A Review of Biomarkers for Alzheimer’s Disease in Down Syndrome

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ABSTRACT

Down syndrome (Trisomy 21; DS) is a unique disease known to be associated with early-onset Alzheimer’s disease (AD). The initial presentation of AD in DS is usually difficult to recognize, owing to the underlying intellectual disabilities. Using biomarkers as a prediction tool for detecting AD in at-risk people with DS may benefit patient care. The objective of this review is to discuss the utility of biomarkers in DS on the basis of the pathophysiology of the disease and to provide an update on recent studies in this field. Only through the comprehensive assessment of clinical symptoms, imaging studies, and biomarker analyses can people with DS who are at risk for AD be diagnosed early. Studies for biomarkers of AD in DS have focused on the common pathophysiology of AD in people with DS and in the general population. The most extensively studied biomarkers are amyloid and tau. Owing to the nature of amyloid precursor protein overproduction in DS, the baseline β-amyloid (Aβ) plasma levels are higher than those in controls. Hence, the changes in Aβ are considered to be a predictive marker for AD in DS. In addition, other markers related to telomere length, neuroinflammation, and methylation have been investigated for their correlation with AD progression. Future studies including different ethnic groups may be helpful to collect sufficient data to monitor drug safety and efficacy, stratify patients at risk for AD, and quantify the benefit of treatment.

Keywords: Alzheimer’s disease; Amyloid; Biomarker; Down syndrome; Tau

INTRODUCTION

Down syndrome (DS) is the most common aneuploidy associated with intellectual disability, with an incidence of approximately 1 in 800 live births [1, 2]. Children with DS often have multi-systemic manifestations, including intellectual disabilities, short stature, facial dysmorphism, congenital heart disease, thyroid dysfunction, leukemia, and various other congenital malformations [3]. With improvements in medical care, the life expectancy of this cohort has increased to the fifties and sixties [4]. People with DS who live into adulthood face additional problems other than those occurring in childhood. A general acceleration of the
Aging process usually occurs starting at 30 years of age involving premature menopause, presbycusis, alopecia, premature graying of hair, Alzheimer’s disease (AD), congestive heart failure, atherosclerosis, diabetes, hypercholesterolemia, autoimmune disease hypertension, and cataracts [5–8]. Among the clinical presentations of accelerated aging, AD is the most significant. The prevalence of AD among patients with DS increases from 8% in the age range of 35–49 years to 55% in the age range of 50–59 years and 75% above the age of 60 years [9], thus further highlighting the importance of AD in DS. This article is based on previously conducted studies and does not describe any new studies on humans or animal subjects performed by any of the authors.

Pathophysiology of Alzheimer’s Disease in Down Syndrome

The neuropathological changes in DS with AD have been described as being similar to those in the general population with AD [10]. However, the timing of the amyloid deposition occurs decades earlier [11]. Postmortem DS brains have been reported to show neurofibrillary tangles, cerebrovascular pathology, white matter pathology, oxidative damage, neuroinflammation, and neuron loss [12–15]. On the basis of the above observations, a multifactorial hypothesis explaining the pathophysiology of AD in DS, in which the two diseases are linked by the amyloid theory, cholesterol metabolism, oxidative stress, immune response, amyloid precursor protein (APP) processing and clearance, and neuroinflammation, has been proposed [16, 17]. This hypothesis suggests that the link between these two diseases indicates a common etiological pathway.

Amyloid and Related Theories

After the discovery of β-amyloid (Aβ) as the major constituent of amyloid plaques, the APP gene, located on chromosome 21, was considered the key component in the amyloid cascade hypothesis [16]. The accumulation of Aβ in the brains of DS patients may be explained by the hypothesis of the “gene dosage effect”. In a DS fetal brain, the expression of APP genes is 1.6 times higher than that in a euploid brain [18]. Overexpression of APP contributes to the accumulation of diffuse, extracellular deposits of Aβ in the brain during the second and third decades of life in DS patients [6]. Subsequently, formation of fibrillar plaques by the end of the fourth decade has been observed [19]. Neurofibrillary degeneration results in impaired neuron function and eventual cell destruction, with patterns similar to that in AD [6]. Recently, researchers have suggested that the neurotoxicity of Aβ comes directly from the induction of oxidative stress and indirectly from the activation of microglia [9]. According to the evidence suggesting that oxidative stress and energy depletion induce intracellular accumulation of Aβ, alterations in mitochondrial energy metabolism and reactive oxygen species (ROS) production might be involved in the pathogenesis of neuro-degeneration in DS [20–22]. However, the location of Aβ deposition is different between normal subjects and those with DS. The Aβ deposits in early onset AD begin in the basal cortex, whereas Aβ deposits in DS occur in the hippocampus [16, 23]. This observation has been explained by differences in the aggregation kinetics of Aβ in DS due to the higher concentration of the Aβ peptide [16]. In addition, the overexpression of the APP gene as well as factors involved in APP gene expression (ETS2), post-translational modification (SUMO3, DYRK1A, SNC27, and mir-155), and APP protein processing and clearance (PICALM, SORL1, BACE1, and BACE2) are considered to modify the aggregation and deposition of Aβ plaques, thus further affecting the age of onset of AD in DS [16, 24–30].

The formation of neurofibrillary tangles is correlated with cognitive decline [16, 31]. In addition to tau, other genes involved in neurofibrillary tangle formation in AD have been proposed on the basis of studies in the general population. The APOE genotype may affect the development of cognitive abilities that tend to be preserved in early stages of AD in DS [32]. For example, the APOE ε4 polymorphism has been demonstrated to be significantly associated with AD and DS [33, 34]. Furthermore, ESR2 rs4986938 allele C and CYP19 rs1870049

△ Adis
heterozygous (C/T) have been reported [33, 35, 36].

**Neuroinflammation**

Approximately 12 genes involved in inflammation are located on chromosome 21 (CXADR, ADAMTS1, ADAMTS5, TIAM1, SOD1, IFNAR1, IFNAR2, IFNγR2, CBS, S100B, and PRMT2) [37]. The triplication of these genes is considered to affect the inflammatory response to stimuli in microglia/macrophages [37]. Markers for microglia activation, including M2a (CHI3L3, LI-Ra), M2b (CD86), and M2c (TGFB), are elevated in the brains of DS subjects [38], thus resulting in a neurotoxic environment that causes neuronal damage. Furthermore, chromosome 21 carries 299 long non-coding genes and 29 microRNAs, and these microRNAs may also contribute to the onset of dementia in DS [39]. Researchers have hypothesized that the abnormal expression of microRNA (miR-21, miR-103a-1, miR-13a-2, miR-107, miR-9, miR-266, miR-101, miR-124, and miR-34b/c) may play a crucial role in the pathological process of AD [40, 41].

**Diagnosis of Alzheimer’s Disease in Down Syndrome**

The diagnosis of AD in DS is challenging because people with DS already have an intellectual disability that hampers the clinical presentation of cognitive decline. Thus, the routine evaluation batteries used in AD, such as the Mini-Mental State Exam (MMSE), are not applicable for people with DS. Assessing DS in people at a very early stage of AD is more difficult, because the most commonly observed initial changes in DS with AD are usually subtle rather than the cognitive decline or changes in activities of daily living (ADLs) associated with AD in the general population [42, 43]. Before the diagnosis of AD, people with DS may present with behavioral/mood changes for a long time; these changes are usually defined as behavioral and psychological symptoms in dementia (BPSD) [42, 44]. BPSD may present with various behavior and psychological symptoms, including activity disturbance, affective disturbance, apathy, isolation, depression, agitation, aggressiveness, anxiety, phobias, diurnal rhythm disturbance, sleep disorders, psychosis, hallucination, paranoia, delusions, appetite and eating abnormalities, disinhibition, and euphoria [42]. However, the clinical diagnosis of BPSD is also challenging because of the underlying intellectual disability, and the prediction of the transformation of BPSD into dementia is also difficult. In this situation, use of other tools, such as clinical assessment tools, neuroimaging, or biomarkers, to evaluate the pathological changes of AD in DS may be an alternative.

The tools used for the clinical assessment of AD in people with DS must be different from those used for AD in the general population, owing to the underlying intellectual disability. A variety of testing batteries have been reported to evaluate changes in DS, including the Adaptive Behavior Dementia Questionnaire (ABDQ), the Dementia Scale for Down Syndrome (DSDS), the Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQIID), the Dementia Questionnaire for Mentally Retarded Persons (DMR), and the recently developed Rapid Assessment for Developmental Disabilities (RADD) [45–49]. These questionnaires evaluate functional changes by considering their baseline function levels and then quantifying the degree of functional change. Further neuropsychological assessments for cognitive decline are recommended when patients test positive in this form of report. After the functional decline is recognized, a further imaging evaluation, such as with magnetic resonance imaging (MRI) and/or positron emission tomography (PET), may be correlated with the clinical observations.

The amyloid load measured by PET, for example, the Pittsburgh compound B PET (PiB PET), has been used in the assessment of AD in the general population [50]. In DS, the accumulation of amyloid by PiB PET and Florbetaben F18 PET has also been demonstrated [51–53]. In contrast to the observation in the general population, the amyloid deposition in people with DS was first found in the striatum, followed by the rostral prefrontal-cingulo-parietal region, the caudal frontal, rostral temporal,
primary sensorimotor and occipital regions, and then the medio-temporal regions and other basal ganglia, and the deposition occurs earlier than in the general population [17, 51, 53, 54]. Whether the PET imaging results correlate with cognitive function in adults with DS remains controversial [17, 54]. This method provides a way to identify risk in conjunction with other clinical observations, as well as biomarkers, as proposed in AD in the general population [16, 52, 55]. In addition, PET studies of glucose metabolism can also be used to identify AD changes in DS, as well as to provide evidence of brain atrophy [56]. One critical future direction would be to perform longitudinal studies in patients starting from an original baseline before 40 years of age, and to use DS patients as a target group for pre-clinical anti-AD drug therapy, because of the high incidence of disease after the age of 40.

**Biomarkers for the Detection of AD in DS**

Biomarkers have been reported to be used not only to diagnose but also to follow up on AD progress in the general population [17]. The pattern of biomarker changes in AD in DS have been considered to be similar to those in AD [57]. The initial study of AD in DS measured biomarkers (amyloid and tau) in cerebrospinal fluid (CSF) [58, 59]. Owing to the nature of APP overproduction in DS, the baseline plasma levels of Aβ1-40 and Aβ1-42 and the Aβ1-40/Aβ1-40 ratio are higher than those in control [60–64]. A positive correlation of tau and a negative correlation of Aβ1-42 have been reported with age [58]. Subsequently, a method for the detection of plasma amyloid (Aβ-40 and Aβ-42) was developed, and several studies have documented correlations of the changes in amyloid in DS with AD (Table 1) [60, 62, 65–70]. The majority of the reports have concluded that higher levels of Aβ1-42 or the Aβ1-42/Aβ1-40 ratio are associated with the onset of AD in DS [62, 70, 71]. However, the results in the plasma are opposite from those in the CSF, as CSF Aβ1-42 levels have been consistently reported to be lower than control levels, as determined through different testing methods [58, 72, 73].

The inconsistency between the plasma and CSF results remains a puzzle. To correlate these results with imaging findings, Rafii et al. have demonstrated a greater hippocampal atrophy with a greater amyloid load and an inverse relationship between amyloid load and regional glucose metabolism [57]. However, the cognitive and functional measures do not correlate with the amyloid load but instead correlate with the regional FDG PET [57]. In addition to Aβ1-40 and Aβ1-42, other peptides from β-amyloid have been studied. Portelius et al. have reported higher levels of Aβ1-28 and AβX-40 and lower levels of sAPPα and sAPPβ in the CSF of DS subjects compared with healthy controls [73, 74]. For tau protein, increased total tau (T-tau) has been reported in CSF [58, 74]. Because of the small amount of protein in the blood, tau levels were difficult to measure from peripheral blood until the development of the immunomagnetic reduction (IMR) method [53]. Through this method, we have observed a higher baseline tau protein level in people with DS with a negative correlation with functional ability [71]. This result may be explained by the burn-out phenomenon that is also seen in AD in the general population [55, 71, 75].

In addition to amyloid and tau, several biomarkers have been studied in DS in recent years. Compared with healthy controls, people with DS have been reported to have higher levels of ProNGF, MMP-1, MMP-3, MMP-9, TNF-α, IL-6, IL-10, and S-adenosylhomocysteine (SAH), a lower SAM/SAH (S-adenosylmethionine/S-adenosylhomocysteine) ratio and CpG methylation percentage, and lower levels of amyloid precursor-like protein 1 (APLP1) peptides (APL1β25, APL1β27, and APL1β28) and CSF Orexin-A [63, 73, 76]. A lower serum 3--methoxy-4-hydroxyphenylglycol (MHPG) level and shortening of the telomere length predicts the conversion of AD into DS [77, 78]. With the combination of amyloid and inflammatory markers, these biomarkers may be strong predictors of cognitive deterioration [76]. We believe that, with the launch of the DS biomarker initiative project [57], more markers will be identified in the near future to aid in predicting the occurrence of AD in DS.
| References       | Year | Study design | Population studied | Sample | Biomarker | Method | Results                                                                 |
|------------------|------|--------------|--------------------|--------|-----------|--------|-------------------------------------------------------------------------|
| Tamaoka et al. [72] | 1999 | CS           | 5 DS               | CSF    | Aβ1-40    | NA     | DS compared with control: lower Aβ1-42                                  |
|                  |      |              | 34 HC              | Aβ1-42 |           |        |                                                                          |
| Schupf et al. [60] | 2001 | CS           | 64 nDS nAD         | Plasma | Aβ1-40    | ELISA  | DS compared with control: higher Aβ1-40 and Aβ1-42                      |
|                  |      |              | 97 DS nAD          | Aβ1-42 |           | 6E10   |                                                                          |
|                  |      |              | 11 DS wAD          | Aβ1-42 |           | R165   | DS wAD compared with DS nAD: Higher Aβ1-42                              |
|                  |      |              |                    |        |           | R162   |                                                                          |
| Tapiola et al. [58] | 2001 | CS           | 12 DS              | CSF    | Aβ1-42    | ELISA  | DS: Tau increased with age; Aβ1-42 decreased with age                   |
|                  |      |              | 19 HC              | Tau    |           | 6E10   |                                                                          |
|                  |      |              |                    |        |           | R162   | DS compared with control: lower Aβ1-42                                  |
|                  |      |              |                    |        |           | R164   |                                                                          |
|                  |      |              |                    |        |           | hTAU   |                                                                          |
| Mehta et al.     | 2003 |              | 50 DS              | Plasma | Aβ1-40    | ELISA  | DS compared with control: higher Aβ1-42 in old DS                       |
|                  |      |              | 50 nDS             | Aβ1-42 |           | 6E10   |                                                                          |
|                  |      |              |                    |        |           | R165   |                                                                          |
|                  |      |              |                    |        |           | R226   |                                                                          |
| Schupf et al. [62] | 2007 | LF for 5 years | 207 DS            | Plasma | Aβ1-40    | ELISA  | DS wAD compared with DS nAD: higher Aβ1-42 at baseline                 |
|                  |      |              |                   | Aβ1-42 |           | 6E10   | Elevation in plasma Aβ1-42 was associated with earlier onset of AD and increased risk of death in DS. |
|                  |      |              |                    |        |           | R165   |                                                                          |
|                  |      |              |                    |        |           | R162   |                                                                          |
| Jones et al. [68] | 2009 | CS           | 60 DS              | Plasma | Aβ1-40    | ELISA (BioSource Intl)        | DS wAD compared with DS nAD: no association                       |
|                  |      |              |                   | Aβ1-42 |           | R226   |                                                                          |
| References          | Year | Study design | Population studied | Sample | Biomarker Method | Results                                                                 |
|---------------------|------|--------------|--------------------|--------|------------------|-------------------------------------------------------------------------|
| Matsuoka et al. [70] | 2009 | CS           | 198 DS             | Plasma | Aβ1-40, Aβ1-42   | Aβ1-42/ Aβ1-40 ratio was associated with presence of AD                |
| Schupf et al. [66]  | 2010 | LF for 14–20 m | 225 DS             | Plasma | Aβ1-40, Aβ1-42   | Decrease in Aβ1-42 levels, Aβ1-42/Aβ1-40 ratio, and increase in Aβ-40 levels were related to conversion to AD during follow up. |
| Prasher et al. [67] | 2010 | LF for 6.7 years | 83 DS nAD, 44 DS wAD | Plasma | Aβ1-40, Aβ1-42   | DS wAD compared with DS nAD: lower Aβ1-40. Higher Aβ1-42/Aβ1-40 ratio |
| Head et al. [69]    | 2010 | CS + LF      | 40 DS              | Plasma | Aβ1-40, Aβ1-42   | DS had higher Aβ than control                                           |
| Coppus et al. [65]  | 2012 | CS + LF      | 506 DS             | Plasma | Aβ1-40, Aβ1-42   | High Aβ1–40 and Aβ1–42 were determinants of the risk of dementia in people with DS |
| Portelius et al. [73]| 2014 | CS           | 12 DS, 20 HC       | CSF    | Aβ peptide, APL1β25, APL1β27, APL1β28 | DS compared with control: decreased Aβ1β25, APL1β27, APL1β28; higher Aβ1-28 |
| References       | Year | Study design | Population studied | Sample | Biomarker          | Method              | Results                                                                 |
|------------------|------|--------------|-------------------|--------|--------------------|---------------------|-------------------------------------------------------------------------|
| Portelius et al. | 2014 | CS           | 12 DS             | CSF    | Aβ1-42             | Immunoassay          | DS compared with control: higher AβX-40, sAPPα, sAPPβ; lower Orexin-A |
|                  |      |              | 20 HC             |        | AβX-38/40/42       | MesoScale Discovery  | DS subject: Orexin-A decreased with age, T-tau and YKL-40 increased with age |
|                  |      |              |                   | sAPPα/β| T-Tau              | ELISA               |                                                                         |
|                  |      |              |                   | P-Tau  |                    | Innotest             |                                                                         |
|                  |      |              |                   | YKL-40 |                    |                     |                                                                         |
|                  |      |              |                   | CC chemokine Ligand 2 | Orexin-A |                     |                                                                         |
| Rafii et al.     | 2015 | LF 3 years   | 12 DS nAD         | Plasma | AβX-38/40/42       | Immunoassay          | Greater hippocampal atrophy with amyloid load, inverse relationship between amyloid load and regional glucose metabolism |
|                  |      |              |                   |        |                    | MesoScale Discovery  | Cognitive and functional measure did not correlate with amyloid load but correlated with regional FDG PET |
| Dekker et al.    | 2015 | CS           | 151 DS            | Serum  | NA/A               | RP-HPLC              | DS wAD and DS converted to AD compared to DS nAD and HC: lower MHPG level |
|                  |      |              | 22 HC             |        | MHPG               |                      |                                                                         |
|                  |      |              |                   |        | 5-HT                |                      |                                                                         |
|                  |      |              |                   |        | 5-HIAA             |                      |                                                                         |
|                  |      |              |                   |        | DA                 |                      |                                                                         |
|                  |      |              |                   |        | HVA                |                      |                                                                         |
|                  |      |              |                   |        | DOPAC              |                      |                                                                         |
| Jenkins et al.   | 2016 | LF           | 5 DS              | Blood  | Telomere length    | PNA probe Cen2 Dako  | DS wAD compared with control: shortening of telomere length over time |
|                  |      |              | 2.9 years         |        |                    |                     |                                                                         |
| Year  | Study design | Population studied | Sample | Biomarker Method | Results |
|-------|--------------|---------------------|--------|------------------|---------|
| 2016  | CS           | DS 31 HC            | Blood  | Aβ1-42, P-T181-tau | DS compared with control: higher Aβ1-42, P-T181-tau |
|       |              | 21 DS 44 HC          | Plasma  | Aβ1-40, ProNGF    | DS compared with control: higher Aβ1-40, ProNGF |
|       |              | 10 DS AD             | Plasma  | Aβ1-42           | DS compared with control: higher Aβ1-42, ProNGF, MMP-1, MMP-3, MMP-9, TNF-α, IL-6 and IL-10. |
| 2016  | LF           | HC 31, DS 10 AD     | Plasma  | Aβ1-40, ProNGF, Neuroserpin, Plasminogen, MMP-1, MMP-3, MMP-9, IFN-γ, TNF-α, IL-6, IL-8, IL-10 | DS compared with control: higher Aβ1-40, ProNGF, Neuroserpin, Plasminogen, MMP-1, MMP-3, MMP-9, IFN-γ, TNF-α, IL-6, IL-8, IL-10. |
|       |              | DS 44 HC            | Plasma  | Aβ1-40, ProNGF    | DS compared with control: higher Aβ1-40, ProNGF, Neuroserpin, Plasminogen, MMP-1, MMP-3, MMP-9, IFN-γ, TNF-α, IL-6, IL-8, IL-10. |
|       |              | 31 DS               | Plasma  | Aβ1-40           | DS compared with control: higher Aβ1-40, ProNGF, Neuroserpin, Plasminogen, MMP-1, MMP-3, MMP-9, IFN-γ, TNF-α, IL-6, IL-8, IL-10. |
|       |              | 10 DS AD            | Plasma  | Aβ1-42           | DS compared with control: higher Aβ1-42, ProNGF, Neuroserpin, Plasminogen, MMP-1, MMP-3, MMP-9, IFN-γ, TNF-α, IL-6, IL-8, IL-10. |
|       |              | DS 31               | Plasma  | Aβ1-42           | DS compared with control: higher Aβ1-42, ProNGF, Neuroserpin, Plasminogen, MMP-1, MMP-3, MMP-9, IFN-γ, TNF-α, IL-6, IL-8, IL-10. |
|       |              | DS 60 nDS elder     | Plasma  | Aβ1-42           | DS compared with control: higher Aβ1-42, ProNGF, Neuroserpin, Plasminogen, MMP-1, MMP-3, MMP-9, IFN-γ, TNF-α, IL-6, IL-8, IL-10. |

**Notes:**
- CS: Case-Control Study
- LF: Longitudinal Study
- ELISA: Enzyme-Linked Immunosorbent Assay
- Meso-Scale Discovery: Meso Scale Discovery
- Innogenetics: Innogenetics
- QIAGEN PSQ96 MA: QIAGEN's PSQ96 MassARRAY® System
- pyrosequencing: pyrosequencing

**Table 1 continued**
CONCLUSION

Given the underlying intellectual disability, AD in people with DS is usually difficult to diagnose. In addition to clinical presentations and imaging studies, biomarkers such as amyloid and tau aid in predicting AD in people with DS. Increasing numbers of biomarkers are being reported and may increase the prediction rate in early diagnosis.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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