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Plasma β amyloid and the risk of Alzheimer's disease in Down syndrome

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Abstract

Extracellular deposition of amyloid beta peptide (Aβ) has been implicated as a critical step in the pathogenesis of Alzheimer's disease (AD). In Down syndrome (DS), Alzheimer's disease is assumed to be caused by the triplication and overexpression of the gene for amyloid precursor protein (APP), located on chromosome 21. Plasma concentrations of Aβ1–40 and Aβ1–42 were determined in a population based study of 506 persons with DS, who were screened annually for dementia. We used Cox proportional hazards models to determine the risk of dementia. Demented persons with DS have a significantly higher plasma Aβ1–40 concentration than the nondemented ($p = 0.05$). Those with the highest concentrations of Aβ1–40 and Aβ1–42 have a higher risk to develop dementia. The risk to develop dementia during follow-up (mean 4.7 years) increased to 2.56 (95% confidence interval, 1.39–4.71) for Aβ1–42 and 2.16 (95% confidence interval, 1.14–4.10) for Aβ1–40. High plasma concentration of plasma Aβ1–40 and Aβ1–42 are determinants of the risk of dementia in persons with DS.

Keywords: Down syndrome; Amyloid precursor protein; Abeta; Alzheimer's disease

1. Introduction

Increasing evidence suggests that a key event in the pathogenesis of Alzheimer's disease (AD) is the altered production, aggregation, and deposition of amyloid beta peptide (Aβ), a proteolytic fragment derived from amyloid precursor protein (APP). APP is cleaved by a combination of β and γ secretase enzyme activity to produce the longer more toxic 42 amino acid long peptide (Aβ1–42) or the shorter, more soluble 40-amino acid peptide (Aβ1–40) (Selkoe, 1994). The increased risk of AD in people with Down syndrome (DS) is well known (Coppus et al., 2006; Schupf and Sergievsky, 2002). In DS, AD is assumed to be caused by the triplication and overexpression of the gene for APP, located on chromosome 21 and leading to the accumulation of cerebral β-amyloid (Wisniewski et al., 1985). Increased levels of Aβ1–42 have been found in familial forms of early onset AD. This relationship is seen both in families with mutations in the gene for APP and in the presenilin genes (Kosaka et al., 1997). Studies of the relation of plasma levels of Aβ1–42 and Aβ1–40 to risk of late onset AD in the general population have been inconsistent. High plasma levels of Aβ1–42 and Aβ1–40 were associated with the increased risk of development of AD in the Northern Manhattan Study of Aging and Dementia (Mayeux et al., 2003) and high plasma levels of Aβ40 in the Rotterdam study (van Oijen et al., 2006), but others suggested that Aβ40 is lower

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in those at increased risk of dementia (Sundelöf et al., 2008). Further, a low Aβ1–42:Aβ1–40 ratio has been associated with an increased Alzheimer risk (Graff-Radford et al., 2007; Lambert et al., 2009) which may imply a preferential increase of plasma Aβ1–40 over Aβ1–42 before the disease, or a preferential decrease of Aβ1–42 over Aβ1–40. The most recent and largest population-based study, the prospective 3-city study found a decrease of Aβ1–42:Aβ1–40 ratio to be most predictive (Lambert et al., 2009). When testing the association of Aβ1–42 and Aβ1–40 individually, Aβ1–42 was decreased in persons who developed dementia later in life, but this relationship was not significant. Aβ1–40, on the other hand, was significantly increased in patients who developed dementia.

In DS, plasma levels of Aβ1–42 and Aβ1–40 are consistently higher than in age-matched controls at all ages regardless of dementia status (Cavani et al., 2000; Mehta et al., 2003, 2007; Schupf et al., 2001; Tokuda et al., 1997). Levels of Aβ1–42 and/or Aβ1–40 seem to increase with age and are associated with the presence of dementia in some studies (Mehta et al., 2007; Schupf et al., 2001, 2007) but not in all (Jones et al., 2009; Matsuoka et al., 2009). In DS patients, plasma levels changed after the onset of dementia but findings are not consistent. In a longitudinal study (Prasher et al., 2010), plasma Aβ1–40 decreased over time after the onset of dementia and plasma Aβ1–42 increased with increasing duration of dementia. Another longitudinal study (Schupf et al., 2010) showed that plasma Aβ1–42 levels decreased and Aβ1–40 levels increased after the onset of dementia. Differences in the timing of the Aβ measurements with respect to the dementia diagnosis could be responsible for the differences in the results between these longitudinal studies.

The aim of this study was to evaluate Aβ plasma levels as possible biomarkers of amyloid accumulation in the brain in people with DS. We investigated this in the largest longitudinal study of elderly persons with DS (Coppus et al., 2006).

2. Methods

2.1. Study population

We conducted a study of 506 persons with DS, aged 45 years and older, who were enrolled from 1 December 1999 to 1 December 2003 in a community-based study on DS and aging in the Netherlands. Informed consent procedures and recruiting of subjects have been described in detail elsewhere (Coppus et al., 2006). At the time of study entry, each person received a complete assessment including interviews with relatives, caregivers, and the general practitioner. The medical records were reviewed. All persons underwent a general physical and neurological examination. At baseline, fasting venous blood samples were taken in the morning. Plasma concentration of Aβ1–40 and Aβ1–42 was measured in 405 (80%) persons who consented to give (sufficient) blood. All participants were assessed once yearly up to the reference date of 1 January 2007 or date of death. For this study the diagnosis of DS was re-evaluated based on clinical characteristics according to the criteria described by Roizen and Patterson (2003). In 236 cases (58%) the clinical diagnosis was confirmed by available cytogenetic characterization.

2.2. Clinical assessments

Premorbid severity of intellectual disability (ID) was classified into 2 groups, using the International Classification of Diseases (ICD)-10: mild/moderate (IQ 35–70) and severe/profound (IQ $<$ 35). Apolipoprotein E (APOE) genotype was determined as described in a previous study (Coppus et al., 2008). Participants were classified according to the presence or absence of an APOEε4 allele. Body mass index (BMI) was computed as weight in kilograms divided by height in square meters.

All persons were assessed for AD using the ICD-10 (World Health Organization, 1992) criteria and according to the guidelines produced by an international consensus panel established under the auspices of the Ageing Special Interest Group of the International Association for the Scientific Study of Intellectual Disabilities (IASSID) (Aylward et al., 1997). The diagnosis of dementia was supported using the Dementia Questionnaire for persons with an intellectual disability (DMR) (Evenhuis, 1992, 1996) and the Social Competence Rating Scale for persons with an intellectual disability (SRZ) (Krayer and Bildt, 2004). Persons who were not demented were screened annually. Those who fulfilled the criteria for AD, at baseline or during follow-up, were followed more intensively at 6-month intervals. These patients also received a clinical work-up, to exclude other physical and psychiatric factors as possible causes of deterioration.

For the prevalent cases of dementia, age at entry was used to estimate the age at diagnosis of dementia. Age at diagnosis of patients with incident dementia was determined as the midpoint between the age of the person last known to be at risk for dementia and age at diagnosis.

2.3. Measurements

Fasting blood samples were obtained following standardized protocols. Plasma was prepared by a 20-minute centrifugation step at 2650*g* and stored at −80 °C and only thawed immediately before Aβ quantification. Plasma Aβ concentrations were measured using a bead-based immunoassay using xMAP technology (Innogenetics) on a Luminex200 platform using the manufacturer's protocols. In this study, we used data obtained for full-length Aβ peptides, i.e., Aβ1–40 and Aβ1–42, and their ratio, for analysis.

2.4. Statistics

In preliminary analyses we used χ^2 to analyze categorical variables and Student *t* test and analysis of variance to compare characteristics of participants and Aβ peptide lev-

Table 1
Characteristics by final diagnosis

Characteristics	All	AD at baseline	AD at follow-up	Nondemented
n (%)	405 (100)	62 (15.3)	79 (19.5)	264 (65.2)
Age mean (SD) [a]	51.6 (5.1)	54.0 (5.9)[a]	53.3 (5.4)[b]	50.6 (4.4)
Gender, women, *n* (%)	154 (38)	26 (41.9)	33 (41.8)	95 (36)
APOE ε4 allele, *n* (%)	111 (27.6)	22 (36.1)	21 (27.3)	68 (25.8)
Aβ1–40, mean (SD) [c],[d]	337.4 (104.9)	352.3 (103.5)[c]	362.6 (113.5)[d]	326.4 (101.3)
Aβ1–42, mean (SD)	51.4 (15.2)	50.0 (17.5)	54.0 (14.7)	51.0 (14.8)
Aβ1–42:Aβ1–40, mean (SD)	0.16 (0.06)	0.15 (0.06)	0.16 (0.06)	0.16 (0.05)

Key: AD at baseline, prevalent dementia; AD at follow-up, incident dementia.
[a] $p < 0.001$ in comparison with nondemented persons.
[b] $p < 0.001$ in comparison with nondemented persons.
[c] $p = 0.04$ in comparison with nondemented persons.
[d] $p = 0.01$ in comparison with nondemented persons.

els by dementia status. Because not all of the data sets showed normal distribution, we used the Mann-Whitney *U* test and Kruskal-Wallis to compare levels of Aβ1–40, Aβ1–42, and their ratio by dementia status. To study the association between baseline levels of Aβ1–42 and Aβ1–40 and other characteristics, we used Spearman rank correlation analysis.

Among those who were not demented at baseline, we used Kaplan-Meier life table methods and Cox proportional hazards models to estimate cumulative incidence and the hazard rate (HR) of dementia by tertile of Aβ. The lowest tertiles were used as reference categories, first in models adjusted for age and sex (model 1) and then in models which adjusted for age, sex, BMI, level of ID, and the presence of at least 1 APOEε4 allele (model 2).

The median value of Aβ1–40 (324 pg/mL) and the median value of Aβ1–42 (51 pg/mL) were used as a cutoff point defining high level Aβ versus low level. We used Kaplan-Meier life table methods and Cox proportional hazards models to estimate cumulative incidence and the HR of dementia comparing the highest levels with a combination of the lowest levels of Aβ1–40 and Aβ1–42. The time to event variable was follow-up time until reference date, death, or the incidence of dementia.

3. Results

3.1. Characteristics

At baseline assessment, there were 62 (15.3%) persons with clinically diagnosed AD. Over the follow-up period with a mean of 4.7 years (minimum 0.1 to maximum 7.6 years), 79 (23.2%) persons out of 343 without dementia developed AD, and 80 (20%) persons died. The mean time from baseline to dementia onset was 2.19 (± 1.4) years. Persons who had AD or developed AD were more likely to be older (Table 1). The frequency of the APOEε4 allele was greater in those with dementia than those without but this difference was not significant (Table 1). Comparing the (incident) demented and nondemented, with and without an APOEε4 allele, there was a significant difference in Aβ1–40 concentration ($p = 0.05$) (Table 2).

Plasma Aβ1–40 and Aβ1–42 levels were correlated ($r = 0.35$; $p = 0.001$). Levels of Aβ1–40 but not Aβ1–42, were significantly related to age at diagnosis of dementia ($r = 0.22$; $p = 0.009$; and $r = 0.06$; $p = 0.46$, respectively).

At baseline, 8 (13%) of the 62 prevalent demented persons received a diagnosis, Reisberg stage 7, end-stage of dementia (Reisberg et al., 1982). There was no significant difference in Aβ concentrations that reflects the severity of dementia.

3.2. Aβ plasma levels and the risk of dementia

Plasma Aβ1–42 levels were highest among those who developed AD during follow-up (54.0 ± 14.7 pg/mL) and lowest among those with dementia at baseline (50.0 ±17.5 pg/mL). However, these differences were not significant (Table 1). The initial Aβ1–40 levels were significantly higher in persons with AD, prevalent as well as incident cases, than in persons who remained nondemented during follow-up. There was no significant difference in plasma

Table 2
The relation between the presence of an APOE 4 allele and the concentration of Aβ in persons with and without incident dementia

APOE 4 allele	Demented	*n*	Aβ40	Aβ42
−	−	234	329.6 (95% CI, 316.5–342.7)	50.5 (95% CI, 48.5–52.5)
−	+	56	360.2 (95% CI, 329.1–391.2)	53.6 (95% CI, 49.6–57.6)
+	−	90	335.4 (95% CI, 313.5–357.2)	51.2 (95% CI, 48.0–54.4)
+	+	21	372.1 (95% CI, 320.0–424.2)	57.3 (95% CI, 51.3–63.2)

Comparing the 4 groups: mean concentration (95% confidence interval [CI]) Aβ40: *df* 3; Kruskal-Wallis; $p = 0.05$; Aβ42: *df* 3; Kruskal-Wallis; $p = 0.15$.
Key: Aβ, amyloid beta peptide; APOE, apolipoprotein E.

Table 3
Association between plasma Aβ and risk of dementia

	Aβ42		Aβ40		Aβ42:Aβ40	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Lowest tertile	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Middle tertile	1.18 (0.67–2.06)	1.49 (0.79–2.84)	2.00 (1.12–3.59)[a]	2.05 (1.05–4.02)[a]	0.99 (0.59–1.68)	1.05 (0.59–1.87)
Highest tertile	1.78 (1.03–3.08)[a]	2.56 (1.39–4.71)[a]	1.75 (0.98–3.16)	2.16 (1.14–4.09)[a]	0.81 (0.47–1.41)	0.95 (0.52–1.71)
Age	1.11 (1.07–1.16)[a]	1.09 (1.05–1.14)[a]	1.11 (1.06–1.15)[a]	1.09 (1.04–1.14)[a]	1.11 (1.07–1.15)[a]	1.09 (1.04–1.14)[a]
Sex	1.18 (0.75–1.85)	1.02 (0.60–1.75)	1.24 (0.79–1.94)	1.10 (0.64–1.88)	1.21 (0.77–1.90)	1.04 (0.61–1.77)
BMI		1.00 (0.95–1.06)		0.99 (0.94–1.06)		1.01 (0.95–1.06)
Level ID		1.22 (0.72–2.08)		1.19 (0.70–2.03)		1.26 (0.74–2.13)
APOE		1.18 (0.69–2.03)		1.21 (0.70–2.07)		1.19 (0.70–2.04)

Hazard ratios (95% confidence interval) for Alzheimer's disease.
Model 1 was adjusted for age and sex.
Model 2 was adjusted for age, sex, body mass index (BMI), level of intellectual disability (ID), and presence of at least 1 APOE ε4 allele.
Key: Aβ, amyloid beta peptide; APOE, apolipoprotein E; Ref., reference category.
[a] $p < 0.05$.

ratio Aβ1–42:Aβ1–40 between demented and nondemented persons in this study population.

Table 3 shows that those in the highest tertile of plasma Aβ1–42 were at significantly higher risk of developing AD during follow-up: HR, 1.78 (95% confidence interval [CI], 1.03–3.08). When including age at the start, sex, BMI, level of intellectual disability, and APOEε4 in the Cox model, the risk of incident AD was 2.56-fold increased (95% CI, 1.39–4.71). As can be seen in Table 3, there was also an association between plasma Aβ40 level and the risk of developing AD. The middle and the highest tertile showed a significantly increased risk of incident dementia compared with the lowest tertile (HR, 2.05; 95% CI, 1.05–4.02; and HR, 2.16; 95% CI, 1.14–4.09, respectively).

Because Aβ1–40 and Aβ1–42 were significantly correlated, we evaluated to what extent the relationship to dementia

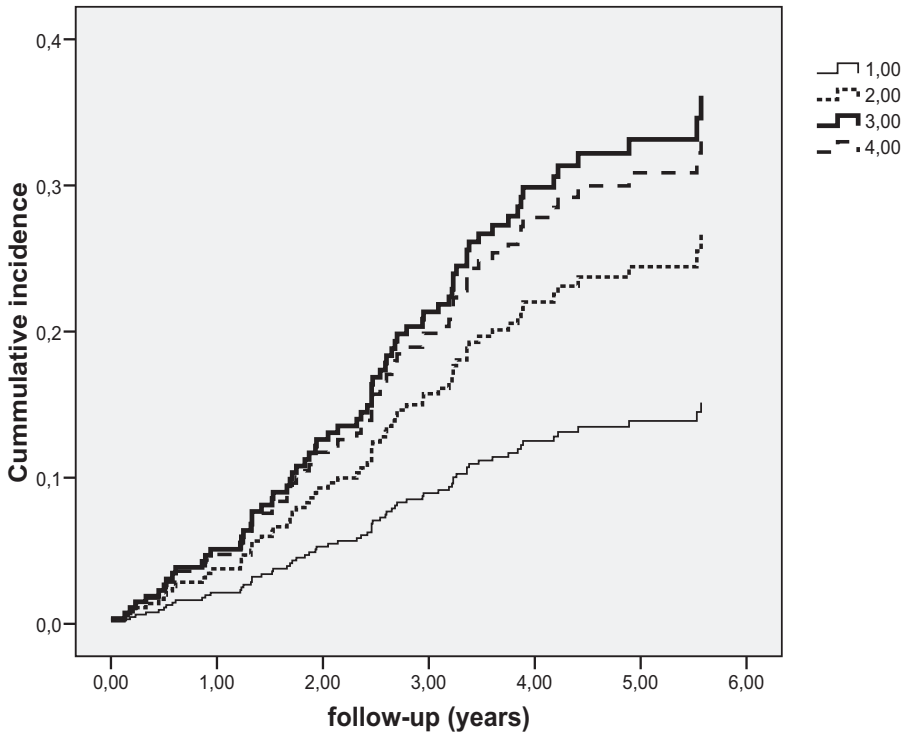

Fig. 1. Risk of Alzheimer's disease during follow-up by a combination of plasma concentrations amyloid beta peptide (Aβ)1–40 and Aβ1–42, adjusted for age, sex, level of intellectual disability, presence of APOE ε4 allele, and body mass index. Plasma concentrations of Aβ1–40 and Aβ1–42 are identified as follows: (1) plasma concentration Aβ1–40 ≤ 324 pg/mL; plasma concentration Aβ1–42 ≤ 51 pg/mL; (2) plasma concentration Aβ1–40 ≤ 324 pg/mL; plasma concentration Aβ1–42 > 51 pg/mL; (3) plasma concentration Aβ1–40 > 324 pg/mL; plasma concentration Aβ1–42 ≤ 51 pg/mL; (4) plasma concentration Aβ1–40 > 324 pg/mL; plasma concentration Aβ1–42 > 51 pg/mL.

Table 4
Relation plasma serum Aβ levels and dementia status in different studies

Reference	Assay antibody Aβ1–40/Aβ1–42	Diagnosis	Study design	*n*	Aβ1–42 pg/mL (SD)	*p*	Aβ1–40 pg/mL (SD)	*p*
Schupf et al., 2001	6E10(Aβ1–16)	Demented	Cross-sectional	11	28.2 (5.9)	0.006	157.2 (35.6)	ns
	R162/R165	Nondemented		97	22.4 (6.1)		132.1 (44.4)	
Schupf et al., 2007	6E10(Aβ1–16)	Demented (prevalent)	Longitudinal	30	25.8 (7.5)	0.04	153.1 (50.7)	ns
	R162/R165	Demented (incident)	Prospective	44	24.1 (5.9)		162.5 (55.1)	
		Nondemented		130	22.7 (6.1)		171.5 (54.3)	
Matsuoka et al., 2009[a]	Elisa (Aβ1) 82E1 1A10/1C3	Demented	Cross-sectional	52	419 (660)	ns	242 (321)	ns
		Nondemented		145	339 (577)		288 (384)	
Prasher et al., 2010	6E10(Aβ1–16)	Demented	Longitudinal retrospective	44	33.2 (15.9)	ns	179.6 (59.7)	ns
	R162/R165	Nondemented		83	33.8 (15.0)		177.8 (67.8)	
Jones et al., 2009[b]	6E10(Aβ1–16)	Demented	Cross-sectional	21	27.8 (16.6)	ns	125.6 (84.1)	ns
	R162-R209/R226	Nondemented		39	27.1 (11.4)		121.3 (50.7)	
Head et al., 2010[c]	BAN50(Aβ1–16)	Demented	Cross-sectional	52	18.6 (3.8)	ns	235.5 (22.8)	ns
	BA27/BC05	Nondemented		26	16.1 (1.8)		224.2 (24.2)	
Schupf et al., 2010[d]	6E10(Aβ1–16)	Demented (incident)	Longitudinal	61	25.4 (7.4)	ns	160.7 (53.1)	ns
	R162/R165	Nondemented	Prospective	164	26.2 (11.0)		151.9 (52.5)	
Coppus (2011; this study)[d]	xMAP technology	Demented (prevalent)	Longitudinal	62	50.0 (17.5)	ns	352.3 (103.5)	0.05
		Demented (incident)	Prospective	79	54.0 (14.7)		362.6 (113.5)	
		Nondemented		264	51.0 (14.8)		326.4 (101.3)	

Key: Aβ, amyloid beta peptide; N, number of participants; ns, not significant; SE, standard error; SD, standard deviation.
[a] fmol/mL (SD), adjusted for age and sex (not converted).
[b] SD calculated from SE and N.
[c] Aβ values converted from pmol/L to pg/mL (1 pg/mL = 0.284 pmol/L); SD calculated from SE and N.
[d] Baseline levels.

is dependent on the combination of Aβ1–40 and Aβ1–42. Fig. 1 shows that those with a plasma Aβ1–42 level above the median but with an Aβ1–40 level below the median are not at increased risk of Alzheimer's disease ($p = 0.16$). However, the highest risk of dementia was found in those with high concentrations of Aβ1–40 in the absence or presence of high concentrations of Aβ1–42 (HR, 2.39; 95% CI, 1.16–4.91; and HR, 2.22; 95% CI, 1.16–4.24, respectively).

4. Discussion

In the present study, as far as we know the largest study in elderly people with DS, we examined the relation between Aβ plasma levels and the risk of developing dementia during follow-up. Compared with Down persons without dementia, the prevalent and incident demented persons had significantly higher plasma Aβ1–40 concentrations at baseline. Plasma Aβ1–42 concentrations and the ratio Aβ1–42:Aβ1–40 were lower, although not significant, in those with dementia at baseline. As can been seen in Table 4, results from studies examining concentrations of plasma levels of Aβ1–40 and Aβ1–42 in demented and nondemented persons have been controversial (Head et al., 2010; Jones et al., 2009; Matsuoka et al., 2009; Prasher et al., 2010; Schupf et al., 2007, 2010). Differences in assay procedures, subject characteristics, and collection procedures among others may have contributed to the variable findings. Even findings within the same population (the 2 studies of Schupf et al., 2007, 2010) are not consistent, although all these studies used the required accurate measurement of full-length Aβ1–42 and Aβ1–40. If any trend can be deducted, the more recent studies are more likely to show consistent effects. In the table, Aβ1–42:Aβ1–40 ratio is not given, as this was not analyzed in all studies.

In our study, plasma Aβ1–40 and Aβ1–42 at baseline were higher in DS persons who developed dementia during follow-up than in persons who remained free from dementia, which suggests that increased plasma concentrations of Aβ are associated with the development of dementia as has been noticed by others (Matsuoka et al., 2009; Schupf et al., 2001, 2007, 2010; Tokuda et al., 1997). In this study we showed that high plasma concentrations of Aβ1–40 were associated with an increased risk of dementia, independent of the concentration of Aβ1–42. Analyses of the Rotterdam study (van Oijen et al., 2006), the Northern Manhattan Study of Aging (Mayeux et al., 2003), and the Three-City Study (Lambert et al., 2009) also revealed that increased levels of Aβ1–40 were predominantly associated with increased risk of developing AD. Several studies show that low levels of Aβ1–42 in cerebrospinal fluid (CSF) are strongly associated with future development of AD (Hansson et al., 2006, 2007). The reduction of Aβ1–42 in CSF seems to reflect aggregation of Aβ1–42 in brain tissue (Hansson et al., 2010). However, it is unclear whether the disturbed metabolism of Aβ1–42 in the AD brain is reflected by changes in Aβ in plasma. In fact, Aβ is produced by many different cells in the body and there seems no clear connection between the levels of Aβ1–42 in plasma and CSF (Hansson et al., 2010; Mehta et al., 2001). On the other hand, several longitudinal studies (Cosentino et al., 2010; Okereke et al., 2009) demonstrated that high initial levels of

plasma Aβ1–42 and Aβ1–40 and stable or decreasing Aβ1–42 at follow-up were associated with faster cognitive decline and development of dementia. Even the Tg2576 mouse model of AD has shown that plasma Aβ levels decrease as brain Aβ levels increase (Kawarabayashi et al., 2001; Kupsch et al., 2001). It is unclear how brain Aβ accumulation and cognitive decline are associated in DS. A recent report of Netzer et al. (2010) suggests that inhibiting Aβ production in the Ts65Dn mouse model of DS, lowered Aβ levels and reduced level of intellectual disability. This raises the possibility that therapy reducing the elevated levels of Aβ may decrease not only the risk of AD but also improve cognition in DS. In our study, contrary to others (Matsuoka et al., 2009), we did not find a significant correlation between Aβ concentrations and level of intellectual disability. Further investigation using positron emission tomography (PET) imaging or amyloid imaging would be very useful.

In DS, plasma analysis of Aβ1–40 and Aβ1–42 as predictors of dementia will be an enormous advantage compared with CSF diagnostics as a lumbar puncture is more invasive compared with a vena puncture and often not possible in people with DS.

Our study suggests that Aβ1–40 and Aβ1–42 levels are both potential predictors of dementia in patients with DS, independent of the risk factors of dementia in DS identified to date (age, sex, APOE, BMI, and level of intellectual disability). This is in line with the large epidemiological prospective studies in the general population. However, comparisons of studies of patients with DS also shows major differences related to the measurements and perhaps study design. More work needs to be carried out to fully understand the way plasma Aβ concentration is related to cognitive decline and the development of AD in the general population as well as in people with DS.

Disclosure statement

The authors disclose no conflicts of interest.

The study protocol was approved by the Medical Ethical Committee of the Erasmus University Medical Centre in Rotterdam, The Netherlands (protocol number: MEC 185.974/1999/202). In addition, the ethical committee of the local institutions provided approval. Written informed consent was obtained from the legal representatives.

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