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Clinical aspects and biomarkers of Alzheimer's disease in Down syndrome

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Abstract

Alzheimer's disease (AD) may affect in excess of 90% of individuals with Down syndrome (DS) after age 60, due to duplication of the APP gene in trisomy of chromosome 21, with neuropathology that is comparable to Sporadic AD and Familial AD (FAD). Previous literature suggested some unique features in clinical presentation of dementia in DS (DSd), which might be due to diagnostic difficulties, or represent a real difference compared to SAD or FAD. We review current knowledge on clinical diagnosis and presentation of dementia in DS in comparison with FAD due to APP mutations and APP duplication. We suggest that the clinical presentation in DS (prominent memory decline and behavioral symptoms, and early development of myoclonus and seizures) are similar to the clinical features associated with APP mutations that is known to have an increased Aβ42/ Aβ40 ratio, and highlight the relative lack of vascular complications associated with cerebral amyloid angiopathy in DS in comparison with those rare individuals with FAD due to duplication APP. We consider the biomarker evidence associated with DS and DSd with reference to Aβ peptide levels and oxidative stress, and suggest future directions for research to explore the potential mechanisms associated with the clinical presentation of DSd.

Keywords

Down syndrome; Alzheimer's disease; Familial; APP mutation; biomarkers

1 Introduction

Almost all older adults with Down syndrome (DS) have the neuropathological hallmarks of Alzheimer's disease (AD) at post-mortem, consisting of progressive build-up of extracellular amyloid- (Aβ) plaques and intraneuronal hyperphosphorylated tau [1], which can now also be demonstrated with in-vivo amyloid PET imaging techniques [2, 3]. As all individuals with DS over the age of 50 who have undergone amyloid PET imaging have been shown to have significant amyloid deposition, AD brain pathology is probably universal in ageing individuals with DS.

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At the gross pathological level, AD in DS is similar to the AD pathology associated with sporadic Alzheimer's disease (SAD), and many types of familial Alzheimer's disease (FAD). However, there are important differences in terms of genetic mechanisms between DS, SAD, and FAD. In DS with trisomy of human chromosome 21, AD is believed to be related to triplication of the APP gene, and the basic mechanism leading to the AD pathology is lifelong overproduction of APP, which is associated with deposition of Aβ [4]. DS is therefore comparable to Aβ overproduction associated with several other FAD mutations, while reduced clearance of Aβ is implicated in SAD [5].

In this review, we will summarize the clinical presentation of AD in DS before considering current knowledge on fluid biomarkers associated with AD in DS in order to highlight similarities and differences with other types of AD, particularly FAD due to APP duplication and other APP mutations.

2 Epidemiology of AD in DS

In keeping with the pathological data, dementia is exceptionally common in older adults with Down syndrome, though as with SAD and FAD with a time lag of several decades after the development of AD pathology. Clinical dementia diagnoses show a sharp age-related increase in prevalence (i.e. cross-sectional rates), from less than 10% by age 49 to more than 30% by age 60 [6]. However, as dementia is now a common cause of death in people with Down syndrome [7], prevalence rates may underestimate overall risk and longitudinal studies show that the cumulative incidence for dementia in people with Down syndrome is in excess of 90% by age 65 [8]. Although prevalence rates may go down with age (particularly after age 60) due to increased mortality in older individuals with DS and dementia (DSd) [9], incidence (rate of new cases) increased steadily with increasing age and did not decline after age 60, from 2.5 per 100 person years in those aged <50 to 13.31 per 100 person years in those aged 60 and older [9].

While age is a strong common risk factor, DSd is thus similar to FAD with a much earlier age of onset, several decades before the typical onset seen in SAD. In families with PSEN1 mutations, for example, the typically age at diagnosis is within the range 35-55 years, but cognitive symptoms may manifest earlier, while those with PSEN2 mutations present between 40-70 years [10]. Individuals with APP mutations tend to have symptom onset between 40-65 years. DSd is thus comparable to FAD in terms of age of onset of dementia.

No gender differences have been found for dementia rates in older adults with DS [9, 11], but the average age of menopause of women with DS was younger than in the general population, and the age at onset of dementia was correlated with the age of menopause for those who developed dementia [12].

3 Clinical diagnosis of AD in DS

Dementia is clinically defined as a progressive brain disorder which particularly affects higher cortical functions such as memory, language and orientation, and which eventually leads to death [13]. There are challenges to diagnosing dementia in individuals with DS. These include premorbid intellectual impairment and functional difficulties that need to be

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distinguished from subsequent decline, varying baseline functioning, and limitations in speech abilities, which means the usual AD screening and diagnostic tools may not be suitable in DS [6, 14]. The development of dementia symptoms also need to be understood in the context of a typical DS cognitive phenotype, including impairments in executive function, memory and motor coordination [15]. Therefore, a diagnostic work-up needs to carefully establish the presence of cognitive deterioration that is typical of AD in DS, with reference to the person's own baseline, while excluding common co-morbidities such as depression or thyroid dysfunction which are also common causes of apparent decline in DS [16]. Several diagnostic systems are available to diagnose dementia. The International Statistical Classification of Diseases (ICD) 10 system's criteria include decline in memory, together with decline in other cognitive abilities such as organization, judgement and information processing and decline of emotional control and social behavior such as emotional lability and apathy [13]. The Diagnostic and Statistical Manual (DSM) system has a similar definition, though does not require the presence of behavioral change in the form of decline in emotional control and social behavior. The DSM-IV was found to be more inclusive than ICD-10 when used in individuals with intellectual disability [17], but predictive validity was less good when used in individuals with more severe intellectual disability and sensory deficits than in the general population despite good inter-rater reliability [18]. Overall a clinical diagnosis of dementia appeared to be more reliable in individuals with DS than these standard criteria and enabled clinicians to diagnose more cases of individuals with DS with AD [18], suggesting that there are some issues when applying standard criteria in the presence of premorbid cognitive impairment. There are however newer versions of criteria, such as the DSM-5 neurocognitive disorder diagnosis, which may help to improve accuracy of diagnosis in DS [19]. Interestingly, the DSM5 and other newer research criteria view DS as a genetic cause of AD, which potentially allows for a diagnosis of probable AD even if symptoms are relatively mild.

4 Presenting symptoms in DS compared to FAD and SAD

Memory decline is viewed as the key symptom associated with AD, and the majority of individuals with SAD and FAD present with early impairment of episodic memory, which gradually progresses to involve other cognitive domains. However, there are possibly some subtle differences between SAD and FAD. Longitudinal studies of FAD mutation carriers showed that the earliest neuropsychological changes were a decline in verbal memory, which occurred approximately 3 years before symptoms became apparent [20]. Similarly, SAD is also preceded by a relatively long prodromal stage, with an amnestic picture, such as that described in mild cognitive impairment [21]. Nevertheless, atypical presentations are often reported in FAD and also exist in SAD. Behavioral and psychiatric symptoms of dementia (BPSD) such as agitation, depression, delusions and hallucinations occur commonly in SAD as the disease progresses. Early BPSD may also occasionally be a feature of PSEN1 and PSEN2 mutations which become more prominent during the course of the disease [10].

4.1 Typical DS dementia presentation

There is ongoing debate whether there are significant differences in dementia presentation in DS compared to SAD or FAD. Previous studies suggested that BPSD's may precede

memory impairment [22] in keeping with a frontal-like syndrome [23]. Several studies have described BPSD's that often precede dementia diagnosis in adults with DS [24 – 26]. Individuals with DSd often present with behavioral problems [27, 28], which can be divided into two types – behavioral excesses such as irritability, aggression or self-abusive behavior, or behavioral deficits such as general slowness, apathy or loss of interest and decreased social engagement; behavioral excesses rather than deficits may trigger referral for dementia assessment [29], suggesting that caregivers' bias may influence reporting and referral for symptoms. Caregivers reported forgetfulness and confusion as well as 'frontal lobe'-related symptoms such as slowness in activities and speech, loss of interest and withdrawal, along with the emergence of emotional and behavior problems as common presenting symptoms of dementia [30]. More recently, Dick et al. compared the neuropsychological profiles of higher-functioning DS individuals with dementia to individuals with advanced SAD while adjusting for gender and levels of functional impairment [31]. They found similarities in presentation, suggesting the underlying pathology may have comparable effects on cognitive profiles in both DS and SAD, at least during the later stages of AD.

Establishing the sequence of early cognitive changes in DS associated with progression during prodromal AD remains a challenge. However, using longitudinal studies, it has been shown that changes in short-term recall and explicit memory may occur several years before a dementia diagnosis [32, 33] and recently it has been reported that immediate memory impairment may be one of the earliest signs of dementia in people with DS [34]. It is not clear what proportion of DS individuals initially present with the typical changes in memory domains that is typical of SAD, or with the atypical presentations associated with some of the FAD mutation carriers. In addition, language-based tasks are inherently difficult for individuals with DS, given the typical DS premorbid cognitive profile (which includes short-term verbal memory deficits) [35]. A better understanding of the sequence of decline in the presymptomatic and early stages of DSd is required to identify suitable outcome measures for future clinical trials.

4.2 Unusual clinical presentations

Visuospatial and visuoperceptual deficits commonly occur in the later stages of both SAD and FAD. The posterior cortical atrophy (PCA) variant of SAD is now well-recognized, with prominent visual processing deficits while memory is relatively preserved until later in the disease [36]. PCA may present with earlier onset and affects parietal, occipital and occipito-temporal brain regions, therefore have an impact on literacy, numeracy and praxis. Some studies have found increased neurofibrillary tangles but similar amyloid plaque density in visual areas, with fewer tangles or plaques in the hippocampus in PCA compared to typical SAD, possibly associated with particular genetic status (including APOE4) [37]. There are no data on PCA-like presentations in DS, but anecdotally some individuals may present with visuoperceptual difficulties including difficulty managing stairs or steps, being scared of sitting on chairs and having difficulty managing toiletting due to not being able to discriminate toilet seats from background colors [38].

4.3 Neurological symptoms and signs

Neurological symptoms and signs tend to be more prominent in FAD than SAD, and is also common in DSd. Up to half of DS dementia cases may present with neurological symptoms, such as seizures and incontinence, which are normally signs associated with advanced disease in SAD, suggesting that dementia presents atypically in DS, or reflecting the diagnostic difficulties, particularly in those with more severe ID [6]. In FAD, seizures seem to be reported more frequently and at an earlier stage in the disease than in SAD, occurring in more than a third with APP mutations [10]. Early myoclonus and seizures are observed in individuals with *APP* mutations and particularly those with *APP* duplications (table 1).

Myoclonus and seizures are also very common in DS dementia, and have been described as the presenting symptom in some cases of especially in those with severe ID [11, 39 – 41]. Seizures are also predictive of rate of decline [42]. Indeed, seizures are so strongly associated with AD in older individuals with DS that the onset of seizures in older age should trigger an assessment for dementia [38]. Seizures are commonly myoclonic or tonic-clonic types, with an earlier picture characterized by myoclonic jerks on awakening, and progression to generalized tonic-clonic seizures. EEG may reveal generalized slowing or spike and wave pattern [43, 44].

Parkinsonism and cerebellar signs do not usually become apparent until several years into the clinical course of SAD, but may be more strongly associated with some forms as FAD, such as PSEN1 and PSEN2 mutations. Cerebellar Aβ deposition is a common feature in both FAD and SAD. Extrapyramidal signs such as rigidity, bradykinesia and an abnormal posture and gait has also been described in DS dementia [40] and by end-stage, all individuals were unable to walk and incontinent, and almost all had seizures [8] and many had Parkinsonian features [39, 41]. Cerebellar ataxia may however be an overlooked sign of dementia in DS, since brains of elderly patients with Down syndrome have also been found to have significant cerebellar Aβ deposition [45].

5 APP mutations and APP duplications compared to DS

The APP gene is situated on chromosome 21, and mutations in this gene is therefore of particular interest in comparison with DS. The majority of pathogenic APP mutations affect the β and γ secretase cleavage sites of the protein, while in the case of APP duplications, there is an extra copy of the whole of the APP region on chromosome 21. These individuals with APP microduplications therefore have the same genetic mechanism for AD as in DS, while not having extra copies of most of the other genes on the rest of chromosome 21 and therefore do not present with features of DS such as intellectual impairment or congenital heart conditions [4].

APP mutations can be classified according to their biological effect on Aβ levels (table 1). Firstly, mutations that increase total Aβ without changing the Aβ42/40 ratio, such as the Swedish mutation at APP670/671, are associated in affected individuals with prominent memory loss and a classic Alzheimer's disease presentation [46].

Other APP mutations result in increased Aβ42 levels, altering the AB42/40 ratio. Of this type, the 'London' *APP* V717I mutation has a change at the 717 codon close to the γ secretase site. Families with this mutation were found to present with early impairment of episodic memory, lack of insight and prominent myoclonus and seizures [47]. A so-called Austrian mutation (T714I) results in a 11x increase in Aβ42 levels, and presented clinically with rapidly progressive and very early onset dementia with early memory loss, seizures, myoclonus, parkinsonism, spasticity, and behavioral symptoms. It was at post-mortem found to be associated with notably absent Aβ40 from amyloid deposits in the brain, and the deposits were largely in the form of "cloudy" diffuse plaques with a non-neuritic cotton-wool appearance [48].

Some APP mutations result in changes in Aβ aggregation. These include the 'Dutch mutation' (E693Q) with a distinct phenotype with severe cerebral amyloid angiopathy (CAA) leading to recurrent cerebral hemorrhage (ICH) and consequent focal neurological symptoms and signs. Most patients also develop dementia [49]. A neighboring mutation at position 692 (Flemish mutation) has also been reported to present with hemorrhages and a progressive dementia associated with CAA [50]. Interestingly, this mutation has been shown to inhibit aggregation, but fibril formation is specifically increased through interaction with gangliosides in the vascular wall, resulting in CAA [51]. The Iowa mutation (D694N) also promotes fibrillogenesis of Aβ with severe CAA on pathological investigation, widespread neurofibrillary tangles and amyloid plaques with particularly prominent Aβ40 deposition often resulting in ICH and hemorrhagic stroke [52].

Duplications of the *APP* gene can also cause FAD with a cognitive phenotype that is similar to SAD, with early progressive impairment of episodic memory but with an onset age of between 39 and 64 years [53–55]. Characteristic features include seizures (up to 57%) as well as prominent amyloid angiopathy (CAA) with hemorrhagic stroke occurring in a third of individuals [56]. In comparison, ICH and stroke appears to be rarer (3-4%) in individuals with DSd [57] despite the similar APP mechanism.

At the clinical level, DSd therefore seems to present with a symptoms similar to those APP mutations that have an altered Aβ42/40 ratio, and unlike FAD due to APP duplication, seems to be somewhat protected against ICH and hemorrhagic stroke, suggesting the potential presence of a mechanism/s associated with chromosome 21 triplication that shifts the risk away from vascular complications. Such a protective mechanism might involve amyloid processing or clearance, vascular protective factors, a unique oxidative stress profile or immune response [56]. We next review biomarker evidence, with a particular focus on biomarkers that might shed light on the apparent difference in clinical presentation of dementia between duplication APP and trisomy 21.

6 Fluid biomarkers of AD in DS (table 2)

Biomarkers are objective measures of a biological or pathogenic process that can be used to estimate the risk for developing a disease, to guide clinical diagnosis, to evaluate prognosis, to monitor progression and/or response to therapeutic interventions [58]. Biomarkers can be

found in different types of fluids, including blood (serum or plasma), cerebrovascular fluid (CSF), and urine.

6.1 Peripheral fluid biomarkers

6.1.1 Blood biomarkers—The advantage of plasma and serum is that they are easily available and considered as relatively non-invasive. In AD several novel blood biomarkers have been proposed, although verification and validation in independent studies remains to be further established [59].

Amyloid-beta: Amyloid-beta plays a central role in the pathogenesis of Alzheimer's disease (AD) and has been postulated as a potential biomarker for AD in the general population [60]. DS subjects show higher plasma Aβ42 and Aβ40 levels compared to cognitively normal subjects without trisomy 21 [61, 62]. Although some studies found no differences comparing DS with and without dementia, an association between Aβ levels and neuropsychological scores in multivariable adjusted models was found [61, 63]. Also, demented DS subjects with longer dementia duration showed higher Aβ42, lower Aβ40 and a higher Aβ42/Aβ40 ratio than those with shorter dementia duration [63]. Two other studies comparing DSd to cognitively normal DS found a higher Aβ42/Aβ40 ratio in DSd [64] and increased Aβ40 levels in DSd subjects [65], having adjusted for age and gender, that remained stable during a follow-up of several years. It is however difficult to draw any conclusions from these studies with regard to Aβ42/Aβ40 ratios in DS given the relatively weak correlation between these peripheral measurements and central Aβ.

Tau: Tau are proteins that stabilize microtubules and they are abundant in neurons of the central nervous system [66]. Plasma tau levels are elevated in AD but with overlapping ranges across diagnostic groups [67], which diminishes the utility of plasma tau as a diagnostic test [67, 68]. DS subjects, with or without dementia, also show higher plasma tau levels compared to age-matched normal subjects [69]. As tau levels correlate with cognitive scores, plasma tau levels in DS may indicate early neurodegeneration [69].

Oxidative stress markers: Although AD is probably associated with multiple etiologies and pathophysiologic mechanisms, oxidative stress appears as a major part of the pathophysiologic process [70]. The anti-oxidant system is affected in DS, even before the onset of AD, and implicated in the cognitive phenotype associated with the chromosomal disorder; however the variations in the phenotype might result from several possible gene or gene product interactions [71]. Studies in young people with DS revealed a systemic and exacerbated oxidative stress [72], which increases with age [73].

In DS subjects, low superoxide dismutase/glutathione peroxidase (SOD1/GPx) ratios are associated with worse memory ability [74] and in a longitudinal study it was shown that superoxide dismutase enzyme levels are associated with memory decline over time [75].

Neopterin, an unconjugated pteridine that is secreted in large quantities by activated macrophages, can be used as a clinical marker of activated cellular immunity and oxidative stress in AD [76]. Plasma neopterin levels have been found to be higher in patients with AD in general [77, 78] and people with DS and AD in particular [79, 80].

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In summary, DS is associated with increased oxidative stress, which is present even in younger individuals, and it appears that markers of oxidative stress worsen during ageing, and with the development of AD in DS. Higher superoxide dismutase levels relative to glutathione peroxidase could protect against decline but it is not clear how this and other effects related to trisomy 21 affect the presentation of dementia in DS, or whether it could explain apparent differences with individuals with FAD due to APP microduplication.

6.1.2 Urine biomarkers—Similarly to blood, the advantage of urine is that it is easily obtainable and non-invasive. Although few urine biomarkers have been studied in the general AD population (such as neural thread protein, a phosphoprotein associated with the neurofibrillary tangles of AD [81, 82], no specific studies of urine biomarker of AD in DS have been conducted to date other than urine markers of oxidative stress or activated cellular immunity.

Isoprostane 8,12-iso-iPF2alpha: Isoprostane 8,12-iso-iPF2alpha are chemically stable, sensitive and specific biomarkers of lipid peroxidation in vivo [83] and have been shown to be increased in Alzheimer's disease [84], and may mediate the neuronal response to oxidative stress [85]. In a longitudinal study in subjects with DS, it was shown that change in iPF2alpha levels over time may have potential as a biomarker for memory decline in DS and potentially also help to track progression of MCI to AD [86].

Neopterin: Similarly to the findings in plasma neopterin levels described above, urine neopterin might also have a potential as a biomarker of AD in DS. In a longitudinal study involving individuals with DS it was shown that neopterin/creatinine levels correlated with cognitive performance over time [87].

6.2 CSF biomarkers

A major advantage of CSF biomarkers is the fact that proteins or peptides that may be directly reflective of brain specific activities as well as disease pathology would most likely diffuse into CSF rather than into any other bodily fluid [88]. However, CSF is not easily available and collection is invasive through lumbar puncture. As a result, few CSF studies in DS have been conducted, with very small numbers of participants [89]. However, in a recent systematic review and meta-analysis of biomarkers for the diagnosis of Alzheimer's disease in the general population it was clearly shown that the core CSF biomarkers of neurodegeneration (amyloid-beta, P-tau and and T-tau) are strongly associated with AD mild cognitive impairment and due to their consistency CSF biomarkers should be used in clinical practice and clinical research [90]. In particular, in AD patients, T-tau is on average 2.5 times higher in CSF compared to controls, P-tau is almost 2 times higher in CSF compared to controls, when Aβ42 is almost 2 times lower in CSF compared to controls [90].

Amyloid-beta—CSF Aβ42 levels are lower in DS compared to non-DS control subjects and correlate negatively with age in the DS population [91]. In early childhood, Aβ levels tend to increase in DS, followed by a gradual decrease (reduced clearance from the brain) once the deposition of Aβ42 into plaques augments, similar to the pattern also observed in SAD and FAD [92]. Well-designed longitudinal data from larger studies to track change over

time, and to compare CSF amyloid-beta levels between demented DS patients and non-demented DS, and to make comparisons with individuals with APP mutations or duplication APP are not yet available.

Tau—CSF tau levels do not differ between DS and control subjects but appear to correlate positively with age in DS individuals [91]. Well-designed large studies comparing CSF tau levels between demented DS patients and non-demented DS are not yet available, and it is thus unknown how changes in CSF tau levels relate to the development of dementia, or whether it might help to distinguish DS individuals with and without AD.

Presenilin-1—Presenelin-1 is one of the core proteins in the gamma sectretase complex, involved in APP processing. CSF presenilin-1 shows an age-dependent increase in cognitively normal controls [93]. However, the total levels of CSF presenilin-1 increased in subjects with autosomal dominant AD that carried PSEN1 mutations but also in DS individuals (ten demented and ten non-demented DS), compared with age-matched controls, even prior to the appearance of symptoms of dementia [93]. The implications of this finding are not clear, but CSF presenilin-1 appears to have potential as an early biomarker for AD in DS.

Oxidative stress markers—Studies involving oxidative stress markers in CSF have only been conducted in small studies of non-DS patients with MCI. Such patients present with higher isoprostane 8, 12-iso-iPF2alpha (iPF2alpha) levels in CSF compared to cognitively normal elderly subjects [94]. This finding suggests that increased brain oxidative damage precedes the onset of symptomatic dementia and that measurement of this isoprostane may identify a subgroup of patients with MCI with increased lipid peroxidation who are at increased risk to progress to symptomatic AD [94]. A well-designed large study comparing CSF iPF2alpha levels between demented DS patients and non-demented DS is not yet available.

7 Conclusions and future directions

The 40-amino-acid peptide Aβ (Aβ 40) is more soluble than the longer Aβ 42 peptide and tends to be the major form of Aβ in the artery walls in CAA, while Aβ 42 is more prominent in plaques. In mutations where Aβ 42 is increased, such as the Indiana and London APP mutations, vascular amyloid seems to be a less prominent feature than parenchymal plaques. In contrast, if a low Aβ 42/40 ratio is present, and in those mutations that result in altered fibril formation, CAA is promoted. The clinical presentation of AD in DS, with cognitive decline and worsening memory impairment in combination with behavioral changes, myoclonus and seizures, are comparable to APP mutations that result in increased Aβ42 levels relative to Aβ40 (and possibly other smaller Aβ peptides). Furthermore, in DS there is some evidence for a degree of protection against the CAA and ICH phenotypes usually associated with APP duplication, although a moderate degree of CAA and microbleeds have been demonstrated in DS neuropathological studies.

Though peripheral fluid biomarkers are more accessible, CSF biomarkers, similarly to their role in AD in the general population, probably have better potential in predicting AD or

monitoring cognitive function in DS, and also need to be used to make comparisons with FAD, particularly the different forms of APP mutations and APP duplication. More studies including CSF biomarkers are needed in DS.

The underlying mechanism for the typical presentation of DSd is not clear. However, Amyloid Protein Precursor (APP) is processed in the endo-lysosomal compartment, and modifications within these pathways may therefore contribute to changes in Aβ concentrations involved in the onset of AD. The endo-lysosomal compartment is morphologically different in DS peripheral cells compared to euploid cells [95], and enlarged endosomes have been described in neuronal cells from post-mortem brains of individuals with SAD and DS [96]. The implications of these differences in terms of amyloid processing and Aβ peptides need to be further explored, as well as to identify the underlying mechanisms.

Finally, markers of oxidative stress have potential as biomarkers of cognitive function in DS populations. However, more longitudinal and case-controlled studies are needed to confirm the exact role of oxidative stress in pathogenesis of AD in DS, as well as its role in the clinical presentation of dementia in DS.

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Table 1

	Biological effect	Memory/cognitive decline	Behavioural/emotional/personality changes	Myoclonus/seizures	Intra-cerebral haemorrhage/stroke
AD-type APP mutations e.g. Swedish mutation – KM670/671NL London Mutation - V717I	Increased total Aβ Unchanged Aβ42/40 Increased total Aβ42 Increased Aβ42/40 ratio	Prominent Prominent	Uncertain/rare Relatively prominent	Late stages Prominent	Absent/Rare Absent/Rare
CAA-type APP mutations e.g. Dutch mutation E693Q; Italian mutation E693K	Altered APP processing, increased Aβ aggregation Reduced Aβ42/40 ratio	Late stages	Absent / Rare	Uncertain	Prominent
Duplication APP CNVs	APP overproduction, Aβ Subspecies ratios unknown	Prominent	Uncertain/ rare	Prominent	Prominent
Down syndrome	APP overproduction, Aβ Subspecies ratio unknown	Prominent	Prominent	Prominent	Occasional stroke