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Review Article

Biomarkers of the Dementia

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Recent advances in biomarker studies on dementia are summarized here. CSF Aβ40, Aβ42, total tau, and phosphorylated tau are the most sensitive biomarkers for diagnosis of Alzheimer's disease (AD) and prediction of onset of AD from mild cognitive impairment (MCI). Based on this progress, new diagnostic criteria for AD, MCI, and preclinical AD were proposed by National Institute of Aging (NIA) and Alzheimer's Association in August 2010. In these new criteria, progress in biomarker identification and amyloid imaging studies in the past 10 years have added critical information. Huge contributions of basic and clinical studies have established clinical evidence supporting these markers. Based on this progress, essential therapy for cure of AD is urgently expected.

1. Introduction

The number of patients with dementia have been increasing exponentially with the aging of society in advanced countries and Asian countries. About 24,300,000 people are expected to have dementia worldwide, and there are already more than 2,000,000 people with dementia in Japan. A half of dementia were caused by Alzheimer disease (AD). The development of AD research has clarified that the pathogenesis of AD is initiated by Aβ amyloidosis with secondary tauopathy and provided a strategy for investigating drugs that may improve or cure AD. Mild cognitive impairment (MCI) as a prodromal stage of AD and the pathogenesis of Dementia with Lewy bodies (DLB) and Frontotemporal lobar degeneration (FTLD) as a non-AD type dementia have also been elucidated. Currently, a consortium study by the Alzheimer Disease Neuroimaging initiative (ADNI) is being performed to establish global clinical evidence regarding a neuropsychiatric test battery, CSF biomarkers, neuroimaging including MRI, FDG-PET, and amyloid PET to predict progression from MCI to AD and to promote studies of basic therapy for AD [1]. Several new biomarkers such as Aβ oligomer, α-synuclein, and TDP-43 are now under investigation for further determination of their usefulness to detect AD and other non-AD type dementia.

2. Cerebrospinal Fluid Aβ40, Aβ42, Tau, and Phosphorylated Tau

These biomarkers have been used for a clinical diagnosis of AD, discrimination from the Vascular dementia (VaD) and non-AD type dementia, exclusion of treatable dementia and MCI, prediction of AD onset and evaluation of the clinical trials of an anti-Aβ antibody, Aβ vaccine therapy, and secretase inhibitors [2–4]. Aβ amounts in cerebrospinal fluid (CSF) are controlled by orexin, suggesting the presence of a daily change in the CSF Aβ amounts, that is, Aβ levels are high while awake and low while a sleep. Collection of CSF by lumbar puncture early in morning in a fasting state is recommended [5]. Aβ is produced mainly in the nerve cells of the brain, and it is secreted about 12 hours later into the CSF, then excreted through the blood-brain barrier 24 hours later into blood (Aβ clearance), and finally degraded in the reticuloendothelial system. Aβ levels are regulated in strict equilibrium among the brain, CSF, and blood [6, 7]. In AD brains, Aβ42 forms insoluble amyloids and accumulates as insoluble amyloid fibrils in the brain. The reason Aβ42 levels are decreased in the CSF of AD patients is considered to be caused by deterioration of physiologic Aβ clearance into the CSF in AD brains [2, 3].

CSF total tau levels increase slightly with aging. However, CSF tau levels show a 3-fold greater increase in AD patients than in normal controls [8]. It is thought that the rise in CSF total tau is related to degeneration of axons and neurons and to severe destructive disease of the nervous system. Several diseases show slightly increased tau levels such as VaD, multiple sclerosis, AIDS dementia, head injury, and tauopathy. However, CSF tau levels show significant increases in Creutzfeldt-Jakob disease (CJD) and meningoencephalitis [8].

3. Methods for Measurement of CSF and Plasma Biomarkers

CSF and plasma Aβ40 and Aβ42 amounts can be measured with an Amyloid ELISA Kit (Wako), which is commercially available and used worldwide. The ELISA kit was developed in Japan by Suzuki et al. and shows extremely highly sensitivity and reproducibility [9]. INNOTEST β-AMYLOID1-42(Innogenetics), for Aβ42 is used widely in Europe and America. Several assay kits for total tau and phosphorylated tau are also used for the measurement of CSF tau. Currently, total tau is measured using INNOTEST hTau Ag (Innogenetics). There are 3 ELISA systems for measurement of phosphorylated tau that recognize the special phosphorylation sites at Ser199 (Mitsubishi Chemical Corp.), Thr181 (Innogenetics) and Thr231 (Applied NeuroSolutions Inc.), and phosphorylated tau levels are increased in CSF of AD on assays using these kits. Of these 3 kits, INNOTEST PHOSPHO-TAU (181) (Innogenetics) is commercially available and used widely. Recently, INNO-BIA AlzBio3 by Innogenetics has been able to measure Aβ1-42, total tau, and P-tau181P simultaneously in 75 μL of CSF, which is a very small amount of CSF.

4. Clinical Evidence, Sensitivity, and Specificity

The first large-scale collaborative multicenter study of CSF Aβ40, Aβ42, and total tau as biomarkers of AD was reported by a Japanese study group in 1998 [4]. A total of 236 subjects were followed and evaluated using a combination index (AD index: CSF Aβ40/Aβ42 $\times$ total tau), which showed a diagnostic sensitivity of 71% $\times$ and specificity of 83% in AD. The diagnostic sensitivity rose to 91% on continuous follow-up study. This study continued until 2004. Finally, diagnostic sensitivity was 80% and specificity was 84% in a total of 507 subjects (157 AD patients, 88 control subjects, 108 non-Alzheimer-type dementia patients, 154 nondementia disease patients) [10]. An European and American large scale multicenter study reported that a combination assay of Aβ42 and tau in CSF samples from 100 controls, 84 non-dementia neurological diseases, 150 AD, and 79 non-AD type dementia showed a diagnostic sensitivity of 85% and specificity of 86% [11]. A large-scale multicenter Japanese study of CSF total tau alone in 1,031 subjects (366 AD, 168 non-AD dementia, 316 non-dementia neurological diseases, and 181 normal controls) reported a sensitivity of 59% and specificity of 90% for diagnosis of AD [8]. After these studies, many combination studies reported decreased Aβ42 and increased tau in CSF from AD patients. Practical guidelines for dementia proposed by the American Academy of Neurology in 2001, which were based on a systematic review of all reports between 1994 and 1999, showed that there were 4 Class II or Class III studies on CSF Aβ42 reporting a diagnostic sensitivity of 78~92% and specificity of 81~83%. Regarding CSF tau levels in AD, there were also 4 Class II or Class III studies reporting a diagnostic sensitivity of 80~97% and specificity of 86~95%. Three Class II or III reports were selected for a systematic review of combination study of Aβ42 and total tau in CSF. This review also evaluated the sensitivity as 85% and specificity as 87% [12]. A community-based prospective study showed that the diagnostic sensitivity for AD was 94% (probable AD), 88% in possible AD, and 75% in MCI. The specificity was 100% (mental diseases) and 89% in non-dementia subjects. The specificity was low in DLB (67%) and VaD (48%). Sensitivity was increased in subjects having the ApoE ε4 genotype [13]. A comparative study based on pathological findings reported that the diagnostic sensitivity was 85% and specificity was 84% [14]. Meta-analysis of 17 reports on CSF Aβ42 and 34 reports on CSF total tau (3,133 AD subjects in total with comparison to 1,481 normal controls subjects) was performed in 2003, and showed a final diagnostic sensitivity of 92% and specificity of 89% [15]. Global standardization of the assay system using normal subjects has also been carried out.

In the examination of CSF phosphorylated tau, the first study of p-tau199 was reported as a large-scale multicenter collaborative study by a Japanese group. A total of 570 subjects were analyzed (236 AD, 239 non-AD and non-dementia neurological diseases, and 95 normal controls) and showed a diagnostic sensitivity of 85% and specificity of 85% in a comparison between AD and non-AD disease controls [16]. Assay systems using different epitopes of phosphorylated tau (p-tau231, p-tau181, and p-tau199) have been internationally standardized. When the sensitivity was fixed above 85%, the respective specificities were 83% for p-tau231, 79% for p-tau199, and 60–71% for p-tau181 [17]. Currently, the assay system for p-tau181 tau is widely used to measure phosphorylated tau in CSF. Systematic review of CSF biomarkers for AD in 2001 analyzed 41 studies (2,500 AD, 1,400 controls) of CSF total tau, 15 studies (600 AD, 450 controls) of Aβ42 and 11 studies (800 AD, 370 controls) of p-tau, 5 studies (Mild AD) for diagnosis of early AD, and 9 studies of MCI and showed that the respective specificities and sensitivities were 90% and 81% for CSF total tau, 90% and 86% for CSF A42, 92% and 80% for CSF phosphorylated tau, and 83~100% and 85~95% in the combination assay with CSF Aβ42 and total tau [18]. A summary of major large-scale multicenter studies of CSF biomarkers for the diagnosis of AD is shown in Table 1.

5. CSF Biomarkers for Prediction of the Onset of AD from MCI

During these past several years, studies of CSF biomarkers have investigated the prediction of progression from MCI to

Table 1: Eleven major studies of CSF biomarkers for AD published between 1998 and 2009.

Study	year	subjects	biomarker	sensitivity	specificity	other
Kanai	1998	93 AD, 54 cont, 33 nAD, 56 ND	Aβ40, Aβ42, †Tau	71~91%	83%	Multicenter, prospective
Hulstaert	1999	150 AD, 100 cont, 79 nAD, 84 ND	Aβ42, †Tau	85%	86%	10 European center
Knopman	2001	3 Class II, III studies	Aβ42, †Tau	80~97%	86~95%	System review AAN
Andreasen	2001	163 AD, 23 VaD, 20 MCI, 9 DLB, 8 ND, 18 cont	Aβ42, †Tau	75~94%	89~100%	1 Y-prospective
Itoh	2001	236 AD, 239 nAD/ND, 95 cont,	PTau199	85%	85%	multicenter
Shoji	2002	366 AD, 181 cont, 168 nAD, 316 ND	†Tau	59%	90%	multicenter
Clark	2003	106 dementia, 73 cont	Aβ42, †Tau	85%	84%	2~8 Y follow up autopsy confirmed
Sunderland	2003	17Aβ42 studies, 34 tau studies (3133 AD versus 1481 control)	Aβ42, †Tau	92%	89%	Meta-analysis
Blennow	2003	41Tau studies (2500 AD versus 1400 cont) 15Aβ42 studies (600 AD versus 450 cont) 11p-Tau studies (800 AD versus 370 cont)	Aβ42, †Tau, PTau Aβ42/tTau	86% 90% 92% 85~94%	90% 81% 80% 83~100%	Systematic review Early AD, MCI
Hampel	2004	161 AD/FTD/DLB/VaD, 45 cont	PTau231 pTau181 pTau199	85%	83%, 79%, 60~71%	International harmonization
GTT3	2004	243 AD, 91 cont, 152 nAD, 157 ND	Aβ40, Aβ42, †Tau	80%	84%	Continuous GTT1

AD (Table 2). A study following 52 MCI subjects for 8.4 months found that 29 MCI subjects developed AD and the specificity of CSF Aβ42 assay was 90% [19]. Follow-up study of 273 subjects (55 MCI, 100 AD, 14 DLB, 11 FTD) for 2 years showed that 38% (20/55) of MCI patients already showed alteration of at least 2 CSF biomarkers including Aβ42, total tau, and p-tau181 at the time of the study initiation. Eleven MCI subjects developed dementia 1 year later, while the remaining 33 subjects stable. Eleven showed a further progression of cognitive impairment, still not fulfilling the diagnostic criteria for dementia. Ten of 11 MCI patients who progressed to AD showed alteration of at least 2 CSF biomarkers, and all 11 converters showed high p181tau levels in CSF. Conversely, 29 (88%) of the 33 stable MCI subjects did not show any alteration of CSF biomarkers [20]. The longest prospective study (4–6 years) followed 137 MCI and 39 normal subjects. Of these 57 subjects (42%) developed AD and 21 subjects (15%) developed dementia due to other causes during followup. Fifty-six subjects (41%) did not show any change during an average followup of 5.2 years. Using CSF Aβ42 and total tau assay, onset of AD was predicted with a sensitivity of 95% and specificity of 83%. The hazard ratio was 17.7. The addition of p181tau assay further improved sensitivity and specificity to 95% and 97%, respectively [21]. In comparison studies between CSF biomarkers and amyloid imaging by PIB-PET, CSF Aβ42 levels were decreased and total and p181 tau levels were increased in very mild AD. CSF Aβ42 levels completely related to brain amyloid deposits detected by PIB-PET in patients with or without dementia [22]. The CSF total tau/Aβ42 ratio and the p181 tau/Aβ42 ratio predicted the exacerbation of CDR score [9].

The usefulness of CSF biomarkers for predicting the progression form MCI to AD was strictly validated by the international consortium study, ADNI performed between 2004 and 2009. In US-ADNI, 819 healthy subjects (55~90 y; 229 normal, 398 MCI, 192 mild AD) were selected based on less than 4 points on Hatchiski Ischemic score, more than 6 points on GDS score, and a history of more than 6 years of education. MMSE scores ranged from 24 to 30 points in normal controls and MCI, 20–26 points in AD patients. CDR sore was 0 in normal controls, 0.5 in MCI, and 0.5~1 in AD. On logical memory test II of WMS-R, the score was evaluated as normal ($\geqq$9: normal subjects with more

Table 2: Major studies of CSF biomarker to predict progression from MCI to AD published between 2004 and 2010.

Study	Year	Case	Follow-up	MCI to AD	Marker	Sensitivity	Specificity	Other
Hampel	2004	52 MCI 93 AD 10 cont	8.4 M	29/52 (56%)	Aβ42, †Tau	Aβ42 59% †Tau 83%	Aβ42 100% †Tau 90%	European cohort
Parnetti	2006	55 MCI 100 AD 14 DLB 11 FTD	1 Y	11/55 (20%) 38% of MCI has 2 marker abnormalities	Aβ42, †Tau, pTau181	2 biomarker abnormality in AD converters (91%)	Normal markers in stable MCI (88%)	Mayo Clinic Cohort
Hansson	2006	137 MCI 39 cont	4~7 Y	57 AD (42%) 21 nonAD dementia (15%) 56 stable MCI (41%)	Aβ42, †Tau, pTau181	Aβ42/†Tau 95% Aβ42/†Tau/pTau181 95%	Aβ42/†Tau 83% Aβ42/†Tau/pTau181 87%	Prospective study
Show	2009	100 AD 191 MCI 114 cont	1 Y	37/191 (19%)	Aβ42, †Tau, pTau181	Tau/Aβ42 predicted 89% of AD converters CSF Aβ42 highly correlated with brain pathology		US-ADNI
Mattsson	2009	750 MCI 529 AD 304 cont	>2 Y	271 AD/750 MCI (36%) 59 nonAD dementia/750 MCI	Aβ42, †Tau, pTau181	83%	73%	12 centers Europe/US
Visser	2009	60 SCI 37 naMCI 71 aMCI 89 cont	3 Y	8/22 CSF/AD naMCI (36%) 27/53 CSF/AD aMCI (51%)	Aβ42, †Tau, pTau181	CSF/AD was observed in control 31%, SCI 52%, naMCI 68%, aMCI 79% All AD had CSF/AD CSF/AD is a significant risk in aMCI		DESCRIPA study Europe study

SCI: subjective cognitive impairment; naMCI: nonamnesctic MCI; aMCI: amnestic MCI; CSF/AD: CSF AD profile (decreased Aβ42/increased tau).

than 16 years of education, $\geqq$5: normal subjects with 8~15 years of education, $\geqq$3: normal subjects with 0~7 years of education), and as MCI or AD ($\leqq$8: subjects with more than 16 years of education, $\leqq$4: subjects with 8~15 years of education, $\leqq$2: subjects with 0~7 years of education). The result one year later showed that the mean AD conversion/year was 16.5% (1.4% in those converting from normal to MCI, 16.5% in those converting from MCI to AD, 8 cases reverted from MCI to normal and 2 cases reverted from AD to MCI). About 50% of MCI patients take anticholinesterase or memantine (ChEI: 44% in MCI, 85% in AD; memantine: 11% in MCI, 47% in AD: Combination use of ChEI and memantine: 9% in MCI, 41% in AD). Average deteriorations of ADAS-cog score were 1.1 points/year in MCI and 4.3 points/year in AD. Among all CSF biomarkers, Aβ42 at the initial evaluation was the most reliable marker predicting conversion from MCI to AD and the progression of cognitive impairment. CSF Aβ42 was the most sensitive biomarker for AD in a follow-up study of 100 mild AD, 196 MCI, and 114 normal elderly controls and an associated correlation study using age-matched 52 normal control and 56 AD brains (sensitivity 97%, specificity 77%). The sensitivity and specificity of CSF total tau assay were 70% and 92%, respectively. The sensitivity was 68% and the specificity was 73% for a CSF p-tau181 assay. The sensitivity of the total tau/Aβ42 ratio was 86%, and its specificity was 85%. Aβ42, total tau, and the number of ApoE ε4 alleles were the most sensitive biomarkers in the ADNI cohort. Using CSF total tau/Aβ42 ratio, 33 converters (89%) were predicted before onset among 37 subjects who progressed from MCI to AD within one year [1, 23]. US-ADNI Penn Biomarker core reported that decreased CSF Aβ42 levels and increased total tau levels were prediction markers for AD with the highest evidence level, and that Aβ42 was the earliest marker among total tau, F^{18}FDG-PET, and MRI examination [24]. In addition, there were subgroups of normal subjects who showed rapid deterioration of cognitive function [25]. Hippocampal atrophy detected by MRI was closely related to CSF p-181Tau levels in the ApoE 4 carrier group and CSF total tau in the ApoE 4 noncarrier group. Amyloid accumulation in the precuneus detected by the PIB amyloid PET correlated with hippocampal atrophy [26]. CSF p-tau181 amounts were related with cognitive impairment in the normal group, while CSF Aβ42 amounts were correlated with those in the MCI group. These 2 biomarkers more sensitively detected cognitive impairment than ADAS-cog in the normal and MCI groups. In all groups, subjects with alteration of both Aβ42 and p-tau181 levels showed faster deterioration of cognitive function [27].

A prospective study for more than 2 years by 12 European and American centers reported that 271 patients with MCI developed AD and 59 developed non-AD-type dementia among 750 MCI patients. The sensitivity and specificity of using CSF Aβ42, total tau, and p-tau181 were 83% and 72%, respectively [28]. In the DESCRIPA study, 60 SCI subjects (subjective cognitive impairment), 37 non-amnestic

Table 3: Major studies of plasma Aβ40 and Aβ42.

Study	Year	Follow	Subject	Marker	Results	Journal
Matsubara	1999	—	36 AD 206 cont 6 DS	Lipoprotein free Aβ40, Aβ42	Increased plasma lipoprotein free Aβ42 in AD and Down Syndrome	Ann Neurol
Van Oijen	2006	8.6 Y Rotterdam study	1,756/6,713	Aβ40, Aβ42 Aβ42/Aβ40	396 cases developed dementia during follow up Increased Aβ40 level was a risk for onset of dementia Increased Aβ42/Aβ40 ratio decreased the risk for onset of dementia	Lancet Neurol
Graff-Radford	2007	3.7 Y Mayo Cohort	563 control	Aβ40, Aβ42 Aβ42/Aβ40	53 cases developed MCI and AD Significantly increased risk for onset of MCI and AD (3.1) in lower 25% group with decreased Aβ42/Aβ40 ratio	Arch Neurol
Schupf	2008	4.6 Y	1,125 control	Aβ40, Aβ42 Protofibrillar Aβ42	104 cases developed AD (9.2%) High Aβ42 level increased threefold risk for onset of AD Once developing AD, plasma Aβ42, Aβ42/Aβ40 ratio and protofibrillar Aβ42 were significantly decreased	PNAS
Xu	2008	—	113 AD 205 control	Autoantibody Aβ40, Aβ42	Anti-Aβ42 dimer antibody was absent in AD Aβ40/42 ratio increase with progression of AD	Brain Res
Lambert	2009	4 Y	233 dementia 958 control 8,414 source	Aβ40, Aβ42	prospective 3 city study Aβ42/Aβ40 ratio showed short-term risk of dementia	Neurol
Okereke	2009	10 Y prospective	481 Nurses	Aβ40, Aβ42	Presenile (mean 64 Y) high Aβ42/ Aβ40 ratio correlated with cognitive function 10 years later	Arch Neurol

MCI (naMCI), 71 amnestic MCI (aMCI), and 89 normal controls were followed for 3 years and examined by CSF biomarkers. In the naMCI group with AD-like alteration of CSF biomarkers (AD profile), 8 (36%) of 22 cases developed AD. In the aMC group, 27 (51%) of 53 cases showing with CSF AD profile developed AD. The CSF AD profile was recognized in 31% of control, 52% of SCI, 68% of naMCI and 79% of aMCI. All converters showed the CSF AD profile and the combination of decreased Aβ42 and increased total tau/p-181tau levels in CSF was a significant risk factor in the aMCI group [29] (Table 2).

6. Plasma Aβ40 and Aβ42 as Risk Factors for AD

Since measurement of plasma Aβ42 and Aβ40 by Matsubara, the decreased ratio of Aβ42 and Aβ40 has been reported as a risk factor for AD onset [30]. The Rotterdam study prospectively studied 1,756 subjects randomly selected from 6,713 participants for an average of 8.6 years and reported that 392 subjects developed dementia. In this study, plasma Aβ40 levels at the start related to the risk of the dementia onset. The age- and sex-adjusted upper quartile with a high plasma Aβ40 showed a hazard ratio of 1.07∼1.46 compared with the other 75% of the group. The upper quartile with a high Aβ42/Aβ40 ratio showed a decreased hazard ratio for onset of dementia of 0.74∼0.47 [31]. The Mayo Clinic prospective study consisted of 563 subjects with a mean age of 78 years old followed for 3.7 years. It was reported that 53 of these subjects developed MCI and AD. Significant increase in the risk of MCI and AD onset was recognized in the lower quartile with a low plasma Aβ42/Aβ40 ratio. Relative risk was 3.1 on comparison between the upper quartile and lower quartile. After a adjusting for age and ApoE genotypes, significant deterioration was recognized in subjects with a low plasma Aβ42/Aβ40 ratio [32]. A prospective study of 1,125 cognitively normal elderly subjects for 4.6 year showed that 104 subjects (9.2%) developed AD. High plasma Aβ42 levels at the start of study increased threefold the risk of AD onset. Once AD developed, however, plasma Aβ42, Aβ42/Aβ40 ratio, and protofibrillar Aβ42 were significantly decreased [33]. The presence of anti-Aβ autoantibody was suggested in human plasma, and the Aβ40/Aβ42 ratio was closely related to progression of cognitive impairment in AD patients [34]. By 2009, two additional large-scale studies were reported [35, 36], and the results of the ADNI study are

expected in the near future. These findings are summarized in Table 3.

7. Development of Other Biomarkers

Homocysteine in CSF and plasma were measured in US-ADNI. Significant differences among normal, MCI, and AD groups were observed in plasma, but were not recognized in the CSF. At the same time, there was no significant difference in CSF Isoprostane measured as a marker of oxidation stress [24]. A report of the establishment of ELISA for Aβ oligomer, the main causative molecule of AD, has been attracting attention for measurement of plasma in AD subjects. Plasma Aβ oligomer could be detected in 3 of 10 normal subjects and 19 of 36 AD patients. The level of plasma Aβ oligomer correlated with those of Aβ monomer, and both amounts progressively decreased in familial AD patients [37]. Studies examining CSF α-synuclein and TDP-43 levels as biomarkers for DLB, FTLD-TDP, and ALS were reported from Japan. Levels of CSFα-synuclein were measured by ELISA in 16 DLB and 21 AD patients, but there were no significant differences; however, a correlation with disease duration was recognized in the DLB group [38]. Measurement of CSF DJ-1 and α-synuclein by ELISA in 117 Parkinson's disease (PD) patients, 132 normal control and 50 AD patients suggested that age and contamination of blood caused some artifacts, but showed that both markers were decreased in PD compared with those in normal controls and AD. The sensitivity and specificity for CSF DJ-1 were 90% and 70%, and those for CSF α-synuclein were 92% and 58%, respectively [39]. Assay of CSF TDP-43 was established by Tokuda, and increased levels of TDP-43 were found in early ALS suggesting an early diagnostic marker of ALS. A further detailed study of the usefulness of CSF TDP-43 in ALS and FTDP-TDP is desired in the near future [40].

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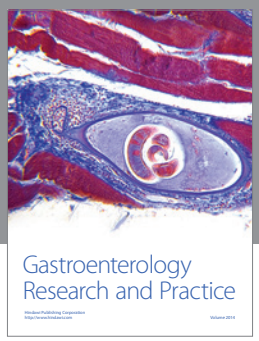

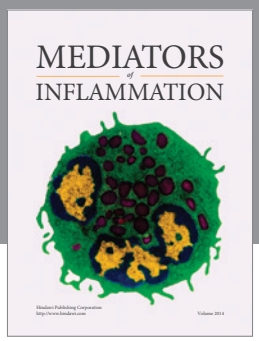

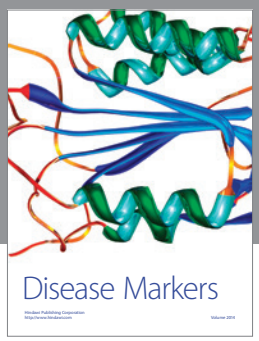

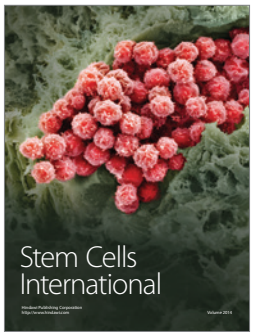

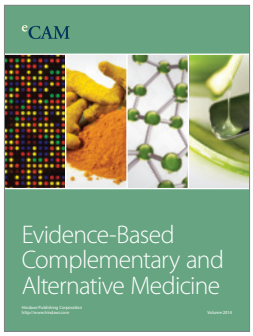

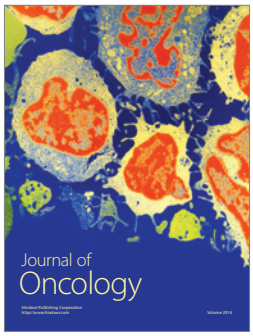

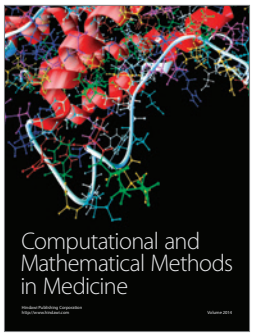

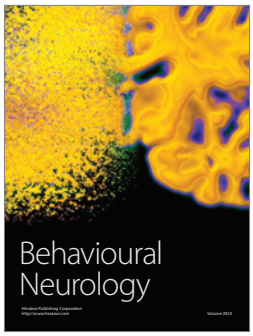

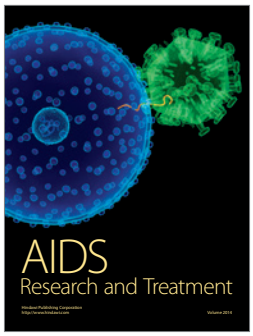

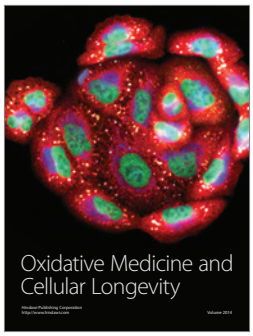

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