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Rapid Assessments to Differentiate Dementia Using Plasma Biomarkers in Primary Care

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Abstract

Introduction: The aging of society has increased the incidence of dementia, which is more common among older individuals. Older individuals are typically cared for by primary care providers in hospitals. However, more than 60% of patients with early-stage dementia are unrecognized in primary care. Several groups have developed dementia screening tools for primary care purposes. In this work, assessments based on plasma biomarkers for differentiating among various types of dementia were developed for primary care applications.

Methods: Forty-six patients with very mild dementia (VMD) or mild cognitive impairment (MCI), fifty patients with Alzheimer's disease (AD), and four patients with non-AD dementia were enrolled. Plasma amyloid-beta 1–40 ($A\beta_{1-40}$), $A\beta_{1-42}$, total Tau (T-Tau), and phosphorylated Tau (p-Tau181) were assayed using immunomagnetic reduction for each subject.

Results: The results show that non-AD dementia can be discriminated from other forms of dementia using plasma $A\beta_{1-40}$, with a cutoff value of 50.03 pg/ml resulting in an area under the curve (AUC) of 0.794. The plasma $A\beta_{1-42}$-to-$A\beta_{1-40}$ ratio can serve as an index for discriminating AD from VMD and MCI, with a cutoff value of 0.3015 resulting in an AUC of 0.674.

Discussions: A biomarker panel measuring the levels of plasma $A\beta_{1-40}$ and the ratio of $A\beta_{1-42}$ to $A\beta_{1-40}$ could potentially assist primary care practitioners in evaluating whether a patient suffers from non-AD dementia, AD, or VMD and MCI.

Keywords: Dementia plasma biomarker panel • Dementia • Alzheimer's disease • Amyloid-beta protein • Tau protein.

Introduction

The prevalence of dementia among older people has been increasing. In a 2013 national survey of dementia prevalence in Taiwan, the prevalence of dementia among individuals older than 65 years was 8% [1]. Dementia represents an essential public health issue. In general, older individuals routinely visit Primary Care (PC) to receive treatment rather than the Neurological Division, particularly for their first neurological screenings. The appropriate screening and identification of dementia among older individuals in the PC setting are critical to ensure the timely initiation of management, treatment, or intervention strategies for patients with mild (MCI) or subjective cognitive impairment. However, screening for cognitive impairment or dementia is not commonly performed by PC practitioners. Hypertension, hyperlipidemia, or type II diabetes are the common diseases treated by PC practitioners [2–4]. Symptoms of cognitive impairment may not be apparent during a routine PC visit, and cognitive impairment is traditionally diagnosed in a PC setting based on clinical suspicion in response to the patient's symptoms or caregivers' concerns [5]. From 1992 to 2006, the reported accuracy of mild dementia diagnoses among PC providers was 14%–69% [6–13]. The missed or delayed diagnosis of dementia occurs frequently.

In the early 2000's, PC physicians utilized cognitive tests or evaluated patients' functional abilities to assess mild dementia. Cruz-Orduña et al. reported that the sensitivity of detection based on patient-reported or suspected cognitive impairment over a 49-year period increased to 75% with the use of the Mini-Mental State Examination (MMSE) or the Functional Activities Questionnaire (FAQ) [14].

Chronic conditions have been demonstrated to contribute to dementia prediction [15–17]. Tsai et al. integrated various risk factors, such as age, sex, body mass index, education, stroke, diabetes, hypertension, hyperlipidemia, head trauma, and depression, with the evaluation of cognitive tests for the assessment of dementia in PC settings [18], which resulted in a model capable of differentiating patients with dementia from normal controls with a sensitivity greater than 90%.

Significant progress in enhancing the sensitivity of dementia diagnoses in PC settings has identified additional diagnostic needs, such as the identification of information that would allow PC physicians to recognize

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which type of dementia a patient is presenting to ensure the timely application of appropriate management or treatment strategies.

Although the efficacy of monoclonal antibodies for Alzheimer's disease (AD) treatment remains uncertain, an increasing number of studies have explored the diagnosis of AD using biomarkers. The assessment of plasma biomarkers represents a convenient and cheap diagnostic method compared with the current gold standard of positron emission tomography (PET), which may allow for plasma biomarkers to be tested annually. Several papers reported by neurologists demonstrated the feasibility of assaying plasma biomarkers for identifying AD [19–22], Parkinson's disease [23–25], or frontotemporal dementia [26]. These results suggest the possibility of developing assessments that use plasma biomarkers to differentiate among various types of dementia in PC settings. In this work, 100 patients with various types of dementia were recruited. Plasma amyloid-beta 1-40 ($A\beta_{1-40}$), $A\beta_{1-42}$, total Tau (T-Tau), and phosphorylated Tau (p-Tau181) were assayed using immunomagnetic reduction for each subject. Rapid assessments for the differentiation of dementia types using plasma biomarkers were developed for the PC setting.

Material and Methods

Recruitment of subjects

All patients aged 50 years or older were recruited from neurological clinics at National Yang Ming University Hospital (NYMUH). All participants received cognitive assessments. Dementia was diagnosed according to the National Institute on Aging and Alzheimer's Association (NIA-AA) criteria [27]. Trained research assistants also administered the Chinese version of the Mini-Mental State Examination (MMSE) [28], which features a total score of 30. The Clinical Dementia Rating (CDR) was also used to determine the severity of dementia after separate semi-structured interviews with the patient and a knowledgeable informant were conducted by a neurologist or psychologist. The CDR scores are categorized as follows: 0 for normal, 0.5 for MCI or very mild dementia (VMD) [29,30], 1 for mild dementia, 2 for moderate dementia, and 3 for severe dementia [31]. Individuals with VMD were classified according to the presentation of mild impairment in two or more cognitive domains and a slight decline in daily function; cognitive deficits sufficient to interfere with independence in daily life, community affairs, or at-home hobbies; or based on the outcome of the CDR. MCI was diagnosed according to the NIA-AA-recommended criteria, defined as a change in cognition with impairment in one or more cognitive domains but no evidence of impairment in social or occupational functions as assessed by the CDR, activities of daily living (ADL) [32], and instrumental activities of daily living (IADL) [33]. The final diagnosis was reviewed after one year of follow-up.

The research was approved by the Institutional Review Board (IRB) of NYMUH (IRB No.2017A033 and No. 2018A004). Written informed consent was obtained from all participants in the study. All patients with dementia and their proxies provided written informed consent. Informed consent could only be signed directly by patients with MCI because the IRB agreed that patients with MCI, who suffered from cognitive impairments in one or more cognitive domains but presented with no evidence of impairment in social or occupational functions, were capable of understanding the study procedures and non-invasive assessments being performed in this study. We also explained this informed consent requirement to any proxies who accompanied MCI patients.

All participants received medical, neurological, neuropsychological, and psychiatric assessments and blood examinations. The neurological assessments performed for each participant included a cerebral computed tomography scan to exclude intracranial pathologies (i.e., brain tumors or stroke) that may have contributed to cognitive decline.

Plasma preparation

A 9-ml EDTA tube (455036, Greiner) was used to draw blood. No fasting was required for the blood draw. The tube was gently inverted 10 times immediately after the blood draw. A swing-out (bucket) rotor was used to centrifuge the blood at 15–25 °C at 1500–2500 × g for 15 minutes. Then, 1 ml plasma (supernatant) was transferred to a fresh 1.5-ml Eppendorf tube. All aliquoted plasma samples were stored at −80 °C within 4.5 hours after the blood draw and prior to performing biomarker assays.

Assays of plasma biomarkers

The frozen human plasma sample was moved from −80 °C to wet ice and room temperature. To assaying $A\beta_{1-40}$, T-Tau, and p-Tau181 (Tau phosphorylated at threonine 181), 40 μl plasma was mixed with 80 μl of the respective reagent (MF-AB0-0060, MF-TAU-0060, and MF-PT1-0060; MagQu). For assaying $A\beta_{1-42}$, 60 μl plasma was mixed with 60 μl reagent (MF-AB2-0060, MagQu). For each batch of measurements, calibrators (CA-DEX-0060, CA-DEX-0080, MagQu) and control solutions were used. An immunomagnetic reduction (XacPro-S361, MagQu) analyzer was utilized. For each sample, duplicate measurements were performed for each biomarker. The averaged concentration of the duplicate measurements was reported.

Statistical analysis

Continuous variables for each measurement are presented as the mean ± standard deviation. SPSS (version 22.0) for Windows (SPSS Inc., Chicago, IL, USA) was used to perform statistical analyses. Baseline demographic characteristics, including age, MMSE score, and CDR-Sum of Boxes (SOB) scores, were coded as continuous variables and compared using a T-test to determine p-values. Receiver operating characteristic curves were analyzed for each plasma biomarker to explore cutoff values, sensitivity, specificity, and area under the curve (AUC) for the differentiation of various types of dementia. All statistical tests were two-tailed, and significance levels were established at p-values of less than 0.05.

Results

A total of 46 patients with VMD or MCI, referred to as VMD+MCI; 50 patients with AD; and 4 patients with non-AD dementia were enrolled. In the non-AD group, one patient had dementia with Lewy bodies, one patient had depression, one patient was folic acid deficient, and one patient had VMD with depression. Among the 46 VMD+MCI patients, 11 patients had VMD, and 35 patients had MCI. Notably, the 11 VMD patients progressed to AD within 3 years following their assessment in this study, indicating that VMD in these patients likely represented the early stages of AD. The demographic information of all enrolled subjects is listed in Table 1. Women comprised 50.0%, 50.0%, and 65.2% of the non-AD, AD, and VMD+MCI groups, respectively. The mean ages were 68.5 ± 12.4 years in the non-AD group, 78.4 ± 8.19 years in the AD group, and 72.2 ± 8.6 years in the VMD+MCI group. No significant differences in age were observed among the non-AD, AD, and VMD+MCI groups ($p>0.05$). The CDR-SOB scores were 2.00 ± 1.78, 3.77 ± 2.65, 1.95 ± 1.27 for the non-AD, AD, and VMD+MCI groups, respectively. Patients with AD showed significantly higher scores on the CDR-SOB than non-AD and VMD+MCI patients ($p<0.01$). The MMSE scores were 24.3 ± 5.7, 20.0 ± 5.5, and 23.9 ± 4.3 for the non-AD, AD, and VMD+MCI, respectively. AD shows significantly lower scores of MMSE than non-AD and VMD+MCI ($p<0.01$).

Table 1. Demographic information of the enrolled subjects

1	Non-AD	AD	VMD+MCI		
			VMD	MCI	Combined
n (female%)	4 (50%)	50 (50.0%)	11 (63.6%)	35 (65.7%)	46 (65.2%)
Age (years)	68.5 ± 12.4	78.4 ± 8.19	74.6 ± 5.7	71.5 ± 9.3	72.2 ± 8.6
CDR-SOB	2.00 ± 1.78	3.77 ± 2.65	2.55 ± 1.06	1.76 ± 1.28	1.95 ± 1.27
MMSE	24.3 ± 5.7	20.0 ± 5.5	23.3 ± 4.2	24.1 ± 4.4	23.9 ± 4.3
$A\beta_{1-40}$ (pg/ml)	48.99 ± 1.27	51.92 ± 4.16	54.74 ± 4.16	54.24 ± 4.20	54.36 ± 4.15
$A\beta_{1-42}$ (pg/ml)	15.65 ± 1.06	16.41 ± 1.27	15.71 ± 0.97	15.93 ± 1.00	15.88 ± 0.99
T-Tau (pg/ml)	19.97 ± 2.29	21.58 ± 4.04	19.17 ± 2.18	19.73 ± 2.57	19.60 ± 2.47
p-Tau181 (pg/ml)	3.12 ± 0.48	3.41 ± 0.73	3.01 ± 0.54	3.19 ± 0.53	3.14 ± 0.53

AD: Alzheimer's disease; VMD: very mild dementia; MCI: mild cognitive impairment; CDR-SOB: clinical dementia ranking-sum of boxes; MMSE: Mini-Mental State Examination.; Aβ: amyloid-beta

The measured $A\beta_{1-40}$ levels in the plasma were 48.99 ± 1.27 pg/ml for the non-AD group, 51.92 ± 4.16 pg/ml for the AD group, and 54.36 ± 4.15 pg/ml for the VMD+MCI group. The plasma $A\beta_{1-40}$ level in the non-AD group was significantly lower than those in the AD and VMD+MCI groups ($p<0.01$). The plasma $A\beta_{1-42}$ levels were 15.65 ± 1.06 pg/ml for the non-AD group, 16.41 ± 1.27 pg/ml for the AD group, and 15.88 ± 0.99 pg/ml for the VMD+MCI group. The AD group showed a significantly higher $A\beta_{1-42}$ level than that for the VMD+MCI group ($p<0.05$), but not compared with the level for the non-AD ($p>0.05$). The T-Tau levels in plasma were 19.98 ± 2.29 pg/ml for the non-AD group, 21.58 ± 4.04 pg/ml for the AD group, and 19.60 ± 2.47 pg/ml for the VMD+MCI. The AD group presented significantly higher levels of plasma T-Tau than those of the non-AD and VMD+MCI groups ($p<0.05$). The measured p-Tau181 levels in plasma for the non-AD (3.12 ± 0.48 pg/ml), AD (3.41 ± 0.73 pg/ml), and VMD+MCI (3.14 ± 0.53 pg/ml) groups are listed in Table 1. No significant differences in plasma p-Tau181 levels were observed among the non-AD, AD, and VMD+MCI groups ($p>0.05$).

The VMD+MCI group included 11 VMD patients and 35 MCI patients. The VMD (74.6 ± 5.7 years) and MCI (71.5 ± 9.3 years) patients were aged matched. Except for the CDR-SOB scores ($p<0.05$), no significant differences were observed between the VMD and MCI patients, including MMSE scores and plasma $A\beta_{1-40}$, $A\beta_{1-42}$, T-Tau and p-Tau181 levels ($p>0.05$).

Discussion

The goal of this study was to develop a rapid assessment for the differentiation of different types of dementia using plasma biomarkers for the PC setting. As listed in Table 1, the non-AD group showed relatively lower levels of plasma $A\beta_{1-40}$ compared with those in the AD and VMD+MCI groups, suggesting that plasma $A\beta_{1-40}$ level might represent a promising index for discriminating non-AD patients from other groups. Through ROC curve analysis, the plasma $A\beta_{1-40}$ level the cutoff value for discriminating non-AD from AD and VMD+MCI was found to be 50.03 pg/ml. The corresponding clinical sensitivity and specificity were 75% and 100%. The AUC was 0.794.

An ROC curve analysis was performed using individual plasma biomarkers to differentiate AD from VMD+MCI, and the results are listed in Table 2. In addition, several groups have proposed that the combinations of plasma biomarkers might represent a more adequate index for discriminating among various dementia types or severities [19,34]. The results of the ROC curve analysis using combined plasma biomarkers to differentiate AD from VMD+MCI are listed in Table 2.

Among these biomarkers, the p-Tau181 level did not significantly differentiate AD from VMD+MCI ($p>0.05$). However, published papers have demonstrated that plasma p-Tau181 represents a promising index for differentiating AD patients from those with MCI due to AD, who comprised the VMD group in this study [35,36]. Through a careful inspection of the data collected here, the p-value for the comparison of plasma p-Tau181 levels between AD (3.41 ± 0.73 pg/ml) and VMD (3.01 ± 0.54 pg/ml) patients was found to be less than 0.05, whereas the p-value was greater than 0.05 for the comparison of pTau181 levels between the AD and MCI (3.19 ± 0.53 pg/ml) groups, which is consistent with the results of previously published papers.

Table 2. ROC curve analysis for differentiating AD from VMD+MCI using individual or combined plasma biomarkers.

Biomarker	Cutoff value	Sensitivity (95% CI)	Specificity (95% CI)	AUC	p-value
Tau	19.5 pg/ml	0.600 (0.452–0.736)	0.544 (0.390–0.691)	0.635	<0.05
p-Tau181	3.26 pg/ml	0.540 (0.393–0.682)	0.587 (0.432–0.730)	0.6	>0.05
$A\beta_{1-42}$	16.15 pg/ml	0.620 (0.472–0.754)	0.544 (0.390–0.691)	0.622	<0.05
$A\beta_{1-42}$-to-$A\beta_{1-40}$	0.3015	0.640 (0.492–0.771)	0.674 (0.520–0.805)	0.674	<0.05
$A\beta_{1-42}$ × Tau	303.5 pg^2/ml^2	0.640 (0.492–0.771)	0.544 (0.390–0.691)	0.631	<0.05
$A\beta_{1-42}$ × Tau/$A\beta_{1-40}$	5.722 pg/ml	0.652 (0.472–0.734)	0.587 (0.432–0.730)	0.651	<0.05

ROC: receiver operating characteristic; AD: Alzheimer's disease; VMD: very mild dementia; MCI: mild cognitive impairment; AUC: area under the curve; CI: confidence interval; Aβ: amyloid-beta

A listed in Table 2, the $A\beta_{1-42}$-to-$A\beta_{1-40}$ ratio shows the highest AUC value (0.674), whereas $A\beta_{1-42}$ shows the lowest AUC value (0.622) for discriminating AD from VMD+MCI. This result suggests that the $A\beta_{1-42}$-to-$A\beta_{1-40}$ ratio could represent the most effective index for differentiating AD from VMD+MCI. The cutoff value for the $A\beta_{1-42}$-to-$A\beta_{1-40}$ ratio was established as 0.3015 to discriminate AD from VMD+MCI patients. The clinical sensitivity and specificity were 0.640 and 0.674, respectively.

The further discrimination of VMD from MCI patients included in the VMD+MCI group is not necessary for PC settings. Such discrimination should be conducted using neuropsychological tests performed by neuropsychologists or neurophysiologists. For example, as listed in Table

1, the VMD (3.08 ± 1.67) group showed a significantly higher CDR-SOB score than the MCI (1.76 ± 1.28; p<0.01) group. An alternative method for discriminating between VMD and MCI is follow-up monitoring. All VMD patients progressed to AD within 3 years after the visit reported in this study.

A flow chart for rapid assessments using plasma biomarkers to differentiate among non-AD, AD, and VMD+MCI groups is illustrated in Figure 1. First, plasma $A\beta_{1-40}$ levels were assayed. Measured plasma $A\beta_{1-40}$ level below 50.03 pg/ml would be highly indicative of non-AD. Otherwise, the subject is suspected of AD or VMD+MCI. Second, plasma $A\beta_{1-42}$ levels were assayed to obtain the ratio of $A\beta_{1-42}$-to-$A\beta_{1-40}$, with a value above 0.3015 indicating AD and a value below 0.3015 indicating VMD or MCI.

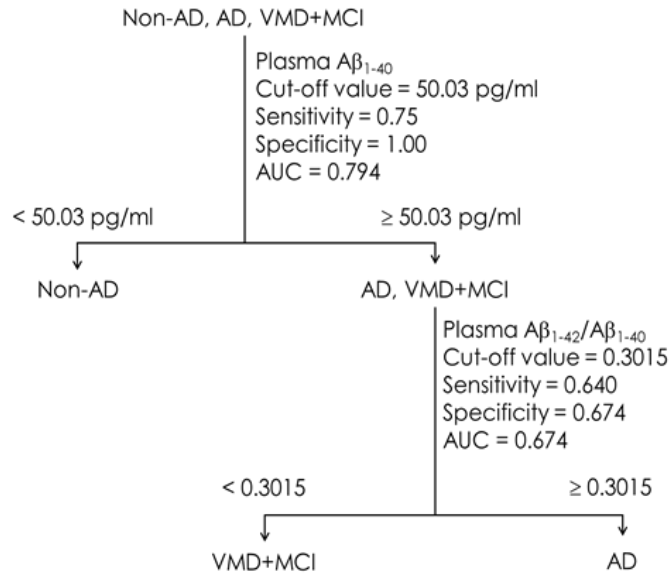

Figure 1. Flow chart showing the assessment of plasma biomarkers to differentiate non-Alzheimer's disease (AD), AD, and very mild dementia (VMD)+mild cognitive impairment (MCI)

The flow chart shown in Figure 1 could assist PC physicians to easily assess the dementia types observed in patients, allowing for the PC physician to provide patients with adequate disease management strategies or refer the patient to neurologist care. Delayed interventions and treatments could be prevented among patients who visit a PC practitioner instead of the Neurological Division.

Conclusion

A rapid assessment for discriminating non-AD, AD, and VMD+MCI patients was demonstrated using plasma biomarkers. The plasma $A\beta_{1-40}$ level can be used to discriminate non-AD, followed by the assessment of the plasma $A\beta_{1-42}$-to-$A\beta_{1-40}$ ratio to differentiated AD from VMD+MCI. The cutoff values for the plasma $A\beta_{1-40}$ level and the $A\beta_{1-42}$-to-$A\beta_{1-40}$ ratio are suggested. This type of biomarker panel has the potential to help doctors in PC settings evaluate the risks of suffering from non-AD dementia, AD, or VMD and MCI in each patient.

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