Published in final edited form as:
Int J Geriatr Psychiatry. 2010 February ; 25(2): 202–207. doi:10.1002/gps.2321.

Plasma Beta Amyloid and Duration of Alzheimer's Disease in Adults with Down Syndrome

V P Prasher[1,*], **S G Sajith**[2], **P Mehta**[3], **W B Zigman**[4], and **N Schupf**[5,6]

[1]Liverpool John Moore University c/o The Greenfields, Monyhull Hospital, Birmingham, UK

[2]Ashley House, Care Principles, Staffordshire, UK

[3]Laboratory of Immunology, NYS Institute for Basic Research in Developmental Disabilities, New York

[4]Laboratory of Community Psychology and Laboratory of Cognitive Psychology, NYS Institute for Basic Research in Developmental Disabilities, New York

[5]Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Medical Centre, New York

[6]Laboratory of Epidemiology, NYS Institute for Basic Research in Developmental Disabilities, New York

Abstract

Objective—To investigate the relation of plasma levels of Aβ peptides (Aβ1-40 and Aβ1-42) and Apolipoprotein E (*APOE*) genotype to dementia status and duration of Alzheimer's disease in adults with Down syndrome (DS).

Methods—Adults with DS were recruited from community settings and followed up for a mean period of 6.7 years. Plasma levels Aβ1-40 and Aβ1-42 and *APOE* genotype were determined at the last visit.

Results—There were 83 nondemented participants and 44 participants with prevalent AD. Overall, plasma levels of Aβ1-42, Aβ1-40 and the ratio Aβ1-42/Aβ1-40 did not differ significantly between the adults with DS. Among demented participants the mean level of Aβ1-40 was significantly lower (157.0 vs. 195.3) and the ratio of Aβ1-42/Aβ1-40 was significantly higher (0.28 vs. 0.16) in those with more than 4 years duration of dementia than in those with 4 or fewer years duration of dementia. This pattern was generally similar in those with and without an APOE ε4 allele.

Conclusions—There is an association between plasma Aβ peptide levels and duration of AD in older persons with DS. The predictive and diagnostic roles of Aβ1-42 and Aβ1-40 measurements for AD, however, remain controversial. Change in Aβ peptide levels with onset of AD and with duration of dementia may account for lack of difference between prevalent cases and nondemented individuals and for variation in the predictive power of Aβ peptide levels.e

Keywords

Beta Amyloid; Alzheimer's Disease; Down Syndrome

*Correspondence to Professor V P Prasher, The Greenfields, Monyhull Hospital, Kings Norton, Birmingham, B30 3QQ, United Kingdom, Tel: +44 (0) 121 465 8762, Fax: +44 (0) 121 449 2293, Email : vprasher@compuserve.com.

Introduction

Alzheimer's disease (AD) neuropathology is characterized by deposition of extracellular beta amyloid (Aβ) in neuritic plaques and vessel walls, as well as intracellular accumulation of neurofibrillary tangles (Mann, 1991). Elevated levels of Aβ peptides, Aβ1-40 and Aβ1-42, the two major species of Aβ, are associated with increased risk for AD. In cross-sectional studies in plasma, increased levels of Aβ1-42 are found in familial forms of early onset AD with mutations in the gene for amyloid precursor protein (APP) and in presenilin (PS1/2) genes (Kosaka *et al.*, 1997), while elevated levels of both Aβ1-42 and Aβ1-40 have been observed among asymptomatic first-degree relatives of patients with late onset AD (Ertekin-Taner *et al.*, 2008; Ringman *et al.*, 2008). Studies of the relation of plasma levels of Aβ peptides to risk of late onset AD in the general population have been inconsistent, with reports of higher Aβ1-42 levels in nondemented elders who subsequently developed AD (Mayeux *et al.*,1999; Mayeux *et al.*,2003), higher or lower levels of Aβ1-40 and later development of AD (van Oijen *et al.*,2006; Sundelof *et al.*,2008), and a lower baseline Aβ1-42/Aβ1-40 ratio and increased risk of AD (Graff-Radford *et al.*, 2007).

In longitudinal studies, Aβ peptides appear to decrease with onset of cognitive decline and once the disease is established. In a sample of nondemented elderly, higher baseline plasma Aβ1-42 levels and greater reductions in Aβ1-42 were associated with decline in cognitive scores (Pomara *et al.*, 2005). Cerebral spinal fluid (CSF), Aβ1-42 levels and the Aβ1-42/ Aβ1-40 ratio are lower than normal among the elderly with mild cognitive impairment, a group at high risk of progression to AD, and among those with clinical dementia (Hansson *et al.*, 2007; Fagan *et al.*,2007). Plasma Aβ1-42, but not Aβ1-40, levels decreased over time in patients with newly acquired AD (Mayeux *et al.*,2003). These observations are consistent with those in the mouse Tg2576 model of AD showing increases in Aβ1-40 and Aβ1-42 with age and then decline in both CSF and plasma Aβ coincident with deposition of Aβ in brain and onset of behavioural deficits (Kawarabayashi *et al.*, 2001). These findings suggest that plasma levels of Aβ peptides increase in the preclinical phase of AD, then decline with onset of clinical dementia.

Adults with Down syndrome (DS) are at high risk for early onset of AD (Schupf *et al.*, 2002; Prasher, 2005; Prasher *et al.*, 2008) due, at least in part, to duplication and overexpression of the gene for APP, located on chromosome 21 (Rumble *et al.*, 1989). Plasma levels of Aβ1-42 and Aβ1-40 and Aβ1-42/Aβ1-40 are higher than in age-matched peers at all ages, regardless of dementia status, ranging from foetuses at 21 weeks gestation and children with DS to adults (Englund *et al.*, 2007; Teller *et al.*, 1996; Schupf *et al.*, 2001; Mehta *et al.*, 2003; Mehta *et al.*, 2007). Levels of Aβ peptides in adults with DS increase both with age and with the onset of dementia (Tokuda *et al.*, 1997; Mehta *et al.*, 1998; Schupf *et al.*, 2001; Mehta *et al.*, 2003; Mehta *et al.*, 2007). Among adults with DS, higher baseline levels of Aβ1-42, but not Aβ1-40, were associated with a two-fold increased risk of developing dementia (Schupf *et al.*, 2007) and plasma Aβ1-42 levels were higher in newly incident cases with AD compared with non-demented individuals (Schupf *et al.*, 2001). However, no study to date has examined the relation of Aβ peptides to duration or progression of dementia in adults with DS. In this study, we evaluate the relationship of plasma Aβ to the presence and duration of AD in adults with DS and examine whether these relationships are modified in those carrying the apolipoprotein E (*APOE)* ε4 allele. We hypothesize that Aβ peptides levels in plasma decrease with duration of dementia, reflecting Aβ peptide deposition in the brain.

Method

i) Participants

Adults with DS (16 years of age and above) known to the local clinical services and involved in ongoing research as part of the West Midlands Down Syndrome Research Group were recruited into the study. Consent or assent was obtained where appropriate. All participants resided in the West Midlands, a geographical region of the United Kingdom. Ethical Committee approval was obtained from the local authority with approval from the NHS Trust and from the Institutional Review Board of the New York State Institute for Basic Research in Developmental Disabilities.

ii) Procedures

Study Design—We employed a prospective cohort design. Baseline assessments included: (a) a standard full psychiatric history and mental state examination. Mental disorders were diagnosed using the ICD-10 Symptom Checklist for Mental Disorders (WHO, 1994) and classified according to ICD-10 research criteria (WHO, 1993); (b) an ascertainment of severity of ID according to ICD-10 criteria (WHO, 1992); (c) a physical examination (including an assessment of hearing and vision); (d) a comprehensive review of medical records; (e) haematological, biochemical, and thyroid screening, and (f) a comprehensive review of all prescribed medications. Participants diagnosed with mental or physical disorders were treated appropriately and then followed up. Record review and review of participant data over all assessments were employed to determine the dementia status of each participant at each assessment interval as recommended by the Working Group for the Establishment of Criteria for the Diagnosis of Dementia in Individuals with Intellectual Disability (Aylward *et al.*, 1997; Burt and Aylward, 2000). This includes a battery of tests administered to the informants as well as participants longitudinally over a period of time to diagnose dementia based on memory decline, decline in other cognitive areas, everyday functioning affected by memory or cognitive decline and changes in emotional/motivational functioning.

Beta Amyloid Measures—Non-fasting blood samples were collected in the morning. Aβ peptides were measured at the last visit. Amyloid Aβ1-42 and Aβ1-40 were measured using a combination of monoclonal antibody 6E10 and rabbit antisera R165 (vs Aβ1-42) and R162 (vs Aβ1-40) in a double-antibody sandwich enzyme-linked immunosorbent assay. The detection limit for these assays was 5 pg/ml. Levels of Aβ1-42 and Aβ1-40 were measured twice using separate aliquots; the mean of the two measures was used in the statistical analyses.

Apolipoprotein E genotype—Two single nucleotide polymorphism (SNPs) within the APOE gene, 334T/C (rs 429358) and 472C/T (rs 7412) were genotyped, using TaqMan SNP Genotyping Assays (Applied Biosystems, Warrington, UK). Fluorescence was measured using an ABI 7900 Sequence Detection System (Applied Biosystems). The frequencies of the APOE isotype-specific alleles, ε2, ε3 and ε4 and APOE genotypes were obtained from nucleotide combinations of the 334 T/C and 472 C/T SNPs (Koch et al., 2002). For analysis, participants were classified as having none or as having one or more APOE ε4 alleles.

Potential Confounders—Potential confounders included sex, age at beta amyloid peptide measure, level of intellectual disability and the presence of an APOE e4 allele. Level of intellectual disability was classified as mild (IQ range 50–69), moderate (IQ, 35 – 49), severe (IQ ,20–34).

iii) Statistical Analyses

Because all Aβ measures were obtained after onset of AD, we examined the relation of Aβ peptides to the presence and duration of dementia. In preliminary analyses examining the

duration of dementia in the cohort, we found that the median duration of dementia at the time of blood draw for abeta analyses was 4,0 years. Thus for the analysis, we used a median split to divide those with AD into two groups representing duration of dementia (≤ 4 years and > 4 years duration), where half the group would have a shorter and half the group a longer duration of dementia at the time of abeta analysis. In preliminary analyses, we used chi-square tests for categorical variables and Student's t-tests and analysis of variance for continuous variables to compare demographic characteristics and Aβ peptide measures by dementia status. First, we used multivariable analysis of variance to examine difference in levels of Aβ1-42, Aβ1-40 and the ratio of Aβ1-42/Aβ1-40 by the presence of dementia, adjusting for age at the time of Aβ measurement, sex, level of ID and the presence of an *APOE* ε4 allele. Then we repeated these analyses in demented participants only to examine differences in Aβ peptide levels by duration of dementia. To determine whether the relationship between duration of AD and Aβ peptide levels was modified by *APOE*, we repeated these analyses within strata defined by the presence of an *APOE* ε4 allele. All analyses were conducted with adjustment for age at the time of Aβ measurement, sex and level of ID.

Results

Relation of Aβ peptides to the presence of dementia

There were 83 non-demented participants and 46 participants with dementia: duration of AD ≤ 4 years, n= 28; duration of AD > 4 years, n = 18. Two participants with duration of AD ≤ 4 years were excluded from the analysis because of missing *APOE* genotypes. Mean duration of follow-up for all participants was 6.7 ± 5.5 years. Mean time from dementia onset to Aβ peptide measurement for demented participants was 4.8 ± 3.5 years. At the time of Aβ measurement, participants with AD were older than their non-demented peers (mean = 56.8 vs. 49.1 years, $p < .001$) and more likely to carry an *APOE* ε4 allele (36.4% vs. 19.3%, $p < .05$), but did not differ in the distribution of sex or level of ID (Table 1). Among the total group of participants, plasma Aβ1-42 and Aβ1-40 levels were correlated with each other (r= .22, p =.02), but were not correlated with age (r=−.07 for Aβ1-40, p= .46 and r= .09 for Aβ1-42, p = .30). We found similar relationships between abeta peptides and age when the correlation analysis was restricted to those without dementia (r= .06 for age and Aβ1-40, p = .55; r= .009 for age and Aβ1-42, p = .40) . Overall, there were no differences in levels of Aβ1-40, Aβ1-42 or the ratio of Aβ1-42/Aβ1-40 between nondemented participants and participants with prevalent dementia (Table 1).

Relation of Aβ peptides to duration of dementia

In analyses restricted to participants with dementia of 4 or fewer years of duration, Aβ1-40 and Aβ1-42 were modestly correlated with each other (r= .38 p = .053), but not with age (r= . 15 for Aβ1-40, p= .45 and r= −.29 for Aβ1-42, p=.15). In contrast, among those with dementia duration > 4 years, Aβ1-40 and Aβ1-42 were not correlated with each other (r=.17, p = .50), whilst Aβ1-40 increased significantly with age (r=.59, p = .01) and levels of Aβ1-42 did not vary with age (r=.19, p=.46).

Compared with participants with dementia duration ≤ 4 years, participants with dementia duration > 4 years were older (58.8 years vs. 55.5 years, p = .03), had a significantly lower level of Aβ1-40 (157.0 vs. 195.3, p = .043) and had a significantly higher Aβ1-42/Aβ1-40 ratio (0.28 vs. 0.16, p=.002), after adjustment for covariates (Table 2). Levels of Aβ1-42 were higher among those with longer duration of AD, but the difference failed to reach statistical significance (37.0 vs. 30.5, p=.24) (Table 2).

We repeated the analyses of dementia duration within strata defined by the absence or presence of the *APOE* ε4 allele to determine whether the relationship between duration of dementia and

Aβ peptide levels was modified by the presence of an *APOE* ε4 allele. Among those without an ε4 allele, levels of Aβ1-42 and the ratio of Aβ1-42/Aβ1-40 were higher in those with dementia > 4 years duration than in those with 4 or fewer years duration (39.6 vs. 26.7 for Aβ1-42, p = .07; 0.25 vs. 0.14 for the ratio Aβ1-42/Aβ1-40, p = .003), while there was no difference in levels of Aβ1-40 by duration of dementia (174.6 vs. 183.7, p = .64), adjusting for covariates (Table 2). Among those with an ε4 allele, Aβ1-40 levels were lower (131.3 vs. 215.7, p = .04) and the Aβ1-42/Aβ1-40 ratio was higher in those with dementia duration > 4 years than in those with dementia duration of 4 or fewer years, while there was no difference in Aβ1-42 levels between the two groups (Table 2).

Discussion

In the present study there were no significant differences in plasma levels of Aβ1-42, Aβ1-40 and the ratio Aβ1-42/Aβ1-40 between non-demented individuals with DS and individuals with DS and prevalent dementia. Further, when duration of dementia was considered, Aβ1-40 levels were lower, Aβ1-42 levels were higher and the ratio of Aβ1-42/Aβ1-40 was higher in those with longer duration of dementia. These differences were seen both in those with and without an APOE ε4 allele, although sample size was small and power was low to detect differences in Aβ peptide levels within the ε4 strata. The lack of overall difference in plasma Aβ peptide levels between nondemented participants and participants with prevalent dementia is likely the result of combining measures of Aβ that are changing over time and with stage of dementia.

The decline in Aβ1-40 and increase in Aβ1-42 and Aβ1-42/Aβ1-40 ratio with increasing duration of dementia was unexpected. We had hypothesized that plasma levels of Aβ peptide peptides would decrease with duration of dementia, reflecting deposition of Aβ in the brain (Kawarabayashi *et al.*, 2001). Dementia in DS is a major risk factor for early mortality, as it is in the general population (Bassuk *et al.*, 2000; Coppus *et al.*, 2006; Fried *et al.*, 1998; Liu *et al.*, 1990). It is possible that as with other end stage organ failure, end stage failure of the brain leads to massive chemical loss into the bloodstream. Further studies are required to determine if such findings can be used as a marker for imminent death.

Our study is limited by small sample size, which limited our ability to evaluate whether the relation of Aβ peptides to duration of dementia differed in those with and without an *APOE* ε4 allele. Numerous studies have shown that the presence of the ε4 allele is a risk factor for incident AD in adults with and without DS (Corder *et al.*, 1993; Mayeux *et al.*, 1993; Prasher *et al.*, 2008; Schupf *et al.*, 1996), but the relation of the ε4 allele to Aβ peptide levels and to rate of progression in AD is less certain (Cosentino *et al.*, 2008; Craft *et al.*, 1998; Frisoni *et al.*, 1995; Mayeux *et al.*, 2003). Our study is limited also by the cross-sectional nature of the analysis. Serial measures of Aβ peptides will be required to confirm that the differences we observed by duration of dementia are related to progression in clinical stages of dementia.

The diagnostic role of Aβ1-42 and Aβ1-40 measurements for AD remains controversial. Certainly serial measurements will be required along with measurements prior to the onset of any dementia. The diagnostic validity of any single measurement is unlikely to be accurate due to the curvilinear distribution of measures. Further research is still required to determine the source of the Aβ1-42 and Aβ1-40 in plasma. These are derived from APP but it needs to be confirmed whether the high levels of APP are from brain cells themselves, or from platelets, or from some other source.

The investigation of neuro-biological markers for AD in older adults with DS with AD remains in its infancy. Certainly, during the next decade a number of significant findings will be discovered which will dramatically change our treatment and possible prevention of dementia

in persons with DS. Collaborative research, between international centres (as in this study) is the only way for meaningful research to be carried out.

Acknowledgments

Name of sponsors:

Supported by

1. NIH grants R01-AG014763, P01-HD35897, R01-HD37425, by the National Down Syndrome Society in collaboration with the NICHD, and by NYS through its Office of Mental Retardation and Developmental Disabilities
2. Unrestricted educational grant from Eisai Limited, UK

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Table 1

Relation of Aβ peptides to dementia status

Characteristic	Nondemented	Demented
Sample size	83	44
Age at Aβ assay (mean ± S.D.)**	49.0 ± 10.2	56.8 ± 4.9
Sex (n,%)		
Male	52 (62.7)	30 (68.3)
Female	31 (37.3)	14 (31.8)
Level of intellectual disability (n %)		
Mild/Moderate	75 (90.4)	41 (93.2)
Severe/Profound	8 (9.6)	3 (6.8)
Aβ Peptide Level (mean ± S.D.)		
Aβ1-40	177.8 ± 67.8	179.6 ± 59.7
Aβ1-42	33.8 ± 15.0	33.2 ± 15.9
Aβ1-42/Aβ1-40	.23 ± .23	.21 ± .13
APOE ε4 Allele (n,%)*	16 (19.3)	16 (36.4)

* $p < 05$

** $p < .001$

Units Aβ1-42 andAβ1-40 are pg/ml

Table 2

Relation of APOE ε4 allele to level of Aβ peptides by duration of AD

	Dementia duration ≤ 4 years	**Dementia duration > 4 years**
All Demented Participants	26	18
Age (mean ± S.D.)	55.5 ± 4.0	58.8. ± 5.6
Aβ1-40 (mean ± S.E.)*	195.3 ± 11.3	157.0 ± 13.7
Aβ1-42 (mean ± S.E.)	30.5 ± 3.3	37.0 ± 4.1
Aβ1-42/Aβ1-40 (mean ±S.E.)**	.16 ± .02	.28 ± .03
No APOE e4 allele	17	11
Aβ1-40 (mean ± S.E.)	183.7 ± 11.2	174.6 ± 14.3
Aβ1-42 (mean ± S.E.)	26.7 ± 4.0	39.6 ± 5.1
Aβ1-42/Aβ1-40 (mean ±S.E.)**	0.14 ± .02	0.25 ± .02
One or more APOE e4 allele	9	7
Aβ1-40 (mean ± S.E.)*	215.7 ± 24.0	131.3 ± 27.3
Aβ1-42 (mean ± S.E.)	36.5 ± 6.4	34.6± 7.2
Aβ1-42/Aβ1-40 (mean ± S.E.)	.18 ± .06	.33 ± .07

Adjusted for age at beta amyloid measure, sex and level of intellectual disability

* p = .< .05

** p < .01

Units Aβ1-42 andAβ1-40 are pg/ml