CEREBROSPINAL FLUID Aβ40 AND Aβ42: NATURAL COURSE AND CLINICAL USEFULNESS

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1. ABSTRACT

Amyloid β protein 40 (Aβ40) and 42 Aβ42, major components of senile plaque amyloids, are physiological peptides present in the brain, cerebrospinal fluid (CSF) and plasma. The levels of CSF Aβ40 and Aβ42(43) show a U-shaped natural course in normal aging. The increase of Aβ42(43) over 60 years of age is inhibited in Alzheimer’s disease (AD). This specific alteration of CSF Aβ42(43) correlates with Aβ deposits in the AD brain providing a biological basis for a biomarker of AD. In the GTT2 study, assays of the CSF Aβ ratio ((Aβ40/Aβ42(43)) showed a diagnostic sensitivity (59%) and specificity (88%) compared with non-AD type dementia and controls. The levels of the Aβ ratio increased from early to late stages of AD. Combination assays of CSF tau and Aβ ratio provided further efficient diagnostic sensitivity (81%) and specificity (87%). The reliability of the assay may prompt worldwide usage of these CSF biomarkers for Alzheimer’s patients.

2. INTRODUCTION

Alzheimer’s disease (AD), one of the most devastating brain diseases, is a medical, sociological and economic problem caused by the increase in the elderly population in modern society. About 5% of the population over 65 years of age suffer from dementia. Progressive dementia destroys the total character of the patient and places family members and caretakers in stressful conditions. These serious problems immediately demand social care systems and development of a treatment for dementia. The majority of patients with dementia have AD. About 700,000 patients presently suffer from AD in Japan. Recent progress in the study of AD has provided the possibility to cure AD using Aβ42 peptide vaccines or γ-secretase inhibitors (1). If biomarkers enable early and accurate diagnosis of AD before the irreversible severe stage of dementia, and help evaluate the drug effects precisely, we could expect rapid progress in the development of new drugs. For this reason, sensitive and specific biological markers of AD should be established immediately.

AD brains are characterized by two pathological features: Aβ amyloidosis comprising extracellular deposits of Aβ40 and Aβ42 (2) tauopathy showing intracellular accumulation of hyperphosphorylated 3 or 4 repeat tau in the form of neurofibrillary tangles. The deposition of Aβ consisting of Aβ40 and Aβ42(43) (2) derived from the Aβ precursor (βAPP) is a specific, early event in the development of AD preceding neurofibrillary tangles and clinical dementia. Familial AD-linked gene mutations in βAPP and presenilins cause the extracellular concentration of Aβ42(43) to increase by 1.5-6-fold in cultured cells, transgenic mice and plasma in FAD patients (3-8). Thus, increased levels of Aβ42(43) are suggested to be an initiating factor for all types of AD (7). The definite diagnosis of sporadic AD, which accounts for almost all AD patients, is based on the neuropathological changes in the brain (9). Sensitive ELISAs have shown that there are decreased levels of CSF Aβ42(43) in AD patients and for
this reason CSF Aβ42(43) has also been proposed as a candidate diagnostic marker for AD (10). Large-scale multicenter studies established the combination assay of tau and Aβ40(42)/(43) as an additional sensitive biomarker for AD (11-13). Although a disturbed clearance of soluble Aβ42(43) from the brain parenchyma into CSF in the AD brain is an explanation for decrease in Aβ42(43) in CSF, knowledge of the origin and metabolism of CSF Aβ40 and Aβ42(43) and the correlation between the amount of CSF Aβ and cerebral Aβ deposits remains poor. Here, we summarize the recent progresses in the study of CSF Aβ and evaluate the clinical usefulness of CSF Aβ40 and Aβ42(43) referring to a GT2 study, a continuous Japanese Study of cerebrospinal fluid biomarkers (14).

3. THE PRESENCE OF Aβ40 AND Aβ42 (43) IN CSF

After the discovery of the presence of Aβ in CSF (15, 16), several studies, using different assay systems, reported various Aβ concentrations in AD and age-matched controls (17-20). Our assay system using BAN-50/BA-27 for Aβ40 and BAN-50/BC-05 for Aβ42 (43) showed that the levels of Aβ40 were 1.65 ± 1.014 fmol/ml (mean ± SD) in normal subjects, 1.886 ± 1.058 fmol/ml in females and 1.425 ± 0.895 fmol/ml in males. The levels of Aβ42(43) were 3.12 ± 0.221 fmol/ml in all subjects, 2.64 ± 1.75 fmol/ml in females and 3.63 ± 254 fmol/ml in males. The Aβ3X ratio (Aβ40/Aβ42 (43)) was 6.3 ± 3.1 in normal subjects, 6.2 ± 3.1 in females and 6.3 ± 3.1 in males (14). A major proportion of the CSF Aβ presents as a free monomeric form or in a lipoprotein bound form complexed with apolipoprotein J (21) or apolipoprotein E (22) in the HDL-form or in a lipoprotein bound form complexed with apolipoprotein J (21) or apolipoprotein E (22) in the HDL-form. Laser desorption mass spectrometry confirmed the presence of heterogeneous 4, 3.7, 3.3 and 3 kD Aβ in CSF by immunoblot assay (25). Amino acid sequencing of affinity purified CSF Aβ revealed that the Aβ species started with the N-termini of Asp1, Glu3, His6, Glu11, and Val12, and that Asp1 represents the predominant amino-terminus. Laser desorption mass spectrometry confirmed the presence in CSF of Aβ species containing 27, 28, 30, 34, 35, 40, 42, and 43 amino acids, all beginning at Asp1; two stable trimers, (Asp1-Met35)3 and (His6-Ala42)3; and one stable dimer containing (Asp1-Val40)2 (26). Although the presence of Aβ oligomer or Aβ seed was suggested in CSF, the amount of Aβ oligomer is minimal and whether the oligomer actually develops into insoluble amyloid in CSF remains to be clarified (27, 28). Two catabolic enzymes regulating the amount and fate of extracellular Aβ in the brain and CSF have been proposed; one is insulin-degrading enzyme, a thiol metalloendopeptidase which degrades about 50% of extracellular Aβ during 18 hours (29), and another is a newly discovered neutral endopeptidase, neprilysin (30).

A large amount (about 500 ml/day) of CSF is produced by the choroid plexus and flows through the ventricle into the subarachnoid space. The major pathways for drainage of CSF are via arachnoid granulations and vili into veins in the dura mater (31). Production of extracellular Aβ in primary cultured neurons from animals, brain microvessels, meningeal vessels and the choroid plexus from humans have been reported (32). The human CSF levels of Aβ42 and Aβ40 rose after severe traumatic brain injury, peaking in the first week and then declining towards normal levels after 2 weeks (33). Zölkkovic et al. showed that plasma soluble Aβ can cross the blood brain barrier (BBB) (34). The radiolabeled Aβ following intravenous injection, bound amyloid deposits in vivo in a transgenic mouse model for AD (35). The transport process across the blood-brain barrier and the blood-CSF barrier is facilitated by binding to apolipoprotein J, the major presence of CSF Aβ, and mediated by glycoprotein 330/megalin, a probable receptor for cellular uptake and transport of the Apolipoprotein J complex at the cerebral vascular endothelium and choroid epithelium (36, 37). However, about 30% of radiolabeled Aβ infused into the rat lateral ventricle was cleaned from ventricular CSF after 3.5 min. Another 30% was removed over the subsequent 6.5 min. Much of the infused Aβ that reached the subarachnoid space was retained by pial arteries and arterioles (38, 39). Recently, Kawarabayashi et al. reported that coincident with the marked deposition of Aβ in the Tg2576 brain, an established transgenic mouse model for AD, there was a highly significant decrease in CSF and plasma Aβ concentrations. These findings suggested that the origin of CSF and plasma Aβ is the brain parenchyma, and that substantial Aβ deposits as senile plaque amyloid disturb the physiological clearance of Aβ through the blood-brain barrier and the blood-CSF barrier (40). Thus, the CSF Aβ concentration is strictly regulated at the physiological level by these synthesis, transport and degrading mechanisms.

4. NATURAL COURSE OF CSF Aβ40 AND Aβ42 (43): AGE-RELATED CHANGES

Soluble Aβ40 and Aβ42(43) levels increase in the brains of normal subjects from their 50’s (41, 42, 43) and in plasma of those from their 60’s (44). Large amounts of insoluble Aβ40 and Aβ42(43) accumulate exponentially in AD brains (45). Increased total CSF Aβ concentrations were shown in elderly subjects (11, 46-47). However, a significantly decreased level of Aβ42(43) was reported in the CSF of AD patients compared with those of controls (10). In the present study, the levels of CSF Aβ40 and Aβ42(43) were physiologically altered and showed a U-shaped natural course in normal aging. High concentrations of Aβ40 and Aβ42(43) from child to youth were downregulated to be constantly low concentrations in adults between 30 and 60 years old. Subsequently, the levels of CSF Aβ40 and Aβ42(43) increased again with age. Third order regression analysis confirmed these age-dependent physiological alterations and showed both Aβs finally decreased in senile subjects over 80 years old (48; Figure 1). No previous studies have indicated significantly increased amounts of CSF Aβ by young populations and the importance of increased levels of CSF Aβ40 and Aβ42(43), at least 1.4-1.9-fold, during normal aging without FAD-linked gene mutations. Concentrations of CSF Aβ40 and Aβ42(43) were age-dependently regulated to be high.
Appearance of Aβ amyloidosis in the AD brain may correspond to the accelerated decline of Aβs in CSF of AD. For this reason, the concept of a selective reduction of CSF Aβ42 in AD should be corrected based on two findings. First, the low concentrations of CSF Aβ42 were observed also in normal adults between 30 and 59 years old. The levels of CSF Aβ42(43) in young AD did not show a significant difference compared with the normal adult group. The presence of overlap of measurements made it difficult to find a significant difference between young AD patients and adult controls. This overlap may decrease the sensitivity of the diagnostic marker of AD, especially in early-onset AD patients who develop dementia before 60 years of age. Second, the levels of Aβ42 were increasing in normal controls over 60 years. Interestingly, only the increase in CSF Aβ42(43) in the over 60 year olds was inhibited in AD. Thus, it is more correct to state that the physiological increase in Aβ42(43) over 60 years of age is selectively inhibited in AD (Figure 2). Progressive accumulation of insoluble Aβ40/42 accumulation and this selective inhibition of the physiological clearance of Aβ42 from the brain to CSF are considered to be major disturbances in developing Aβ amyloidosis in the AD brain (14).

5. CSF Aβ 40 AND Aβ42(43) AS A DIAGNOSTIC MARKER

In 1994, Nakamura et al. started the evaluation of CSF Aβ as a biomarker for AD. They directly measured the amount of total CSF Aβ by immunoprecipitation and immunoblot showing increased amounts of CSF Aβ in early-onset Alzheimer’s disease (n=14) (17). Pirttila et al. reported that total CSF Aβ levels were lower in late onset AD (n=40) and vascular dementia (VD; n=22) compared with non-demented patients with other neurological diseases (n=18) by ELISA (4G8/6E10) (49). A different ELISA (266/10D5) did not show any significant difference between AD (n=18) and normal subjects (n=10) (19). Total CSF Aβ levels decreased during the progression of AD in sporadic AD (18) and in the Swedish APP670/671 mutation family (50). Another ELISA (AM1B/AM1A 266) also did not show any differences between AD and controls (51). Thus, early studies by several assay systems, which could not distinguish Aβ42 and Aβ40, did not show any clear findings about CSF Aβ in AD patients.

In 1995, Motter et al. first showed the selective reduction of Aβ42 in CSF of AD patients compared with total Aβ(10). Using the 266/277-2 antibody ELISA, total Aβ and Aβ42 in CSF from 37 AD, 20 normal controls and 20 neurological diseases were examined. Significantly decreased amounts of Aβ42 were revealed and a cut-off value of 505 pg/ml optimally separated AD patients (sensitivity 100% and specificity 63%). They also showed the presence of elevated CSF tau and reduced Aβ42 was highly predictive of AD (69% sensitivity and 96% specificity). Soon after, we showed that an increased Aβ ratio (Aβ40/Aβ42(43)) was a more efficient marker for AD (51% sensitivity and 82% specificity) and the combination...
The results of GTT2 study I. CSF samples were collected from 92 normal subjects between 8 and 89 years of age. For comparison, 157 CSF samples from AD patients between 40 and 92 years old were also examined. For the age-matched study, normal subjects were divided into 3 groups: young group (< 30 years old), adult group (30 ~ 59 years old) and old group (> 59 years old). AD subjects were divided into young AD (≤ 59 years old) and old AD (> 59 years old) groups. The post-hoc test showed significantly increased levels of Aβ40 in the young and old groups compared with the adult group (p< 0.01). The levels of Aβ40 were 1.9-fold higher in the young group and 1.6-fold higher in the old group compared with the adult group. The levels of Aβ40 were significantly increased in young AD (p < 0.05) and old AD subjects (p < 0.01) compared with the normal adult group (Figure 1a). Significant differences were revealed among the 3 groups (p< 0.0001), and significantly increased levels of Aβ42(43) were observed in the young (p < 0.001) and old (p < 0.01) groups compared with the adult group. The levels of Aβ42(43) were increased 1.7-fold in the young group and 1.4-fold in the old group compared with the adult group. Significantly decreased levels of Aβ42(43) were observed in young ADs compared with the normal young group (p < 0.001) and the normal old group (p < 0.001). No significant difference was recognized between the normal adult group and young ADs, or between young ADs and old ADs (Figure 1b). No significant differences were revealed among the control groups in the Aβ40/Aβ42(43) level. A significantly increased Aβ40/Aβ42(43) was observed in young ADs (12.6 ± 6.3; p < 0.01) and old ADs (15.8 ± 7.9; p < 0.001) compared with the 3 normal groups. The relative ratio of CSF Aβ40 to Aβ42 was not changed by aging, suggesting the synthesis and clearance activity of Aβ40 and Aβ42 in CSF was strictly regulated in subjects at all ages (Figure 1c).
of elevated CSF tau levels and AD index (tau x Aβ40/Aβ42) improved the sensitivity and specificity (69% and 88%, respectively) by ELISA using BAN-50/BA-27 for Aβ40 and BAN-50/BC-05 for Aβ42 (43) (46).

After these studies, 3 independent large-scale multicenter studies confirmed that the combination of CSF tau, Aβ40 or Aβ42(43) was the most useful diagnostic biomarker of AD. The first Japanese study of CSF tau, Aβ40 and Aβ42(43) by Gunma, Tottori and Tohoku University Hospitals (GTT1) examined 236 subjects including 93 AD, 33 non-AD type dementia, 56 nondemented neurological diseases and 54 normal controls. The cut-off value of the Aβ ratio (Aβ40/Aβ42(43)) was 13.3, and showed efficient diagnostic sensitivity (56%) and specificity (73%) (11). The AD index (Aβ ratio x tau; cut-off 3.483) provided efficient sensitivity (71%) and specificity (83%). An improvement of sensitivity (to 91%) was obtained in a 19 month follow up study (11). A USA study by Galasko et al. (12) measured CSF tau and Aβ42 levels in 82 AD, 60 normal controls and 74 neurological diseases from 6 academic medical centers. For Aβ42 levels, the optimal cut-off for differential classification (1.031 μg/ml) showed the diagnostic sensitivity of 78% and specificity of 83%. Their final classification tree analysis using tau and Aβ42 showed 90% sensitivity and 80% specificity. The level of Aβ42 was inversely related to the apolipoprotein E epsilon 4 allele dose and was weakly related to the Mini-Mental State Examination (MMSE) score (12). The largest European study of CSF tau and Aβ42 by Hulstaert et al. examined 463 samples including 150 AD, 100 normal controls, 84 patients with other neurological diseases and 79 patients with non-Alzheimer type of dementia. Eight European and 2 US university centers were involved. At 85% sensitivity, the specificity was 55% (95% CI: 47% to 62%) for Aβ42 alone. Their final diagnostic sensitivity of the combination test was 85% with 86% specificity. The Apo E epsilon 4 gene load was negatively correlated with Aβ42 levels not only in AD but also in non-AD type dementia (13). Thus, independent large-scale multicenter studies have confirmed the clinically useful sensitivity and specificity of the combination assay of CSF tau and Aβ40/Aβ42(43) as a biomarker for AD.

A recent small-scale study (80 AD, 15 MCI, 24 healthy controls, and 15 depression) using a different ELISA (W0-2/G2-10, G2-11) showed that levels of CSF Aβ42 were strongly elevated in early and mid-stages of AD, and thereafter declined with disease progression. In contrast, Aβ40 levels were decreased in early and mid-stages of AD.

The patients with mild cognitive impairment (MCI) and the depression reference group had significantly higher levels of Aβ42 than the healthy control group (52). Another study using ELISA (6E10/R162, R164) showed lower levels of CSF Aβ42 in the AD group (36 AD vs 19 controls), which was consistent with previous studies (53). These studies should enlarge the sample numbers for precise evaluation of the markers before starting actual clinical application for AD patients.

Two follow-up studies confirmed the decline of CSF Aβ42 levels according to progression of AD (11). A 20-month prospective follow-up study showed that low Aβ42 levels start in the earlier stages of AD and continue during disease progression (54,55). A three-year follow-up study also showed that a significant decrease in Aβ42 levels may be an early event in the development of AD occurring even before clinical symptoms (56). About 88% of MCI cases (14/16) already showed high CSF tau and low Aβ42 levels (57). Thus, the decreased levels of CSF Aβ42 appeared before clinical symptoms (MCI) and the very early stage of AD (58).

There are controversies about the correlation between CSF Aβ42 and the apolipoprotein E genotype (59-61). Tamaoka et al. showed that both CSF Aβ40/Aβ42(43) and Aβ1-42(43) were significantly lower in AD patients (n=20) (62) and Down’s syndrome patients (n=5) (63). Decreased Aβ1-42 in CSF was observed in patients suffering with Creutzfeldt-Jakob disease (n=27) (64). Decreased CSF Aβ42 and normal tau levels in dementia with Lewy bodies, corresponded to pathological features that numerous senile plaques but few neurofibrillary tangles were observed in DLB patients (65). CSF Aβ40 concentrations correlated to frontal lobe atrophy in frontotemporal dementia (66).

6. TAPS TO ALZHEIMER’S PATIENTS (14)

These 3 large-scale multicenter studies fulfilled many criteria of the consensus report of the working group on “Molecular and biological markers of Alzheimer’s disease” in 1998 (67). The report proposed that the ideal biomarker for Alzheimer’s disease (AD) should detect a fundamental feature of neuropathology and be validated in neuropathologically-confirmed cases; it should have a sensitivity >80% for detecting AD and a specificity of >80% for distinguishing other dementias; it should be reliable, reproducible, non-invasive, simple to perform, and inexpensive. Recommended steps to establish a biomarker included confirmation by at least two independent studies conducted by qualified investigators with the findings published in peer-reviewed journals. Among the other proposed biochemical markers for sporadic AD, cerebrospinal fluid assays showing low levels of Aβ42 and high levels of tau come closest to fulfilling the criteria as a useful biomarker. However, the usefulness of molecular markers has not been established. A major proportion of FAD is caused by mutations in the presenilin 1, presenilin 2, and amyloid precursor protein genes. However, FAD families are quite rare, only a few percent of all AD patients worldwide. Although the apolipoprotein E epsilon 4 genotype is the strongest risk factor of AD, more than half of the population with apolipoprotein E epsilon 4 will not develop AD by 100 years of age (68). These findings suggest that the genetic test of apolipoprotein E epsilon 4 is not useful as a diagnostic tool for sporadic AD. Ethical issues also should be resolved before actual clinical usage (69, 70). As a non-invasive, simple to perform tool, the assay of plasma Aβ42 is
The findings of GTT2 study II; Detection of early stages of AD. AD index: tau x Aβ40/Aβ42(43); MMSE: minimental state examination; >20: AD patients with an MMSE score over 20 points; 10-20: AD patients with an MMSE score between 10 and 20 points; <10: AD patients with an MMSE score below 20 points. To evaluate the usefulness as a marker to detect early stages of AD, a correlation is required between these markers and the MMSE score. The levels of Aβ42 and the Aβ ratio have been changed in early stages of AD with high MMSE scores (>20 points). The diagnostic sensitivity by the AD index was 81% in the AD with high MMSE scores (>20) group, 84% in the AD with middle MMSE scores (10-20) group and 76% in the low MMSE scores (<10) group. These findings suggest that the CSF biomarkers are useful tools for clinical practice to detect even early stages of AD.

In 1998, a large-scale Japanese multicenter longitudinal study reported the clinical usefulness of measuring tau, amyloid beta protein (Aβ) 1-40 and Aβ1-42(43) in cerebrospinal fluid (CSF) as biomarkers of Alzheimer’s disease (AD) (11). A total of 236 CSF samples from AD patients were examined by this Gunma, Tottori and Tohoku study (GTT1). This was the first study to meet many of the consensus statements of a working group on molecular and biological markers of AD sponsored by the Reagan Research Institute and National Institute on Aging (67). However, the actual usage of the CSF biomarkers for clinical practice is not widely accepted (75). Therefore, we are continuing the study and have added 271 new subjects from other institutes to the original set in GTT1, and, therefore, enlarged the number of cases tested in each group. We summarized the results until April, 2000 as GTT2 (14). A total of 507 subjects, consisting of 157 patients with AD, 108 with non-AD-type dementia, 154 with other neurological diseases, and 88 normal controls were examined (Table 1). Compared with GTT1, improved conclusions can be drawn using either data set. The cut-off value of the AD index changed from 3,483 to 2,857, showing improved sensitivity from 71% to 81% and specificity from 83% to 87%. To evaluate the usefulness as a marker to detect early stages of AD, a correlation is required between these markers and the MMSE score. The levels of Aβ42 and Aβ ratio have been changed in early stages of AD with high MMSE scores (>20 points). The diagnostic sensitivity by the AD index was 81% in the AD with high MMSE scores (>20) group, 84% in the AD with middle MMSE scores (10-20) group and 76% in the low MMSE scores (<10) group. These findings suggest that the CSF biomarkers are useful tools for clinical practice to detect even early stages of AD (Figure 3). Thus, the GTT2 study also shows the diagnostic usefulness of these markers.

A 1-year prospective community population-based study of CSF tau and Aβ42 was conducted by Andreasen et al. (55). A total of 241 patients including probable AD (n = 105), possible AD (n = 58), vascular dementia (n = 23), mild cognitive impairment (n = 20), other types of dementia and nondemented individuals were enrolled. Sensitivity was 94% for probable AD, 88% for possible AD, and 75% for mild cognitive impairment, whereas specificity was 100% for psychiatric disorders and 89% for nondemented. Specificity was lower in Lewy body dementia (67%) mainly because of low CSF-Aβ42 levels and in vascular dementia (48%) mainly because of high CSF-tau levels. Sensitivity for CSF-tau and CSF-Aβ42 increased in patients with AD possessing the ApoE epsilon4 allele, approaching 100%. At a prevalence of AD of 45%, the
positive predictive value was 90% and the negative predictive value was 95% (Table 1).

7. CONCLUSIONS AND PERSPECTIVES

The reliability of the assays may prompt worldwide usage of these CSF biomarkers for AD patients and provide evidence based valuation of drug treatments for AD such as the findings that hyperglycemia contributed to clarify the pathogenesis, diagnosis and treatment of diabetes mellitus. Harmonization of different assay systems of tau and Aβ40/42(43) are desired for worldwide clinical practice of more accurate and early diagnosis of AD before developing new drugs.

8. ACKNOWLEDGEMENTS

We are grateful to Yasuo Harigaya, Etsuro Matsubara, Takeshi Kawarabayashi, Masaki Ikeda, Yasushi Tomidokoro in Department of Neurology, Gunma University School of Medicine, 3-39-22 Maebashi, Gunma 371-8511, Japan and Tetsuro Murakami, Koji Abe in Department of Neurology, Gunma University Graduate School of Medicine and Dentistry, 2-5-1 Shikada-cho, Okayama, 700-8558 Japan. Supported by Grants-in-Aid for the Primary Amyloidosis Research Committee (S Ikeda and T Ishihara), surveys and research on special disease from Primary Amyloidosis Research Committee (S Ikeda and T Ishihara)

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**Abbreviations:** Aβ: amyloid β protein; βAPP : Aβ precursor

**Key words:** Aβ40, Aβ42, Cerebrospinal Fluid, Natural Course, Review

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