Neurol Ther (2017) 6 (Suppl 1):S69–S81
DOI 10.1007/s40120-017-0071-y

REVIEW

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

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Received: March 3, 2017

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

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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 *mi*R-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

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*, *IFNGR2*, *RIPK4*, *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-34, 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 position 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-a, 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.

Table 1 Characteristics of the studies investigating biomarkers of Alzheimer's disease in Down syndrome

References	Year	Study design	Population studied	Sample	Biomarker	Method	Results
Tamaoka et al. [72]	1999	CS	5 DS 34 HC	CSF	Aβ1-40 Aβ1-42	NA	DS compared with control: lower Aβ1-42
Schupf et al. [60]	2001	CS	64 nDS nAD 97 DS nAD 11 DS wAD	Plasma	Aβ1-40 Aβ1-42	ELISA 6E10 R165 R162	DS compared with control: higher Aβ1-40 and Aβ1-42 DS wAD compared with DS nAD: Higher Aβ1-42
Tapiola et al. [58]	2001	CS	12 DS 19 HC	CSF	Aβ1-42 Tau	ELISA 6E10 R162 R164 hTAU	DS: Tau increased with age; Aβ1-42 decreased with age DS compared with control: lower Aβ1-42
Mehta et al.	2003		50 DS 50 nDS	Plasma	Aβ1-40 Aβ1-42	ELISA 6E10 R165 R226	DS compared with control: higher Aβ1-42 in old DS
Schupf et al. [62]	2007	LF for 5 years	207 DS	Plasma	Aβ1-40 Aβ1-42	ELISA 6E10 R165 R162	DS wAD compared with DS nAD: higher Aβ1-42 at baseline Elevation in plasma Aβ1-42 was associated with earlier onset of AD and increased risk of death in DS.
Jones et al. [68]	2009	CS	60 DS	Plasma	Aβ1-40 Aβ1-42	ELISA (BioSource Intl) R226	DS wAD compared with DS nAD: no association

Table 1 continued

References	Year	Study design	Population studied	Sample	Biomarker	Method	Results
Matsuoka et al. [70]	2009	CS	198 DS	Plasma	Aβ1-40 Aβ1-42	ELISA 82E1 1A10 1C3	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	ELISA 6E10 R165 R162	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. Decrease in Aβ1-40 levels decreased AD risk
Prasher et al. [67]	2010	LF for 6.7 years	83 DS nAD 44 DS wAD	Plasma	Aβ1-40 Aβ1-42	ELISA 6E10 R165 R162	DS wAD compared with DS nAD: lower Aβ1-40. Higher Aβ1-42/Aβ1-40 ratio
Head et al. [69]	2010	CS + LF	40 DS 17 nDS wAD 52 DS wAD 26 nDS nAD	Plasma	Aβ1-40 Aβ1-42	ELISA Wako Ltd.	DS had higher Aβ than control Aβ could not dissociate DS wAD and DS nAD
Coppus et al. [65]	2012	CS + LF	506 DS	Plasma	Aβ1-40 Aβ1-42	xMAP Innogenetics	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	MALDI TOF/TOF 6E10 4G8 ELISA APLP1 peptide	DS compared with control: decreased AββΒ1-42, APL1β25, APL1β27 APL1β28; higher Aβ1-28

Table 1 continued

References	Year	Study design	Population studied	Sample	Biomarker	Method	Results
Portelius et al. [74]	2014	CS	12 DS 20 HC	CSF	Aβ1-42 AβX-38/40/42 sAPPα/β T-Tau P-Tau YKL-40 CC chemokine Ligand 2 Orexin-A	Immunoassay MesoScale Discovery ELISA Innotest	DS compared with control: higher AβX-40, sAPPα, sAPPβ; lower Orexin-A DS subject: Orexin-A decreased with age, T-tau and YKL-40 increased with age
Rafii et al. [57]	2015	LF 3 years	12 DS nAD	Plasma	AβX-38/40/42	Immunoassay MesoScale	Greater hippocampal atrophy with amyloid load, inverse relationship between amyloid load and regional glucose metabolism Cognitive and functional measure did not correlate with amyloid load but correlated with regional FDG PET
Dekker et al. [77]	2015	CS	151 DS 22 HC	Serum	NA/A MHPG 5-HT 5-HIAA DA HVA DOPAC	RP-HPLC	DS wAD and DS converted to AD compared to DS nAD and HC: lower MHPG level
Jenkins et al. [78]	2016	LF 2.9 years	5 DS	Blood	Telomere length	PNA probe Cen2 Dako	DS wAD compared with control: shortening of telomere length over time

Table 1 continued

References	Year	Study design	Population studied	Sample	Biomarker	Method	Results
Hamlett et al. [64]	2016	CS	DS HC	Blood	Aβ1-42 P-T181-tau P-S96-tau	ELISA	DS compared with control: higher Aβ1-42, P-T181-tau, and P-S96-tau
Iulita et al. [76]	2016	LF	31 HC 21 DS 10 DS AD	Plasma	Aβ1-38 Aβ1-40 Aβ1-42 ProNGF Neuroserpin Plasminogen MMP-1, MMP-3, MMP-9 IFN-r TNF-α IL-6 IL-8 IL-10	ELISA 6E10 Meso-Scale Discovery	DS compared with control: higher Aβ1-40, Aβ1-42, ProNGF, MMP-1, MMP-3, MMP-9, TNF-a, IL-6 and IL-10.
Obeid et al. [63]	2016	CS	60 nDS elder 44 HC 31 DS	Plasma	Aβ1-42 SAH SAM Methylation	ELISA Innogenetics QIAGEN PSQ96 MA pyrosequencing	DS compared with control: higher SAH, Aβ1-42, lower SAM/SAH ratio and methylation % of ASPA and ITGA2B CpG sites

Table 1 continued

References	Year	Study design	Population studied	Sample	Biomarker	Method	Results
Lee et al. [71]	2017	CS	78 nDS	Blood	Aβ1-40	IMR	DS compared with control: higher Aβ-40 and tau levels, lower Aβ-42 level and Aβ-42/Aβ-40 ratio
			62 AD		Aβ1-42	MagQu	
			35 DS		Tau		
			16 DS_D				DS_D compared with DS: decreased Aβ-40 and increased Aβ-42 levels and Aβ-42/40 ratios

DS Down syndrome, *nDS* non-Down syndrome, *AD* Alzheimer's disease, *nAD* without Alzheimer's disease, *wAD* with Alzheimer's disease, *DS_D* Down syndrome with degeneration, *HC* healthy control, *ELISA* enzyme-linked immunosorbent assay, *IMR* immunomagnetic reduction, *CS* crossed-sectional cohort, *LF* longitudinal follow up, *SAH*, S-adenosylhomocysteine, *SAM* S-adenosylmethionine, *NAA* norepinephrine/epinephrine, *MHPG* 3-methoxy-4-hydroxyphenylglycol, *5-HT* 5-hydroxytryptamine, *5-HIAA* 5-hydroxyindoleacetic acid, *DA* dopamine, *HVA* homovanillic acid, *DOPAC* 3,4-dihydroxyphenylacetic acid, *APL* amyloid precursor-like, *MALDI TOF/TOF* matrix-assisted laser desorption/ionization time-of-flight/time-of-flight

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.

ACKNOWLEDGEMENTS

No funding or sponsorship was received for this study or publication of this article. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Disclosures. Ni-Chung Lee, Yin-Hsiu Chien and Wuh-Liang Hwu have nothing to disclose.

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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