Aβ may be cleared or degraded in the DS brain by the activity of Aβ degrading enzymes. Neprilysin protein concentration is increased in DS and correlates with levels of insoluble Aβ [17]. Considering the therapeutic potential of enhancing Aβ degradation and clearance, this represents a major gap in our knowledge in the study of development and aging in DS.

CSF Aβ

There are few studies of CSF Aβ in DS. In children with DS ranging in age from 6 months to 56 months no differences were noted in CSF Aβ when analyzed in a cross sectional study [95]. However, in 2 children followed over 4 years, progressively increasing CSF Aβ 1-42 was observed over a 4 year span in 2 of these individuals and in particular with CSF Aβ 1-37 and Aβ 1-38, which contrasts with studies in older individuals and may reflect basal rates of Aβ due to APP overexpression. In a study of 5 adults with DS with an average age of 55.3 years, when AD pathology may be present, Aβ1-40 did not distinguish DS from “diseased controls” that did not have AD. Interestingly, Aβ1-42 was significantly decreased in CSF from DS patients [96]. A subsequent study in 12 persons with DS (mean age 41 years) with 3 showing signs of dementia [97] showed a significant decrease in CSF Aβ1-42 as a function of age in DS (25-60 years). Further, CSF Aβ 1-42 was significantly lower in older adults with DS (> 40 years) relative to younger adults with DS(<40 years).

A more recent study of 12 DS participants (mean age 41 years) and 20 healthy controls tested for a battery of CSF peptides that may distinguish the two groups [98]. Although CSF Aβ 1-42 was not different in DS from controls, it was correlated with age in DS and decreased with increasing age. CSF Aβ X-40 was increased in DS compared with controls, however this may have been due to one individual with DS who had a high level of AβX-40. Further, increases in sAPPα and sAPPβ were observed in DS relative to controls but there was also significant overlap with control samples. In a second follow up study, CSF Aβ 1-42 was significantly decreased in DS with shorter Aβ peptides (including 1-34, 1-38, 1-39) also tending to be lower [99]. Further, there was a significant negative correlation between CSF Aβ 1-42 and age (from 21 to 60 years). Overall, there appears to be a relatively consistent decrease in CSF Aβ 1-42 in older adults with DS that is consistent with reports in sporadic AD [100]. These results suggest that CSF Aβ42 is reduced as plaques are formed in the brain parenchyma.

Plasma Aβ

Studies of plasma Aβ have provided variable results with respect to distinguishing demented from nondemented individuals with DS and aging in some cohorts but more consistent outcomes appear in larger cohorts, particularly in prospective studies. In cross-sectional studies, plasma Aβ1-42 and Aβ 1-40 are consistently elevated in DS relative to controls [101-106] but not in fetal plasma samples [107]. Aging in DS is associated with increasing levels of plasma Aβ1-40 [102, 108] but not in other studies [104, 106]. Plasma Aβ 1-42 has been reported to be increased with age in adults over 50 years with DS in one study [105] but this was not replicated in subsequent studies [106, 108-110]. As mentioned earlier, post-translationally truncated and modified pyroglutamate-3 Aβ is elevated in plasma from older DS individuals (Mehta et al., 2014). Further analysis of this pathogenic Aβ species may reveal a potential biomarker for AD conversion in DS.

In cross sectional studies comparing demented adults with DS to those without dementia, most studies report no differences in plasma Aβ1-40 [101, 104, 106, 110, 111] except in one study [112]. However, increased plasma Aβ 1-42 can distinguish demented adults with DS [104] and may improve predictive models for dementia when included [106]. However, ApoE genotype can influence the outcomes [104, 106, 109, 112].

Prospective studies of aging and conversion to dementia in adults with DS have yielded exciting outcomes. Prasher, Schupf and colleagues reported on a study of 83 nondemented and 44 demented adults with DS and compared those with dementia duration of over 4 years compared with under 4 years [111]. In people with DS with dementia over 4 years, plasma Aβ1-40 was lower and the ratio of Aβ1-42/1-40 was higher compared to people with dementia lasting less than 4 years. Schupf and colleagues next reported that increasing levels of plasma Aβ 1-40 and decreased Aβ 1-42 was a good predictor of conversion to dementia in DS [108]. Indeed, adults with DS with decreasing plasma Aβ 1-42 over time were 5 times more likely to become demented within 4 years. Similarly, in a separate prospective study of 405 persons with DS, those adults in the highest levels of plasma Aβ 1-42 and Aβ 1-40 also had the highest risk of developing dementia over, on average, a 4.7 year period of time [112].

Tau Phosphorylation and Neurofibrillary Tangles in DS

AD-associated changes such as tau phosphorylation and aggregation are evident in DS brain, especially in plaque-associated dystrophic neurites and intraneuronal neurofibrillary tangles (NFTs) comprised of the hyperphosphorylated microtubule-associated tau protein (reviewed in [113, 114](Figure 2C). One potential contributing factor may be the overexpression of the dual-specificity tyrosine phosphorylated and regulated kinase 1A gene (*DYRK1A*), which is encoded on chromosome 21. DYRK1A phosphorylates tau protein making it a better substrate for GSK3β phosphorylation, and DYRK1A phosphorylates alternate splicing factors leading to an increase ratio of 3R:4R tau, which is associated with neurodegeneration [115]. Consistent with this finding, there is an increase in the number of DYRK1A-positive and 3R-positive NFTs in middle-aged and older DS brain compared to sporadic AD [115]. Another possible contributing factor is the overexpression of the regulator of calcineurin-1 (RCAN1) or calcipressin1 gene, also encoded on chromosome 21. RCAN1 is elevated in hippocampus and cerebral cortex in AD [116]. RCAN1 inhibits calcineurin, and may enhance tau phosphorylation by lowering calcineurin phosphatase activity and increasing GSK3β levels [114]. APP, which is encoded on chromosome 21 and overexpressed in DS, may also play a role in tau phosphorylation in DS brain as Aβ42 upregulates both DYRK1A [117] and RCAN1 [118]. Thus, overexpression of all 3 genes in DS may cooperate to drive tau pathology and neurodegeneration.

Early tau pathological changes have been observed in the outer molecular layer of hippocampus in middle-aged (30-40 year-old) DS individuals, followed later by NFTs in the hippocampal CA1 region and subiculum, and neuron loss in the entorhinal cortex [119]. In general, NFTs follow a similar distribution in DS as AD, starting in entorhinal cortex and spreading to hippocampus and later neocortex, but at a higher density in DS compared to AD brain [56].

CSF Tau in DS

There are four published reports of CSF tau in DS to our knowledge. The first was in 1999 that described a single individual with DS who was 73 years of age who showed high tau levels relative to controls and to sporadic AD [120]. A second paper published in 2001 by Tapiola and colleagues observed increased tau as a function of age in DS (21-56 years, average age 41 years) that was significant [97]. In children with DS under the age of 56 months, CSF tau did not discriminate children between 6-10 months, 19-44 months or 55-56 months of age [95]. Last, in a study of 12 DS individuals ranging in age from 21-60 years and an average age of 41 years, total tau and phosphorylated tau increased with age [98] in DS although these markers were not different in DS when compared with controls. Further, older DS participants (>40 years) had significantly higher total tau when compared to younger individuals with DS. Thus, although there are few studies of CSF tau in DS, the consensus appears to be increasing levels of total tau.

Oxidative Damage and Aging in DS

In addition to Aβ and NFT neuropathology, several other types of pathology have been reported at different ages that may contribute to the development of dementia either early in the disease or possibly exacerbate cognitive symptoms later in disease. People with DS show higher levels of oxidative stress at all ages than people in the general population. For example, oxidative damage is increased in prenatal DS brains compared to non-DS controls [121, 122] and is higher in adult DS brain compared to similarly aged individuals without DS [36]. Early increases in lipid peroxidation measured by 8,12-iso-iPF2α-VI, is observed in the urine of young subjects (1-15 years) with DS, as compared to age-matched controls [123]. Interestingly, the extent of protein carbonyl accumulation, 3-nitrotyrosine and 4-hyroxy-2-trans-noneal (HNE) (all indicators of oxidative damage) does not appear to increase with age *per se* in DS but HNE levels were higher overall in DS [36]. Other types of oxidative damage to proteins, detected using proteomics approaches, show select proteins are modified that can contribute to several key pathogenic pathways [124-126]. Thus, oxidative damage may be a critical contributor to the development of AD neuropathology in DS.

Mitochondria in DS, responsible for producing cellular energy but also for producing reactive oxygen species (ROS), are dysfunctional and in turn lead to abnormalities in APP processing and enhanced Aβ production [127-129]. Indeed mitochondrial dysfunction has been observed in fetal DS cells [127]. Mutations in mitochondrial DNA have been related to AD changes in DS as well as the general population [130]. Oxidized DNA/RNA is higher in DS and increases in the teens and twenties and is further exacerbated by the presence of Aβ [131]. Thus, some types of oxidative damage increase with age in DS prior to the development of AD neuropathology. These studies suggest that mitochondrial dysfunction may be a critical event driving oxidative damage with age in DS.

Neuroinflammation and Aging in DS

Neuroinflammation is a now recognized as a key component of neurodegenerative disorders and the innate immune response in the brain is sophisticated and robust. In AD, neuroinflammation has been linked to both the exacerbation of amyloid plaques and neurofibrillary tangles, as well as the clearance of amyloid plaques. It is thought that such dichotomous findings can be accounted for by differences in the types of neuroinflammation, whether this is due to the stimulus or the profile of inflammatory mediators expressed. The primary mediators of the neuroinflammatory response in the brain are the microglial cells. For many years it has been known that microglial cells respond to the amyloid plaques and neurofibrillary tangles by becoming activated and expressing various cytokines and chemokines. [132]. Recently several genome wide array studies have shown that several genetic risk factors are associated with inflammation genes [133], most recently the TREM2 gene and the CD33 gene [134].

There are many inflammation genes on chromosome 21, and that are therefore overexpressed in DS [135]. Neuroinflammation is a relatively understudied aspect of DS Although whether inflammation is a life-long phenomenon in DS and/or whether it is

exacerbated with age and AD has yet to be fully explored [135]. For example, complement (C1q) activation has been reported in a 15 year old person with DS [59] (although this person also had evidence of neuritic plaques) but C1q activation is more consistently observed after 29 years of age [59, 136] in parallel with the deposition of fibrillar Aβ. Griffin and colleagues showed that DS brain is associated with increased S100β expression and IL-1β expression [137]. Given that IL-1β is a regulator of many pro-inflammatory processes, upregulation in DS could indicate an exacerbated pro-inflammatory response. Clearly, based on the triplication of many inflammation associated genes in DS neuroinflammation should be a focus of future studies.

Microglial cells, key mediators of inflammation in the brain, also show morphological and pathological changes in people over the age of 40 years with DS (Figure 2D) and may be tightly linked to NFT accumulation [138]. Interestingly, a lack of microglial activation was also reported in this study suggesting that the neuroinflammation theory be reconsidered both in DS and in AD [138]. It should be noted, however, that the classical markers of microglial activation used for immunohistochemical studies do not inform the functional state of the microglial cell. Markers such as MHC-II and CD45 are associated more with an anti-inflammatory / wound repair type of microglial response that includes expression of matrix remodeling proteins, IL-4 and IL-10 (reviewed in [139]).

Neuron Loss in DS

Neuron loss is seen early in subcortical areas of DS brain such as locus coeruleus [140, 141] and basal forebrain nuclei [142], as well as entorhinal cortex [143], followed later by neuron loss in hippocampus and temporal cortex and other cortical areas [144]. As in AD, noadrenergic neuron loss in DS occurs in the rostral area of the locus coeruleus in which neurons project to the cerebral cortex, hypothalamus and forebrain, but not in the caudal region [141]. Cholinergic neuron loss in basal forebrain nuclei that project to hippocampus and cerebral cortex, such as the nucleus basalis of Meynert, increases with age and AD pathology in DS [145]. Thus, it is possible that early synapse loss in AD and DS cortex may reflect retrograde neurodegeneration in subcortical nuclei. In addition, while overall entorhinal cortex volume was reduced 42% in older DS brain, the number of intact, NFT-free neurons was reduced by 90% compared to controls, suggesting that neurofibrillary degeneration was the main cause for neuron loss in DS [143]. However, Mann and colleagues reported proportionally less overall neuron loss in older DS brain than sporadic AD brain due to the lower number of neurons in these brain regions in young DS individuals compared to young controls, and thereby suggesting that those with DS have less neuronal reserve [144].

White Matter Degeneration in DS

In addition to AD cortical pathology, there is some evidence of white matter (WM) degeneration that is more extensive in DS relative to non-DS autopsy cases or that increase with age and disease. Further, diffusion tensor imaging (DTI) studies have shown white matter degradation in non-DS women with a family history of dementia and at least one apolipoprotein E4 allele. While structural imaging studies have suggested a greater AD risk

in non-DS individuals with WM degeneration [146], there are few systematic studies of large collections of DS autopsy samples or DTI. Therefore, there are many gaps in our knowledge regarding the role of WM pathology and dementia.

Aβ deposits and APP accumulation has been observed in the WM of the frontal cortex in DS [84, 147]. Ubiquitin positive punctuate deposits, that correspond to WM degeneration in the frontal cortex, increases after 21 years of age in DS [148]. Interestingly, this pattern was virtually identical to non-DS autopsy cases. Corpora amylacea, thought to reflect swollen glial processes has also been observed in the frontal WM of a 32 year old DS case [149]. The most recent study of WM pathology in DS showed that αB-crystallin, which is a member of the heat shock protein family, was increased as a function of age up to 23 years in DS (older ages were not included in the study) [150]. Given the role of αB-crystallin in acting as a molecular chaperone to prevent aggregation of proteins and maintaining proteins in a folding-competent state under stress conditions, this suggests that the DS brain is under potentially chronic levels of stress and that WM is particularly vulnerable. Indeed, DRYK1a (a gene on chromosome 21), is expressed at higher levels in DS compared to controls when WM of the corpus callosum was examined [151] and may be a contributor to WM vulnerability to stress. Thus, in combination, there are several studies over the past two decades suggesting frontal cortex WM pathology and degeneration with age in DS.

WM degeneration may be caused by the development of AD or the aging process but is also strongly associated with cerebrovascular disease and associated risks. Although the risk of cerebrovascular accident in aging persons with intellectual disability is not different from the general population, the number of people with DS included in this study was small [152, 153]. In several ways, people with DS may be protected from cerebrovascular incidents given reports of generally lower blood pressure [154] and lower incidence of atherosclerosis [79, 153, 155]. However, Aβ is deposited along blood vessel walls in people with DS in older ages and this can lead to cerebrovascular compromise and hemorrhage [87].

Possible Synaptic Compensatory Responses in DS Brain

There are over 200 genes on chromosome 21 that may not only contribute to pathological events observed in the aging DS brain, but also may be protective [156]. For example, in vivo imaging studies of glucose utilization shows increased activity in the DS entorhinal cortex prior to the development of dementia [157]. Consistent with this observation are the results of an autopsy study showing a possible sprouting phenotype in the hippocampus of similarly aged DS brains [119]. More recently, in a study measuring the protein levels of synaptophysin and synaptojanin 1, the latter is on chromosome 21 and overexpressed in DS, interesting dissociations from sporadic AD was observed. In DS, despite a reduction of synaptophysin protein levels with AD, similar to that seen in sporadic AD, synaptojanin 1 was increased in DS with AD [158]. Further, higher levels of synaptojanin 1 were correlated with several measures of Aβ suggesting the two events may be related. It will be interesting in future studies to characterize other proteins with genes on chromosome 21 to determine of other possible compensatory events occur with or precede the development of AD neuropathology. Given that there is approximately a decade delay between the development

of AD pathology and clinical signs of dementia, protective genes may delay impaired neuronal function in DS.

Future Directions

Although this review is not exhaustive, there are gaps in our knowledge regarding the progression of AD neuropathology as a function of age in DS. For example, it is unclear if the regional and temporal progression of AD neuropathology in DS is similar or different from sporadic AD. Further, a detailed examination and systematic description of the distribution of neuritic and diffuse plaques and CAA within the hippocampus and cortex as well as other brain regions such as striatum and cerebellum, and how this varies with age and dementia in DS, would be helpful in the future. The development of networked collections of autopsy cases, with standardized collection procedures and including biochemical analyses will provide significant new advances. It will be critical to determine how various pathologies as we discussed here may interact over time to lead to dementia. In turn, understanding the progression of events and more fully characterizing which pathologies evolve at which ages in DS will lead to new therapeutic opportunities, which may include preventative approaches.

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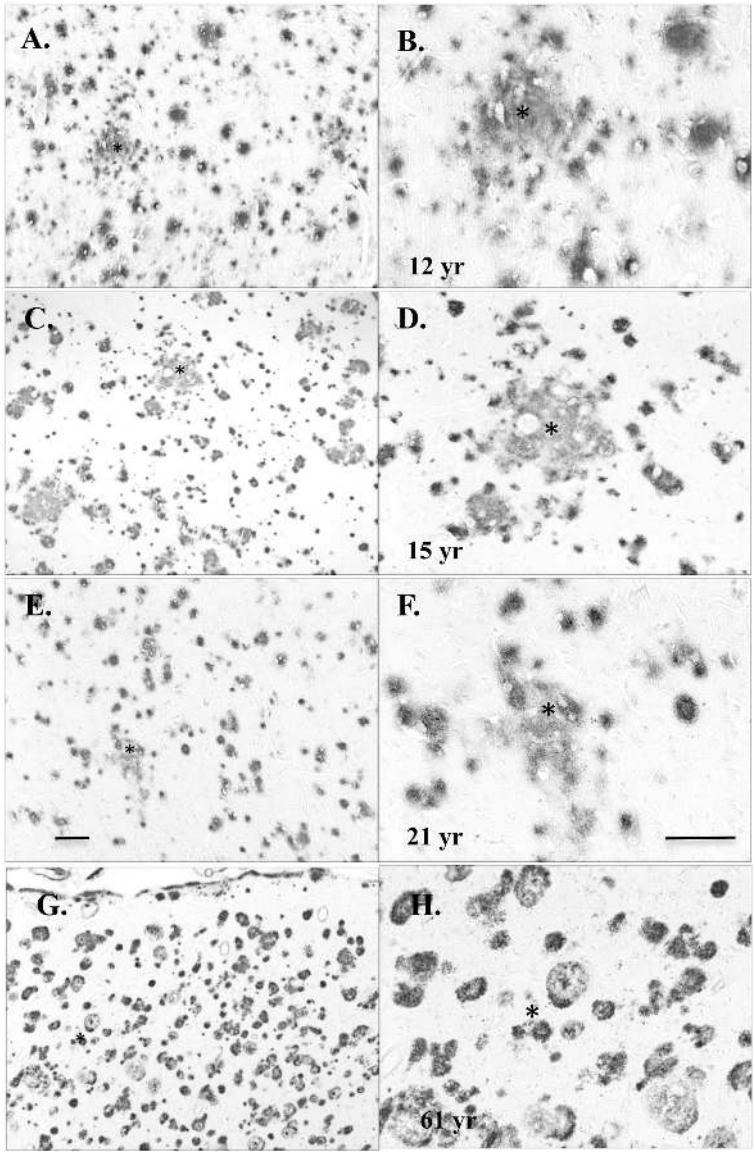

Figure 1.

Aβ42 immunostaining in the frontal cortex of DS autopsy cases ranging in age from (A, B) 12 years, (C, D) 15 years, (E, F) 21 years and (G, H) 61 years. Note the extensive diffuse plaque deposition in younger cases compared with compared with cored and compacted plaques, subpial plaques and vascular amyloid in the older DS brain. (C42 pAb kindly provided by Dr. Takaomi Saido at the RIKEN Brain Institute, Japan and described in [38]). Plaques denoted by an asterisk at low magnification on the left (A, C, E, G) are shown at high magnification on the right (B, D, F, H). Scale bars, 100 microns.

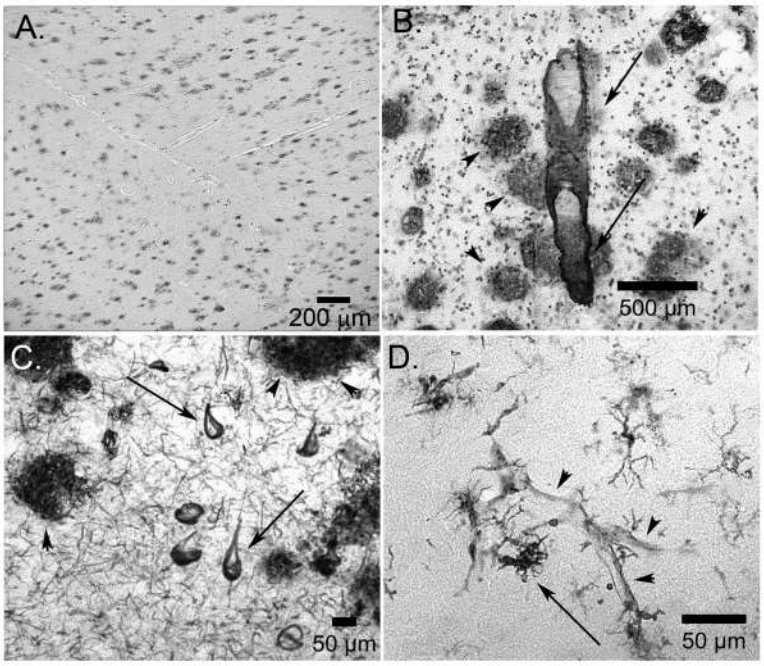

Figure 2.

Neuropathological features of DS brain. (A) Diffuse plaque labeling using an antibody against Aβ(R1282, gift from Dr. D. Selkoe, Boston, MA) in the temporal cortex of an individual with DS aged 21 years. (B) Significant cerebral amyloid angiopathy in a 46 year old male with DS and AD detected by immunostaining of the frontal cortex with Aβ1-40 antibody (arrows), which can be distinguished from extracellular plaques (arrowheads). (C) Neurofibrillary tangles labeled using the PHF-1 antibody (provided by Dr. Peter Davies-arrows) in the frontal cortex of a 46 year old male with DS and AD. (D) Immunostaining using IBA-1 for microglial cells shows significant hypertrophy (arrows) and association with the cerebrovasculature (arrowheads) suggesting neuroinflammation.