DEMENTIAS - ORIGINAL ARTICLE

Cerebrospinal fluid amyloid-β 2-42 is decreased in Alzheimer's, but not in frontotemporal dementia

**Mirko Bibl · Marion Gallus · Volker Welge ·
Hermann Esselmann · Stefanie Wolf ·
Eckart Rüther · Jens Wiltfang**

Abstract Alzheimer's dementia (AD) and frontotemporal dementias (FTD) are common and their clinical differential diagnosis may be complicated by overlapping symptoms, which is why biomarkers may have an important role to play. Cerebrospinal fluids (CSF) Aβ2-42 and 1-42 have been shown to be similarly decreased in AD, but 1-42 did not display sufficient specificity for exclusion of other dementias from AD. The objective of the present study was to clarify the diagnostic value of Aβ2-42 peptides for the differential diagnosis of AD from FTD. For this purpose, 20 non-demented disease controls (NDC), 22 patients with AD and 17 with FTD were comparatively analysed by a novel sequential aminoterminally and carboxyterminally specific immunoprecipitation protocol with subsequent Aβ-SDS-PAGE/immunoblot, allowing the quantification of peptides 1-38^{ox}, 2-40 and 2-42 along with Aβ 1-37, 1-38, 1-39, 1-40, 1-40^{ox} and 1-42. CSF Aβ1-42 was decreased in AD as compared to NDC, but not to FTD. In a subgroup of the patients analyzed, the decrease of Abeta2-42 in AD was evident as compared to both NDC and FTD. Aβ1-38 was decreased in FTD as compared to NDC and AD. For differentiating AD from FTD, Aβ1-42 demonstrated sufficient diagnostic accuracies only when combined with Aβ1-38. Aβ2-42 yielded diagnostic accuracies of over 85 % as a single marker. These accuracy figures could be improved by combining Aβ2-42 to Aβ1-38. Aβ2-42 seems to be a promising biomarker for differentiating AD from other degenerative dementias, such as FTD.

Keywords Alzheimer's dementia · Frontotemporal dementia · Cerebrospinal fluid · Aminoterminally truncated · Amyloid-β peptides · Aβ2-42

Abbreviations

Aβ	Peptides amyloid-beta peptides
Aβ-SDS-PAGE/ immunoblot	Amyloid-beta-sodium-dodecyl-sulphate-polyacrylamide-gel electrophoresis with western immunoblot
AD	Alzheimer's dementia
CCD-camera	Charge-coupled device camera
CSF	Cerebrospinal fluid
DSM IV	Diagnostic and statistical manual of mental disorders, fourth edition
FTD	Frontotemporal dementia
MMSE	Mini-mental-status examination
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association

M. Bibl (✉) · S. Wolf
Department of Psychiatry, University of Goettingen,
von-Siebold-Str. 5, 37075 Goettingen, Germany
e-mail: m.bibl@kliniken-essen-mitte.de

Present Address:
M. Bibl
Department of Psychiatry, Psychotherapy and Addiction
Medicine, Kliniken Essen-Mitte, University of Duisburg-Essen,
Henricistrasse 92, 45136 Essen, Germany

M. Gallus · V. Welge
Department of Psychiatry, Psychotherapy and Addiction
Medicine, Kliniken Essen-Mitte, University of Duisburg-Essen,
Henricistrasse 92, 45136 Essen, Germany

H. Esselmann · J. Wiltfang
Department of Psychiatry and Psychotherapy,
University of Duisburg-Essen, 45147 Essen, Germany

E. Rüther
Department of Psychiatry and Psychotherapy,
Ludwig-Maximilian-University of Munich,
Geschwister-Scholl-Platz 1, 80539 Munich, Germany

Introduction

Alzheimer's dementia (AD) and frontotemporal dementias (FTD) share several clinical and neurochemical similarities, which complicates their differential diagnosis. A major neuropathological hallmark of AD is the extracellular deposition of amyloid-beta (Aβ) peptides into neuritic plaques, and plaque forming appears to play a central role in the neurodegenerative process of AD (Glenner and Wong 1984). Aβ peptides that are carboxyterminally elongated (e.g., Aβ1-42) and/or aminoterminally truncated (e.g., Aβ2-40 or Aβ2-42) as referenced to Aβ1-40 are specifically prone to aggregation and are considered to have a high toxic potential. Correspondingly, carboxyterminally elongated and aminoterminally truncated Aβ peptides as well as their pyroglutamate and oxidized derivates represent major constituents of human amyloid plaques (Güntert et al. 2006). In neurochemical terms, this process is widely considered to underlie the phenomenon of decreased CSF Aβ42 levels in AD (Motter et al. 1995; Fagan et al. 2006). Although plaque forming is a feature rarely seen in FTD, some FTD cases share reduced levels of CSF Aβ42 with AD patients (Hulstaert et al. 1999; Blennow 2004). Thus, alternative mechanisms for explaining these findings should be considered as well, such as distinct CSF Aβ peptide pools that may differ in their adherence to possible carrier proteins or their tendency to form supramolecular aggregates. Due to the overlap of levels for CSF Aβ42 between AD and FTD, the results published on its accuracy for discriminating the two disorders have remained unconvincing to date (Sjögren et al. 2000; Andreasen et al. 2001; Riemenschneider et al. 2002; Galasko and Marder 2002). More consistently, AD and FTD could be differentiated by Aβ peptide ratios, considering CSF Aβ42 as related to Aβ40 or Aβ38, especially as the latter peptide displayed reduced CSF concentrations in FTD (Bibl et al. 2007a, b; Welge et al. 2009).

Recently, we were able to quantify the oxidized form of Aβ1-38 (1-38$^{\text{ox}}$) as well as the aminoterminally truncated Aβ peptides 2-40 and 2-42 in the CSF of AD patients in comparison to non-demented disease controls (NDC) (Bibl et al. 2011a). One notable finding was that CSF Aβ2-42 was reduced to a similar extent to Aβ1-42 in AD and both similarly yielded reasonable accuracies for the detection of AD among NDC (Bibl et al. 2011b).

Here, we addressed the question whether Aβ2-42 may also potentially aid differential diagnosis of AD and FTD.

Patients and methods

59 CSF samples from the memory clinic of the University of Goettingen were referred to our laboratory between 2003 and 2006 and investigated in 2007. CSF concentrations of the Aβ peptides 1-37, 1-38, 1-38$^{\text{ox}}$, 1-39, 1-40, 1-40$^{\text{ox}}$, 1-42, 2-40 and 2-42 were analysed. Aliquots of a subgroup of these samples had been studied previously under another objective (Bibl et al. 2007b, 2011b).

Cognitive impairment was assessed by MMSE at minimum. More detailed neuropsychological testing, including clock drawing and CERAD test battery, was additionally carried out in the majority of patients with cognitive complaints (33/46). Precisely, 5/9, 16/20 and 12/17 patients underwent neuropsychological testing in the groups of depressive cognitive complainers (DCC), AD and FTD, respectively. Detailed neuropsychological assessment was hindered in two patients with FTD by severe lingual or cognitive deficits.

Diagnoses were rendered blinded to the neurochemical outcome measures based on a thorough medical history, clinical examination, neuropsychological assessment, clinical records and best clinical judgment. Investigations were carried out with the informed consent of patients or their authorized caregiver. The study was conducted under the guidelines of the Declaration of Helsinki (1996) and approved by the ethics committee of the University of Goettingen (Number 21997).

Non-demented disease controls

The group consisted of two subgroups:

Neurological diseases without organic brain affection

The 11 patients (six women and five men) underwent lumbar puncture to investigate central nervous affection in case of polyneuropathy ($n = 8$), benign paroxysmal positioning vertigo ($n = 1$), epilepsy ($n = 1$), and autosomal dominant hereditary spastic spinal palsy ($n = 1$).

Depressive cognitive complainers

The 9 depressive patients (3 women and six men) underwent lumbar puncture for differential diagnosis of cognitive complaints during the course of disease. The diagnosis of depression was made according to the criteria of DSM IV and cognitive impairment was assessed by MMSE at minimum. Patients with persistent cognitive decline for more than 6 months and MMSE score below 26 were excluded.

Patients with Alzheimer's disease

22 patients (12 women and 10 men) fulfilled DSM IV criteria and NINCDS-ADRDA criteria for clinical diagnosis of AD (McKhann et al. 1984). Structural (CT or

MRI) or functional (SPECT or PET) brain imaging displayed global cortical atrophy or temporal, parietotemporal, frontotemporal focal atrophy or marked hypometabolism of these regions.

Patients with frontotemporal dementia

Frontotemporal dementia ($n = 17$, eight women and nine men) was diagnosed according to the consensus criteria (Neary et al. 1998) Structural (CT or MRI) or functional (SPECT or PET) brain imaging revealed frontal or frontotemporal focal atrophy or marked hypometabolism.

Preanalytical treatment of CSF for Aβ-SDS-PAGE immunoblot

CSF was drawn from patients by lumbar puncture, sampled in polypropylene vials, centrifuged (1,000g, 10 min, 4 °C) and aliquots of 200 µl were stored at −80 °C within 24 h for subsequent Aβ-SDS-PAGE/immunoblot analysis.

Preanalytical concentration of CSF by immunoprecipitation (IP) was performed as recorded previously (Wiltfang et al. 2002). The aminoterminally selective mouse monoclonal antibody 1E8 (Wiltfang et al. 2001; Tammer et al. 2002) was employed along with the carboxyterminally selective 13E9 (Schering AG, Berlin, Germany, Wiltfang et al. 2002) and 6D5 (Schering AG, Berlin, Germany, Wiltfang et al. 2002) directed against the carboxyterminus of Aβ1-40 and Aβ1-42, respectively. The antibody 1E8 was purchased from Nano Tools, Teningen, Germany, antibodies 13E9 and 6D5 were provided by Schering AG, Berlin, Germany.

Aβ-SDS-PAGE/immunoblot

Aβ-SDS-PAGE/immunoblot was conducted as published elsewhere (Wiltfang et al. 2002; Bibl et al. 2004). Briefly, gels were run at a constant current of 24 mA per gel and at room temperature for 1 h, and semidry Western blotting was performed onto PVDF-membranes. For immunological detection of Aβ peptides on PVDF-membranes, the aminoterminally selective mouse monoclonal antibody 1E8 was applied overnight at 4 °C. Membranes were further incubated with a biotinylated anti-mouse polyclonal antibody (Vector Laboratories, Burlingame, CA, USA) and horseradish peroxidase coupled streptavidin (Amersham Pharmacia Biotech, Buckinghamshire, England) for 1 h each. Washing steps were performed in between. Chemiluminescent visualization by ECL solution was followed by quantification using a charge-coupled device (CCD) camera. Detection of the emitted light signal was performed by a CCD camera (FluorSMax MultiImager; Bio-Rad), using a series of 1, 5, 20, 60, 120, and 300 s for data acquisition. CSF samples of each individual patient were run as triplicates and band intensities were quantified from individual blots of each patient relative to a four-point dilution series of synthetic Aβ peptides using Quantity One software (version 4.1, Bio-Rad). Aβ2-42, Aβ2-40, Aβ1-40^{ox} and Aβ1-38^{ox} were normalized to the synthetic standard peptide Aβ1-37, the one with the lowest concentration within the standard Aβ peptide mix.

The detection sensitivity of the assay was 0.6 pg (Aβ1-38, Aβ1-40) and 1 pg (Aβ1-37, Aβ1-39, Aβ1-42). The inter- and intra-assay coefficients of variation for 20–80 pg of synthetic Aβ peptides were <10 % (Wiltfang et al. 2002; Bibl et al. 2004).

Statistical analysis

Patient groups were characterized by mean and standard deviation. Aβ peptide concentrations were expressed in their absolute (ng/ml) and relative quantities as Aβ peptide ratios (Aβ1-X/Aβ1-Y). The Mann–Whitney U test was employed to determine significant differences of diagnostic groups. Correlations of measured values were estimated by Spearman's Rho. The two-sided level of significance was taken as $p < 0.05$. The global diagnostic accuracies were assessed by the area under the curve (AUC) of receiver operating characteristic curve (ROC). Cut-off points were determined at the maximum Youden index, providing a minimum sensitivity of ≥ 80 %. The statistical software package SPSS, version 12.0 served for computations.

Results

Based on a previously published sequential aminoterminally and carboxyterminally specific immunoprecipitation protocol followed by subsequent Aβ-SDS-PAGE/immunoblot analysis, the CSF concentrations of the Aβ peptides 1-37, 1-38, 1-38^{ox}, 1-39, 1-40, 1-40^{ox}, 1-42, 2-40 and 2-42 could be analysed in the groups NDC, AD and FTD (Fig. 1). The Aβ peptides 1-38^{ox}, 2-40 and 2-42 could not be detected consistently in CSF. Aβ1-38^{ox} was lacking in 2 NDC, 2 AD and 2 FTD patients ($n = 6/59$), Aβ2-40 in 5 NDC, 7 AD and 7 FTD patients ($n = 19/59$) and Aβ2-42 in 8 NDC, 11 AD and 8 FTD patient ($n = 27/59$) samples. Mean age, MMSE, absolute quantities (ng/ml) and ratios of CSF Aβ peptides are summarized in Table 1.

Correlations

Throughout all investigated patient groups, the different Aβ peptides were strongly correlated with each other. In NDC, higher absolute levels of CSF Aβ2-42 were

Fig. 1 Aβ-SDS-PAGE/ immunoblot of unconcentrated (*lane 1, 4, 7*), carboxyterminally specific immunoprecipitated (13E9, IP1) (*lane 2, 5, 8*) and the aminoterminally (1E8, IP2) enriched supernatant of IP1 (*lane 3, 6, 9*) CSF. Quantifications of band densities were determined relative to a four point dilution series of a synthetic Aβ 1-37, 1-38, 1-39, 1-40 and 1-42 peptide mix (*lane 10–13*)
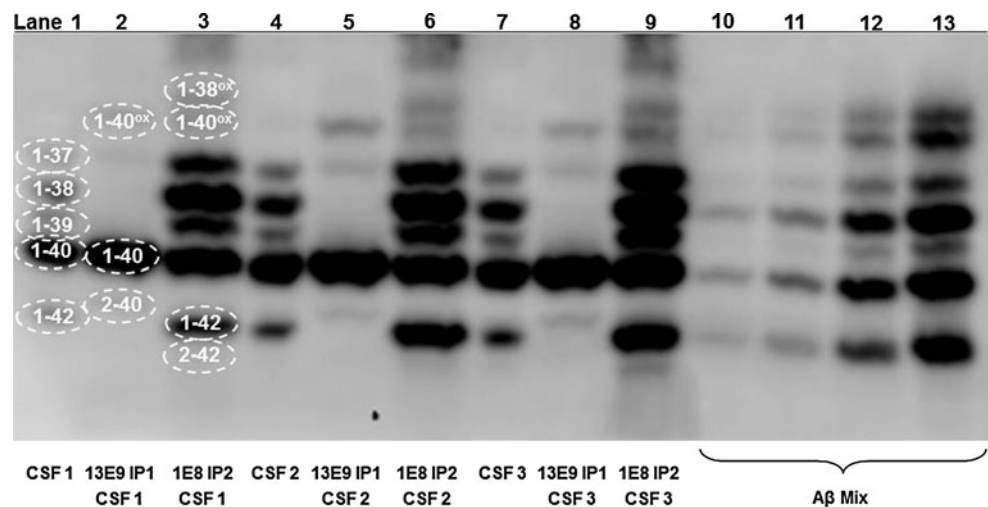

Table 1 CSF Aβ peptide patterns

Diagnosis	NDC (n = 20)		AD (n = 22)		FTD (n = 17)	
	Mean	±SD	Mean	±SD	Mean	±SD
Age	59.1	11.7	70.8	8.6	62.8	5.7
MMSE	28.6	0.5	22.5	4.4	20.9	9.9
Aβ1-37[a]	0.926	0.336	0.849	0.255	0.799	0.532
Aβ1-38[a]	2.261	0.787	2.257	0.554	1.433	0.554
Aβ1-38oxa	0.149	0.045	0.146	0.039	0.124	0.040
Aβ1-39[a]	0.959	0.343	0.944	0.312	0.798	0.487
Aβ1-40[a]	7.142	2.868	6.246	2.287	5.108	2.967
Aβ1-40oxa	0.229	0.108	0.209	0.071	0.212	0.103
Aβ1-42[a]	1.521	0.604	0.702	0.302	1.056	0.631
Aβ2-40[a]	0.156	0.026	0.143	0.042	0.124	0.052
Aβ2-42[a]	0.242	0.162	0.091	0.054	0.188	0.097
Aβ1-42/Aβ1-40[b]	0.228	0.088	0.122	0.050	0.220	0.103
Aβ1-42/Aβ1-38[b]	0.693	0.222	0.327	0.168	0.727	0.317
Aβ2-42/Aβ1-40[b]	0.040	0.026	0.014	0.009	0.040	0.015
Aβ2-42/Aβ1-38[b]	0.108	0.047	0.040	0.017	0.118	0.050

[a] Total Aβ peptide concentration (ng/ml)

[b] Aβ peptide ratios

positively correlated with age. In AD, the ratio Aβ1-42/ Aβ1-40 correlated negatively with age and Aβ2-42/Aβ1-38 positively with male sex. In FTD, the ratios CSF Aβ1-42/ Aβ1-40 and Aβ1-42/Aβ1-38 were positively correlated with the MMSE score. Otherwise, none of the investigated markers correlated with sex, age or the severity of dementia as measured by MMSE.

Group differences

The mean age of NDC ($p = 2 \times 10^{-3}$) and FTD ($p = 1 \times 10^{-2}$) was significantly younger than that of the AD group. NDC and FTD did not differ in mean age. The dementia groups did not differ in severity of dementia as measured by MMSE score.

Neurochemical phenotype of AD versus NDC

Absolute CSF Aβ1-42 ($p = 1.6 \times 10^{-5}$) and Aβ2-42 ($p = 5.4 \times 10^{-5}$) concentrations were decreased in AD to a similar degree (Figs. 2, 3). Correspondingly, the ratios of Aβ1-42/Aβ1-40 ($p = 4.5 \times 10^{-5}$), Aβ1-42/Aβ1-38 ($p = 8.3 \times 10^{-6}$), Aβ2-42/Aβ1-40 ($p = 2.1 \times 10^{-4}$) and Aβ2-42/Aβ1-38 ($p = 4.4 \times 10^{-5}$) were decreased in AD.

Neurochemical phenotype of FTD versus NDC

FTD presented with decreased levels of CSF Aβ1-38 ($p = 2.5 \times 10^{-3}$) (Fig. 4), paralleled by lowered concentrations for CSF Aβ1-40 ($p = 4.2 \times 10^{-2}$) and Aβ1-42 ($p = 4.2 \times 10^{-2}$).
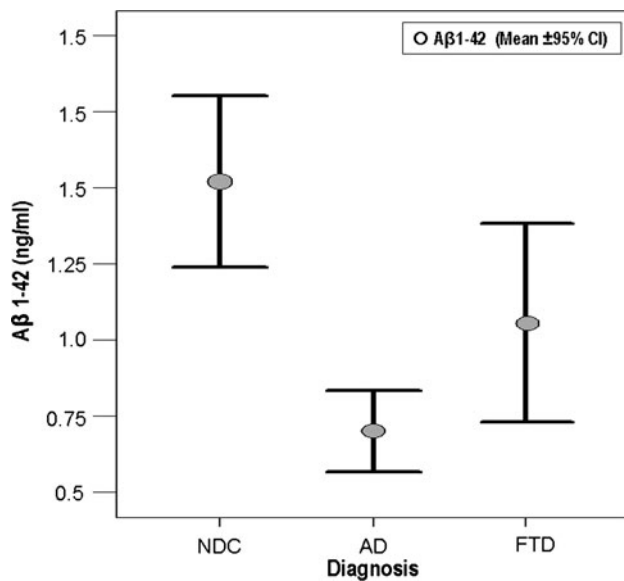
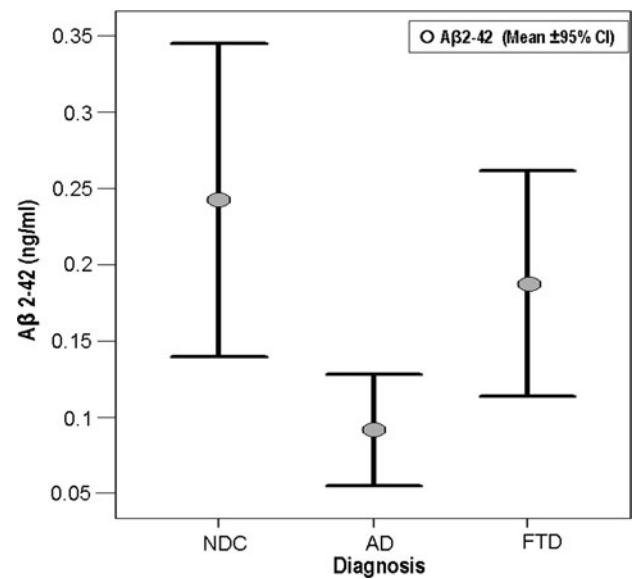**Fig. 2** Mean and 95 % confidence interval (CI) of CSF Aβ1-42 concentrations (ng/ml) for NDC, AD and FTD

Fig. 3 Mean and 95 % confidence interval (CI) of CSF Aβ2-42 concentrations (ng/ml) for NDC, AD and FTD

Neurochemical phenotype of AD versus FTD

In absolute terms Aβ2-42 ($p = 5.7 \times 10^{-3}$) was decreased in AD, whereas Aβ1-38 was decreased in FTD ($p = 5.4 \times 10^{-5}$) (Figs. 3, 4). Accordingly, the ratios of Aβ2-42/Aβ1-40 ($p = 5.4 \times 10^{-4}$) and Aβ2-42/Aβ1-38 ($p = 1.3 \times 10^{-6}$) were markedly reduced in AD as compared to FTD. Although Aβ1-42 did not differ significantly between AD and FTD in absolute terms, its relative abundances expressed as Aβ1-42/Aβ1-40 ($p = 1.2 \times 10^{-3}$) and Aβ1-42/Aβ1-38 ($p = 1.3 \times 10^{-6}$) were decreased in AD in comparison to FTD.

Neurochemically supported differential diagnosis of AD versus FTD

ROC curve analysis was performed comparatively for absolute and relative concentrations of CSF Aβ1-42 and Aβ2-42.

The decreased absolute concentration of Aβ1-42 yielded a maximum sensitivity and specificity of 95 and 53 %, respectively, for the diagnosis of AD versus FTD. By combining Aβ1-42 with Aβ1-40 (Aβ1-42/Aβ1-40), the specificity could be slightly improved to 65 %. The combination of Aβ1-42 with Aβ1-38 (Aβ1-42/Aβ1-38) yielded a sufficient sensitivity and specificity of 82 % in discriminating AD and FTD.

Diminished CSF Aβ2-42 levels as well as its combination with Aβ1-40 (Aβ2-42/Aβ1-40) enabled the discrimination of AD from FTD with a satisfactory sensitivity of 91 % and a specificity of 92 %. The combination of Aβ2-42 with Aβ1-38 (Aβ2-42/Aβ1-38) improved the
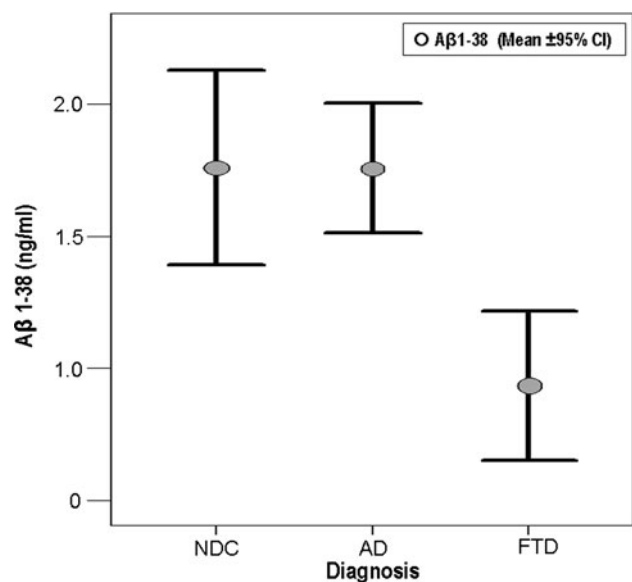

Fig. 4 Mean and 95 % confidence interval (CI) of CSF Aβ1-38 concentrations (ng/ml) for NDC, AD and FTD

sensitivity for AD detection to 100 %, at a stable specificity for exclusion of FTD (89 %) (Table 2).

Discussion

Using a novel sequential aminoterminally and carboxyterminally specific immunoprecipitation protocol and subsequent analysis in the Aβ-SDS-PAGE/immunoblot, a pattern of CSF Aβ peptides 1-38ox, 2-40 and 2-42 in

Table 2 Cut off points, sensitivities and specificities

Differential diagnosis	Parameter	Cut off	Sensitivity (%)	Specificity (%)	Youden index	AUC	95 % CI
AD versus FTD	$A\beta1$-42	1.02	95	53	0.48	0.674	0.489–0.858
	$A\beta1$-42/1-40	0.19	91	65	0.56	0.797	0.653–0.941
	$A\beta1$-42/1-38	0.45	82	82	0.64	0.917	0.835–0.999
	$A\beta2$-42	0.11	91	89	0.80	0.859	0.671–1.00
	$A\beta2$-42/1-40	0.03	91	89	0.80	0.929	0.805–1.00
	$A\beta2$-42/1-38	0.08	100	89	0.89	0.929	0.792–1.00

addition to $A\beta$ 1-37, 1-38, 1-39, 1-40, 1-40^{ox} and 1-42 was quantified in 20 NDC and 22 AD in comparison to 17 FTD patients. This novel methodological approach was described recently and its results on the respective $A\beta$ peptide patterns expressed in NDC and AD have been published elsewhere. The main finding in these investigations was that $A\beta1$-42 and $A\beta2$-42 were decreased to a similar degree in AD and yielded similar accuracies among NDC (Bibl et al. 2011a, b).

Biomarker aspects

The differential diagnosis between AD and FTD is a frequent challenge in clinical practice and may be supported by lower levels of p-tau (Hampel et al. 2004) as well as by disease-specific $A\beta$ peptide patterns, showing lower and higher levels of $A\beta1$-38 and $A\beta1$-42 in the latter case (Bibl et al. 2007a, b). Otherwise, CSF $A\beta1$-42 did not show satisfactory accuracies for discriminating AD and FTD as a single biomarker in many studies, obviously due to overlapping values (Blennow 2004).

Both $A\beta1$-42 and $A\beta2$-42 seem to be deeply involved in the process of AD-specific plaque building (Wiltfang et al. 2001), which may also be expressed by its equivalent decrease of CSF in AD (Bibl et al. 2011b). In the present study, the decrease of CSF $A\beta2$-42 appeared to be more specific for AD as compared to FTD than low $A\beta1$-42 levels. $A\beta2$-42 showed only little overlap of values between AD and FTD and thus enabled higher accuracies for their discrimination. Interestingly, the improvement of accuracy in AD diagnosis from $A\beta1$-42 to $A\beta2$-42 levels mainly regarded the specificity for FTD exclusion, which led to satisfactory accuracies for $A\beta2$-42 even as a single biomarker. Although these results seem promising for possible applicability of CSF $A\beta2$-42 as a single biomarker for the differential diagnosis of AD from other dementias, one has to be cautious of the small sample size for this peptide within the analysed patient groups. Notably, $A\beta2$-42 could only be detected in twelve NDC, eleven AD and nine FTD patients. Similarly, $A\beta1$-38^{ox} and $A\beta2$-40 were lacking in some analysed samples, most probably because their concentrations fell below the detection limit

of our analytical protocol. Another explanation might be that they are inconsistently expressed in CSF. However, the appearance of these peptides in CSF did not correlate with the status of diagnosis.

According to the recommendations of an international working group, a minimum sensitivity for AD detection and specificity for exclusion of other dementias of 80 % should be fulfilled by an applicable AD biomarker (Working Group on Molecular and Biochemical Markers of Alzheimer's Disease. 1998). In terms of $A\beta1$-42, these accuracy figures could only be reached by its combination with $A\beta1$-38, which was reduced in FTD. The reduction of CSF $A\beta1$-38 as a disease indicative feature for FTD was previously published in unconcentrated CSF as analysed by the $A\beta$-SDS-PAGE/immunoblot (Bibl et al. 2007a, b) and could be retraced using electrochemiluminescence and ELISA methods in our own investigations (Bibl et al. 2011c) and those of others (Gabelle et al. 2011). The reduction of CSF $A\beta1$-38 in FTD was reproducible under the methodological specifications of our present analytical protocol and was thus capable of adjusting the lack of specificity of $A\beta1$-42 alone by combining both parameters with $A\beta1$-42/$A\beta1$-38 for discriminating AD from FTD.

Taken together, the analysis of $A\beta1$-42/$A\beta1$-38 as well as $A\beta2$-42 alone and in combination with either $A\beta1$-40 or $A\beta1$-38 fulfilled the accuracy requirements for an applicable AD biomarker, as stated by the Working Group on Molecular and Biochemical Markers of Alzheimer's Disease (1998) in the present study setting. The most promising finding was the AD-specific decrease of $A\beta2$-42 in comparison to FTD, as this raises hope for its use as a single amyloid-based biomarker for discriminating AD from other dementias. However, its accuracy figures may be challenged by other differential diagnostically relevant neurodegenerative disorders, where plaque forming is a more frequent event, such as dementia with Lewy bodies.

Possible underlying pathogenic mechanisms

Both $A\beta1$-42 and $A\beta2$-42 seem to be deeply involved in the process of plaque forming, which is a core feature of the disease process in AD, but not in FTD. Aminoterminal

truncations as well as carboxyterminal elongations as referenced to Aβ1-40 are known to render Aβ peptides more prone to aggregation into amyloid plaques, thereby probably producing oligomeric interstates that are regarded as highly neurotoxic (Larson and Lesnè 2012). Interestingly, aminoterminal truncation of Aβ1-X to Aβ2-X is related to aminopeptidase A activity and inhibitors of this enzyme appear to exert neuroprotective effects in cell-based systems (Sevalle et al. 2009) Thus, aminoterminal truncation may be a significant step towards the neurotoxic properties of Aβ peptides. In this coherency, it should be noted that recently published data support the idea of alternative β-secretase activity being responsible for the formation of aminoterminally truncated Aβ peptides (Schieb et al. 2010, 2011).

Especially high levels of aminoterminally truncated and carboxyterminally elongated Aβ species were detected in cored plaques that represent the major plaque type in AD (Güntert et al. 2006). The major plaque forms in non-demented individuals are diffuse plaques that mainly consist of carboxyterminally elongated Aβ species ending with aminoacid 42 (AβX-42), but show aminoterminal truncations less frequently (Güntert et al. 2006). Thus, aminoterminally truncated Aβ peptides seem to be differentially accumulated in AD-specific cored and unspecific diffused plaques. Given that the reduction of CSF Aβ42 species in AD is an expression of their aggregation into plaques, their differentially expressed CSF levels may allow conclusions on the extent of cored and diffused plaque formation. However, under the aspect of decreased Aβ1-42 in FTD as compared to NDC, alternative mechanisms for its reduction in CSF may be taken into account as well, such as altered binding properties to CSF abundant carrier proteins (Bibl et al. 2008).

Another interesting pathophysiological aspect of Aβ2-42 is that it may be involved quite early in the plaque forming process and may serve as a first nidus seeding the aggregation of other Aβ species (Wiltfang et al. 2001). It has been suggested that diffuse plaques mature to cored plaques in AD, accumulating higher rates of aminoterminal truncations (Güntert et al. 2006), which indicates that aminoterminally truncated Aβ peptides play a role in the maturation of plaques as a core pathogenic process of AD. Correspondingly, several mass spectrometric investigations have also described the presence of a range of aminoterminally and carboxyterminally truncated and Aβ peptides in CSF (Vanderstichele et al. 2005; Albertini et al. 2010; Ghidoni et al. 2011). Portelius et al. described a pattern of carboxyterminally truncated Aβ peptides (Portelius et al. 2006, 2007) that displayed disease-specific derangements in AD (Portelius et al. 2009).

Limitations of the study and future prospects

The major concern of our present study is the fact that Aβ 2-42 could only be detected in a portion of patients. Its inconsistent appearance CSF hampers the use of Aβ 2-42 for an applicable AD diagnostic test. The accuracy calculations were solely based on the samples, where Aβ2-42 was detectable. Regarding all patients, where Aβ2-42 was not detectable, one must expect considerable lower accuracy figures. Given this, we are aware of the need to further develop Aβ2-42 as a possible biomarker candidate in terms of using more sensitive detection methods, its integration into more convenient assay formats (e.g., ELISA, multiplex platforms) and subsequent evaluation in larger patient collectives. The actually employed Aβ-SDS-PAGE/immunoblot is a time-consuming and low-throughput method. It may be more appropriate for finding new biomarker candidates than for use in routine analysis.

With respect to the neuropathological heterogeneity of FTD, the reliance on clinical diagnosis limits our results, because of potential misclassification. The evaluation of Aβ2-42 in neuropathologically defined patient groups will be necessary to reinsure our results. For estimating the potential diagnostic value of CSF Aβ2-42 for AD as compared to other dementias, larger studies that include dementias with more frequently overlapping AD pathology, like dementia with Lewy bodies or vascular dementias, are needed.

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