



REVIEW

# Immunomagnetic Reduction Detects Plasma $A\beta_{1-42}$ Levels as a Potential Dominant Indicator Predicting Cognitive Decline

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## ABSTRACT

Although the concentrations of Alzheimer's disease (AD) biomarkers  $A\beta_{1-40}$ ,  $A\beta_{1-42}$  and tau protein are very low in human plasma, ultrasensitive assays such as immunomagnetic reduction (IMR) are able to precisely quantify them. Review articles have described the detailed working mechanism of IMR and revealed the feasibility of detecting early-stage AD by assaying these plasma biomarkers with IMR. In this review, we aimed to compare the significance of these plasma biomarkers in predicting cognitive decline in patients with Down syndrome, stroke, or amnesic mild cognitive impairment based on findings in the literature. We found that plasma  $A\beta_{1-42}$  might play the predominant role in predicting cognitive decline in these patients.

**Keywords:** Cognitive decline; Down syndrome; Immunomagnetic reduction; Plasma biomarkers; Stroke

## Key Summary Points

A convenient examination such as blood tests that can evaluate the progression to dementia or cognitive decline in population at-risk is urgently needed.

The results of reported plasma biomarkers relevant to Alzheimer's disease, such as  $A\beta_{1-40}$ ,  $A\beta_{1-42}$  and Tau, in patients with Down syndrome, stroke and amnesic mild cognitive impairment are discussed

The levels of plasma  $A\beta_{1-42}$  are possibly the most dominant to predict the cognitive decline in these patients.

It would be hopeful to stop the development of dementia or delay cognitive decline by eliminating the abnormal changes in the level of plasma  $A\beta_{1-42}$ .

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## INTRODUCTION

Pathological evidence of Alzheimer's disease (AD) includes the presence of amyloid plaques and tau protein tangles in the brain [1–4], which are typically detected with positron emission tomography (PET) [5–8]. Although amyloid or tau PET has been approved for clinical use, its high cost and low availability seriously limit its utility in clinical practice. Instead, the detection of amyloid  $\beta$  (A $\beta$ ) and tau protein in cerebrospinal fluid (CSF) has been suggested as a method to probe for pathological evidence of AD [9–12]. However, it has not been easy to implement CSF biomarker detection more widely in clinical practice because of the need to perform a lumbar puncture. The detection of A $\beta$  and tau protein in other body fluids such as blood, urine, or saliva has been proposed as an alternative method. Compared to those in the CSF, the levels of A $\beta$  and tau protein in such body fluids are extremely low, on the order of picograms per milliliter [13–15]. Thus, ultrasensitive assays are needed to precisely quantify the levels of A $\beta$  and tau proteins in blood, urine, or saliva. At present, several ultrasensitive assaying technologies have been developed [16–20], but there is no consistency in the measured concentrations of plasma A $\beta$  and tau protein among the different assaying technologies. For example, the levels of plasma amyloid  $\beta$  1–42 (A $\beta$ <sub>1–42</sub>) were found to be reduced in AD patients as compared to normal controls using single-molecule array (SIMOA), whereas they were found to be higher using immunomagnetic reduction assay (IMR). The discrepancies in measured results among assaying technologies could be attributable to several factors, including antibodies, assay methodology, and sample preparation. Hence, it would be better to concentrate on the results obtained by assay with one of these technologies. In this

review, the assay results obtained with superconducting quantum interference device-based immunomagnetic reduction (SQUID IMR) are the subject of interest [21, 22].

Most studies utilizing SQUID IMR have focused on exploring the associations between A $\beta$  or tau protein in plasma and in CSF [15], the results of amyloid or tau PET [23–25] or magnetic resonance imaging [24, 26], or clinical diagnosis [27–29]. These studies have yielded promising results regarding the feasibility of detecting AD in patients by assaying blood A $\beta$  and tau protein. We will not summarize such works in this review, because previous review articles have already investigated the working mechanism and clinical impact of SQUID IMR [30, 31]. Instead, according to published papers [32–35], we will aim to discuss the possible dominance of plasma A $\beta$  and tau protein in the progression to dementia in at-risk patients, such as those with Down syndrome, stroke, or amnesic mild cognitive impairment (aMCI). Such research is so novel that few papers have been published. In this review, five studies are referenced to show the roles of plasma A $\beta$  and tau in the progression to dementia in these at-risk patients. This is a review article that is based on reported studies and does not contain any new studies with human participants or animals performed.

## PREDICTION OF DEMENTIA IN PATIENTS WITH DOWN SYNDROME

Down syndrome (DS) is a common chromosomal abnormality [36]. Due to the presence of a triplicated chromosome 21, DS patients usually suffer from amyloid deposition in the brain, which increases the risk of developing dementia. The onset age of dementia in DS patients is earlier than that in normal controls by 30 years. Thus, a high prevalence of dementia has been observed in DS patients younger than 35 years of age [37]. However, in clinical practice it is very difficult to diagnose dementia in a DS patient, regardless of the results of magnetic resonance imaging, amyloid PET, neuropsychological tests, or CSF biomarker detection.

Therefore, a delayed diagnosis of dementia for DS patients often occurs in the clinic. On the other hand, drawing blood is relatively easy for DS patients. This has motivated studies exploring the feasibility of discriminating dementia in DS patients via plasma biomarkers.

Fang et al. investigated the difference in levels of plasma biomarkers between DS individuals without and with dementia [32]. They enrolled 35 DS patients without dementia and 16 DS patients with dementia, using the Adaptive Behavior Dementia Questionnaire (ABDQ) score to discriminate between the two groups. SQUID IMR was used to assay plasma  $A\beta_{1-42}$ , amyloid  $\beta$  1–40 ( $A\beta_{1-40}$ ), and tau protein (tau) in the enrolled subjects. All three biomarkers were reported to be moderately associated with the ABDQ score, as illustrated in Table 1. Notably, the plasma  $A\beta_{1-42}$  level showed the most significant correlation with the ABDQ score in DS patients. The results of the receiver operating characteristic (ROC) curve analysis for discriminating dementia in DS using the plasma concentrations of  $A\beta_{1-42}$ ,  $A\beta_{1-40}$ , and tau are listed in Table 2. It was observed that the plasma  $A\beta_{1-42}$  level was the predominant indicator for the early detection of neurodegeneration in DS. These results reveal that the plasma  $A\beta_{1-42}$  level might be the most powerful parameter for predicting the progression of dementia in DS.

## IDENTIFICATION AND PREDICTION OF VASCULAR COGNITIVE IMPAIRMENT IN STROKE PATIENTS

Stroke causes serious brain damage or death in afflicted patients. It can also lead to cerebral ischemia, which triggers the deposition of  $A\beta$ , the hyperphosphorylation of tau, and neuroinflammation in the brain [38–40]. Hence, post-

**Table 1** Correlation coefficient  $r$  between plasma biomarkers and the ABDQ score in DS patients (all  $p < 0.05$ ) [32]

Biomarker	$A\beta_{1-42}$	$A\beta_{1-40}$	Tau
$r$	0.621	−0.556	−0.410

**Table 2** Results of ROC curve analysis for determining dementia in DS using plasma biomarkers [32]

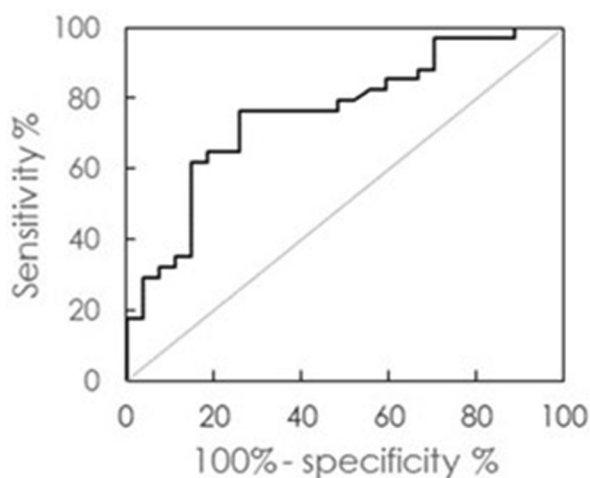
Biomarker	$A\beta_{1-42}$	$A\beta_{1-40}$	Tau
Cutoff value	12.36 pg/ml	92.2 pg/ml	26.04 pg/ml
Sensitivity	0.875	0.813	0.636
Specificity	0.943	0.943	0.883

stroke patients are at risk for the progression of dementia. It has been reported that post-stroke dementia occurs in 7% of patients 1 year after a stroke [41], which increases to 52% at 6 months if mild post-stroke cognitive impairment is included in the diagnosis [42]. Thus, management for both stroke and dementia is needed in patients post-stroke. However, such patients usually experience impairment in activities of daily living, language, etc. [43, 44]. It is difficult to evaluate neurodegeneration in post-stroke patients using neuroimaging or neuropsychological tests. Blood tests, on the other hand, would be a more accessible method.

Tang et al. utilized an IMR assay for plasma  $A\beta_{1-40}$ ,  $A\beta_{1-42}$  and tau in post-stroke patients with ( $n = 34$ , age =  $76.9 \pm 6.2$  years) or without ( $n = 27$ , age =  $71.0 \pm 6.6$  years) dementia [33]. Neuropsychological tests, including the clinical dementia ranking (CDR) scale, the Mini-Mental State Examination (MMSE), and the Montreal Cognitive Assessment (MoCA), were performed for every participant. The clinical diagnosis of vascular dementia was made in accordance with the criteria for dementia from the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN). The results of the study showed values of  $CDR \geq 1$ ,  $MMSE = 13.1 \pm 4.2$ , and  $MoCA = 7.3 \pm 4.7$  for post-stroke patients with dementia, and  $CDR \leq 0.5$ ,  $MMSE = 28.7 \pm 0.9$ , and  $MoCA = 23.6 \pm 3.4$  for those without dementia. Among the measured plasma biomarkers, only the  $A\beta_{1-42}$  level was significantly different between post-stroke patients with ( $17.6 \pm 2.6$  pg/ml) and without dementia ( $15.4 \pm 1.8$  pg/ml,  $p < 0.01$ ). Receiver operating characteristic curve analysis determined a cutoff

value of 15.59 pg/ml for discriminating non-dementia from dementia in post-stroke patients, resulting in clinical sensitivity, specificity, and area under the curve of 0.765, 0.741, and 0.760, respectively, as shown in Fig. 1. Furthermore, plasma  $A\beta_{1-42}$  showed a moderately negative correlation with the MMSE ( $r = -0.46$ ,  $p < 0.01$ ) and MoCA scores ( $r = -0.44$ ,  $p < 0.01$ ) in post-stroke patients, as shown in Table 3. The levels of plasma  $A\beta_{1-40}$  and tau were not associated with the MMSE or MoCA scores. Hence, the plasma  $A\beta_{1-42}$  level is a promising index for determining neurodegeneration in post-stroke patients.

Chi et al. investigated the prediction of cognitive impairment in post-stroke patients 1 year after stroke using levels of plasma biomarkers 3 months after stroke [34]. Forty-two post-stroke patients with and 13 post-stroke patients without cognitive impairment after 1 year were enrolled. The plasma  $A\beta_{1-42}$ ,  $A\beta_{1-40}$ , and tau levels 3 months after stroke were assayed. The level of plasma  $A\beta_{1-42}$  at 3 months was the most significant biomarker in predicting post-stroke cognitive impairment 1 year after stroke. Therefore, plasma  $A\beta_{1-42}$  is a promising index for both predicting and determining cognitive impairment in post-stroke patients.



**Fig. 1** Receiver operating characteristic curve analysis using plasma  $A\beta_{1-42}$  concentration as an index to discriminate non-dementia from dementia in post-stroke patients

**Table 3** Correlations between levels of plasma biomarkers  $A\beta_{1-40}$ ,  $A\beta_{1-42}$ , tau, and MMSE and MoCA scores in post-stroke patients [33]

Biomarker	$A\beta_{1-42}$	$A\beta_{1-40}$	Tau
MMSE			
<i>r</i>	−0.46	0.07	−0.04
<i>p</i> value	0.002	0.631	0.751
MoCA			
<i>r</i>	−0.44	0.17	−0.02
<i>p</i> value	0.001	0.251	0.878

## PREDICTION OF COGNITIVE DECLINE IN AMCI PATIENTS

Amnesic mild cognitive impairment (aMCI) is defined as a transition from normal aging to Alzheimer’s disease (AD). Approximately 30% of aMCI patients progress to AD in 1–1.5 years, and more than 50% progress to AD in 3 years [45, 46]. One of the symptoms during this progression is cognitive decline. In the clinic, the objective is to predict cognitive decline in aMCI patients. Tsai et al. investigated the predictive power for cognitive decline of the baseline levels of plasma biomarkers at a 1.2-year follow-up in aMCI patients [34]. Twenty-four aMCI patients were enrolled. The value of Pearson’s correlation coefficient  $r$  between the baseline levels of the plasma biomarkers and the annual changes in the MMSE score are listed in Table 4. Among the three different plasma biomarkers,  $A\beta_{1-42}$  showed a significant and moderate

**Table 4** Correlations between baseline levels of plasma biomarkers and the annual change in MMSE score in aMCI patients with an average follow-up period of 1.2 years [34]

Biomarker	$A\beta_{1-42}$	$A\beta_{1-40}$	Tau
aMCI ( $n = 24$ )			
Pearson’s <i>r</i>	−0.51	0.003	−0.28
<i>p</i> value	0.012	0.992	0.189

negative correlation with the annual change in the MMSE score.

Similar results were reported independently by Chen et al. and are listed in Table 5. Twenty-two aMCI patients were enrolled [35], and changes in the MMSE scores were measured at the 1–1.5-year follow-up. The value of Pearson's  $r$  between the baseline levels of the plasma biomarkers and the annual change in the MMSE score was analyzed. Compared to the levels of  $A\beta_{1-40}$  and tau, the level of plasma  $A\beta_{1-42}$  at baseline showed the strongest association with the annual change in the MMSE score. The two independent studies by Tsai et al. and Chen et al. illustrate that plasma  $A\beta_{1-42}$  at baseline is a useful parameter for predicting cognitive decline in aMCI.

## CONCLUSIONS

In populations at risk for developing dementia, such as patients with Down syndrome, stroke, and amnesic mild cognitive impairment, it is important to be able to predict the progression to dementia or cognitive decline. In clinical practice, a convenient examination that can evaluate progression to dementia or cognitive decline is urgently needed. According to this review, plasma  $A\beta_{1-42}$  may play a more key role in this prediction than  $A\beta_{1-40}$  or tau. This implies that abnormal levels of  $A\beta_{1-42}$  might be a critical trigger of the onset of dementia or cognitive decline. Therefore, there may be hope for stopping the development of dementia or delaying cognitive decline by eliminating the abnormal changes in the level of plasma  $A\beta_{1-42}$ .

**Table 5** Correlations between baseline levels of plasma biomarkers and the annual change in MMSE score in aMCI patients with an average follow-up period of 1–1.5 years [35]

Biomarker	$A\beta_{1-42}$	$A\beta_{1-40}$	Tau
aMCI ( $n = 22$ )			
Pearson's $r$	−0.512	NA	−0.376
$p$ value	0.015	NA	0.085

Nevertheless, there are limitations in this work that should be mentioned. Notably, because of the novelty of such research, only five studies were available for this review. Additional independent studies should be performed to further explore the promising results described in this review.

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**Compliance with Ethics Guidelines.** This is a review article that is based on reported studies and does not contain any new studies with human participants or animals performed by any of the authors.

**Data Availability.** Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

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