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Assay of Neurodegenerative Biomarkers in Human Plasma of Patients with Parkinson's Disease

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Abstract

Introduction: In addition to α-synuclein, amyloid and tau pathologies have been found in patients with Parkinson's disease (PD). Although the results of assaying these proteins in body fluid have been reported, comprehensive studies on the discriminating power between PD patients and normal controls (NCs), as well as in PD with normal cognition (PD-NC) patients and PD with dementia (PDD) patients, are rare, especially in plasma. In this study, total plasma α-synuclein, amyloid β1-42 ($A\beta_{1-42}$) and total tau protein in NC, PD-NC, and PDD subjects were assayed to explore the roles of these three proteins in PD.

Methods: One hundred eighty-seven NCs, one hundred twenty-eight PD-NC patients and seventy-nine PDD patients were enrolled at five hospitals in Taiwan. Plasma tau, $A\beta_{1-42}$ and α-synuclein were assayed for each enrolled subject using ImmunoMagnetic Reduction (IMR).

Results: Plasma $A\beta_{1-42}$, tau and α-synuclein were significantly increased in PD patients compared to NCs. Further increases in plasma tau and α-synuclein were found in PDD patients compared to PD-NC patients. α-synuclein levels showed relatively strong discriminating power between PD patients and NCs, as well as between PDD and PD-NC patients. Tau levels showed a relatively strong correlation with cognitive decline. In NCs, the expression of the three proteins was independent of age.

Conclusions: These results suggest that both Tau and α-synuclein play roles in the occurrence of PD and dementia in PD patients. However, tau levels are not associated with α-synuclein levels in PD patients, which implies that tau and α-synuclein should be regarded as independent biomarkers of PD.

Keywords: Plasma biomarkers; Parkinson's disease; Immunomagnetic reduction; amyloid; Tau; α-synuclein

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease [1]. The traditional cardinal signs of PD are movement disorders, including resting tremor, cogwheel rigidity, bradykinesia, and postural instability [2]. Currently, the diagnosis of PD in Taiwan is mostly based on the National Institute for Health and Care Excellence (NICE) guidelines updated in 2017 [3]. These guidelines cover diagnosing and managing Parkinson's disease in people aged 18 and over. The guidelines state that Parkinson's disease should be suspected if a patient has tremors, stiffness, slowness of movement, balance problems and/or gait disturbances. Untreated patients

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should be referred quickly to a specialist with expertise in differential diagnosis. The progressive degeneration of dopamine neurons in the substantia nigra of the brain causes Parkinson's disease [4,5]. In Parkinson disease, the misfolding of α-synuclein monomers in neurons leads to the formation of oligomers and fibrils, which further aggregate into protein inclusions called Lewy bodies [6]. The accumulation of these abnormal insoluble α-synuclein proteins in dopamine neurons leads to the gradual death of cells that secrete the neurotransmitter dopamine [7]. Dopamine is responsible for coordinated motor functions in the body, and when dopamine levels are insufficient, symptoms of Parkinson's disease can occur.

Assaying α-synuclein in cerebral spinal fluid (CSF) can be used to assess PD, especially in early-stage PD [8-10]. In addition to α-synuclein, pathological evidence of amyloid plaques and tau tangles in the brain has been shown in PD patients [11-14]. This finding implies that amyloid β and tau protein could also be useful biomarkers for assessing PD. Many groups have demonstrated significant differences in the levels of CSF α-synuclein, amyloid β1-42 ($A\beta_{1-42}$) and total tau protein (Tau) between PD patients and normal controls (NCs) [15-18]. Eighty percent of PD patients suffer from cognitive impairment or dementia in the lifetime of the disease, so-called Parkinson's disease dementia (PDD) [19]. It is necessary to identify the mechanisms related to the progression of PDD in PD to reduce its occurrence. Risk factors associated with progressing to PDD in PD patients include older age, male sex, lack of tremor, postural instability, and subtle impairment on cognitive tests [20,21]. Fluid biomarkers may be promising factors that could be used to predict progression to PDD. Although many studies on CSF α-synuclein, $A\beta_{1-42}$ or Tau in PD and PDD patients have been performed, the reported predictive power of these CSF biomarkers for predicting progressive cognitive decline in PD patients in numerous independent studies has not been consistent [22-27]. Thus, the feasibility of using CSF biomarkers to discriminate PDD from PD or to predict dementia in PD patients is under investigation. Due to side effects [28,29], lumbar puncture is not easy to use in frequent practice. Progress in exploring the role of CSF biomarkers in PD is limited. In contrast to lumbar puncture, blood collection is easy for routine assessment. The investigation of α-synuclein, $A\beta_{1-42}$ or Tau in plasma has attracted the interest of researchers and neurologists. However, the concentrations of these biomarkers in blood are extremely low, at approximately pg/ml or lower. Therefore, ultrasensitive assays are needed to explore these biomarkers in blood. In recent decades, several techniques for detecting proteins at the pg/ml level, such as immunomagnetic reduction (IMR) [30], single molecule array (SIMOA) and immunoprecipitation mass spectrometry (IP-MASS) [31,32], have been developed. Assays of plasma α-synuclein, $A\beta_{1-42}$ or Tau levels have become feasible [33]. Independent studies have revealed significant differences in the levels of plasma α-synuclein between PD/PDD patients and NCs [34-39]. The results demonstrate the feasibility of assessing PD/PDD using plasma α-synuclein. In addition to PD/PDD, atypical parkinsonism syndromes (APSs), such as dementia with Lewy bodies (DLB), multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), are characterized by increased plasma α-synuclein levels [40]. Lin et al. further showed that additional biomarkers, such as phosphorylated Tau and $A\beta_{1-42,}$ should be combined with α-synuclein to differentiate NCs from PD/PDD and APS patients [40]. Starhof et al. reported that PSP patients have higher CSF concentrations of C-reactive protein, tumor necrosis factor α, interleukin-1β (IL-1β), IL-4, and IL-6 than PD patients [41]. NCs, PD patients and PSP patients can be differentiated by combining α-synuclein and Tau with other biomarkers. Abnormal concentrations of plasma $A\beta_{1-42}$ or Tau in PD/PDD patients have been reported [38,42-44]. The effects of regional atrophy in the brain on the concentrations of plasma $A\beta_{1-42}$ and Tau and on cognitive function have been described [38,42]. Furthermore, the prediction of dementia in PD patients using plasma α-synuclein concentrations has been demonstrated [34,37,42]. Although many significant results on plasma biomarkers in PD/PDD patients have been published, comprehensive studies investigating the discriminating power of plasma α-synuclein, $A\beta_{1-42}$ and Tau between PD/PDD patients and NCs, and between PDD patients and PD patients are rare. In this study, one hundred eighty-seven NCs, one hundred eighteen PD-NC patients and seventy-nine PDD patients were enrolled at National Taiwan University Hospital, Show Chwan Memorial Hospital, Tri-Service General Hospital, Taipei Veterans General Hospital and Shuang Ho Hospital. Plasma Tau, $A\beta_{1-42}$ and α-synuclein levels in each enrolled subject were assayed using IMR. The discrimination between PD-NC/PDD patients and NCs and between PDD and PD-NC patients using plasma biomarkers was investigated. The correlation between the plasma biomarkers and the Mini-Mental State Examination (MMSE) score was examined. In addition, the associations among plasma biomarkers were explored. The age and sex distributions of the plasma biomarkers in the NCs are discussed.

Methods

Recruitment of subjects

Participants in this study were given a medical checklist of major systemic diseases, operations and hospitalizations. Participants reporting uncontrolled medical conditions, including heart failure, recent myocardial infarction (in the past 6 months), malignancy (in the past 2 years), or poorly controlled diabetes (HbA1C>8.5); a significant history of depression; a history of repeated strokes with stepwise

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progression; repeated head injury; antipsychotic drug use; definite encephalitis and/or oculogyric crises on no drug treatment; a negative response to large doses of levodopa (if malabsorption was excluded); strictly unilateral features after 3 years; other neurological features (supranuclear gaze palsy, cerebellar signs, early severe autonomic involvement, Babinski sign, early severe dementia with disturbances of language, memory or praxis); exposure to a known neurotoxin; or the presence of cerebral tumors or communicating hydrocephalus on neuroimaging were excluded. Volunteers also received physical examinations. PD and PDD were determined in patients using the United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria [45]. Clinical evaluations included a history of the present illness, a family history, a medical history, and a review of systems, with an emphasis on movement disorders, psychiatric illnesses, and cognitive function. The patient evaluations included the Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr stage (H-Y stage), and the MMSE [46]. PD patients were defined as those exhibiting tremor, postural instability or gait disorders. PDD was defined as a diagnosis of idiopathic PD that developed prior to the onset of dementia, with MMSE scores < 26 for more than 1 year [47]. Enrolled subjects without neurodegenerative diseases and without any of the abovementioned exclusion criteria were categorized as normal controls (NCs). This study was approved by the ethics committees of the hospitals. All research was performed in accordance with the relevant guidelines/regulations. Each participant provided informed consent. One hundred eighty-seven NCs, one hundred twenty-eight PD with normal cognition (PD-NC) patients and seventy-nine PDD patients were enrolled at Kaohsiung Chang Gung Memorial Hospital, National Taiwan University Hospital, Sho Chwan Memorial Hospital, Taipei Medical University Shuang-Ho Hospital, Taipei Veterans Hospital, and Tri-Service General Hospital.

Compliance with ethics guidelines

All of the subjects and/or their primary caregivers provided written informed consent prior to their participation in this investigation. This study was approved by the ethics committees and institutional review boards of all the involved hospitals, Kaohsiung Chang Gung Memorial Hospital, National Taiwan University Hospital, Show Chwan Memorial Hospital, Taipei Medical University Shuang-Ho Hospital (201408011), Taipei Veterans Hospital, and Tri-Service General Hospital (TSGHIRB 1-107-05-111). This study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments.

Preparation of human plasma

Blood was collected in 6-ml or 10-ml K3-EDTA tubes (455036; Greiner Bio-One), and the tubes were immediately inverted gently 10 times. A swing-out (bucket) rotor was used to centrifuge the blood at 20-25 °C and 2,500 × g for 10-15 minutes. Every 1 ml of plasma (supernatant) was transferred to a fresh 1.5 ml Eppendorf tube. All the aliquoted plasma samples were stored at -80 °C within 4.5 hours after blood collection.

Plasma biomarker assays

The tubes with the frozen plasma samples were transferred to ice at -80 °C. After 10-15 minutes, the tubes were moved to room temperature and kept at room temperature for 10-15 minutes. For the Tau/Aβ_{1-42}/α-synuclein assays, 40/60/40 µl of plasma was mixed with 80/60/80 µl of reagent (MF-TAU-0060, MF-AB2-0060, MF-ASC-0060, MagQu) for IMR measurement. For a given biomarker, measurements were performed in duplicate. The reported concentration of each biomarker was the average value of the duplicated measurements. An IMR analyzer (XacPro-S, MagQu) was used for the concentration measurements. All assays were performed in a blinded manner.

Statistical analysis

Continuous variables for each measurement are presented as the mean ± standard deviation. Continuous variables were compared using t tests, and the *p* values were determined. Pearson's correlation, r, was assessed using GraphPad Prism. Receiver operating characteristic (ROC) curve analysis was performed to determine the cutoff value, clinical sensitivity, specificity and area under the curve (AUC).

Results

The demographics of the enrolled subjects are listed in Table 1. The PD group included both the PD with normal cognition (PD-NC) patients and the PD dementia (PDD) patients. First, comparisons of the patient demographics between the NC and PD groups were made. Then, further comparisons between PD-NC and PDD patients were made. The percentage of females was 64.7% in the NC group and 44.2% in the PD group. The subjects in the PD group (65.2 ± 10.3 years) were slightly older than those in the NC group (63.4 ± 6.4 years; $p < 0.05$). The H-Y stage was zero in the NC group and 2.09 ± 1.10 in the PD group ($p < 0.0001$). The NCs had significantly greater MMSE scores (28.6 1.5) than did the PD patients (22.4 ± 5.4; $p < 0.0001$).

The plasma Tau tau levels in the NC group were 18.28 ± 7.54 pg/ml and increased to 24.17 ± 8.81 pg/ml in the PD group ($p < 0.0001$), as shown in Fig. 1(a). The NC group also had significantly lower plasma Aβ_{1-42} levels (15.92 ± 2.23 pg/ml) than did the PD group (16.84 ± 2.62 pg/ml; $p < 0.0001$), as shown in Fig. 1(b). As shown in Fig. 1(c), the plasma α-synuclein concentration in the PD group was 1.952 ± 6.33 pg/ml, which was much greater than that in the NC group (0.084 ± 0.136 pg/ml; $p < 0.0001$).

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There were 128 PD-NC patients and 79 PDD patients. The PDD patients (69.0 ± 8.6 years) were slightly older than the PD-NC patients (63.0 ± 10.6 years; $p < 0.0001$). The disease duration in the PD-NC patients was 0.5-6.9 years, whereas it was 1.2-16.5 years for the PDD patients. The H-Y stage in the PD-NC patients was 1.62 ± 0.85, while that for the PDD patients was higher (2.41 ± 1.13; $p < 0.0001$). In addition, PDD patients had lower MMSE scores (19.5 ± 4.5) than PD-NC patients (26.8 ± 3.3; $p < 0.0001$). Thus, the severity of movement disorders and dementia was worse in the PDD patients compared with the PD-NC patients.

The effect sizes of the plasma biomarkers among the NC, PD-NC and PDD groups are listed in Table 2. The effect size was obtained by calculating the ratio of the means of the concentrations between two groups. For plasma Tau, the effect size for the PD-NC to NC comparison, denoted PD-NC/NC, was 1.32, and that for the PDD/NC comparison was 1.41. This implies that the concentration of plasma Tau in the PD-NC group was 32% greater than that in the NC group and 42% greater than that in the NC group. Thus, the plasma Tau level increased by approximately 10% in PD-NC patients compared with PDD patients, as listed in Table 2 (PDD/PD-NC). The effect size for the plasma $A\beta_{1-42}$ levels for the PD-NC/NC comparison was 1.06 and that for the PDD/NC comparison was 1.05. This finding implies that the concentrations of plasma $A\beta_{1-42}$ in PD-NC and PDD patients were increased by approximately 5% compared to that in the NCs. The PD-NC and PDD groups had equivalent levels of plasma $A\beta_{1-42}$. Regarding the α-synuclein levels, the levels in PD-NC patients were 7.6-fold higher than those in NCs, and PDD patients had much higher levels, almost 50-fold higher than those in the NCs. Thus, PDD patients had plasma α-synuclein levels 6.35-fold greater than those of PD-NC patients. The results shown in Table 2 suggest that Tau, $A\beta_{1-42}$ and α-synuclein are associated with the incidence of PD. Furthermore, α-synuclein and Tau, but not $A\beta_{1-42}$, are related to the progression to dementia in PD patients according to the effect size analysis.

The clinical sensitivity and specificity of plasma biomarkers for differentiating NC from PD and PD-NC from PDD were investigated. Through the receiver operating characteristic (ROC) curve analysis using the individual biomarkers shown in Fig. 1(a)-(c), the cutoff value, clinical sensitivity, specificity and area under the curve (AUC) for differentiating PD patients from NCs were determined. The criterion for determining the optimal cutoff value of a biomarker is to find the maximum value of the Youden index, which is calculated as follows: Sensitivity% + Specificity% - 100%. The cutoff plasma Tau concentration for discriminating PD patients from NCs was 20.41 pg/ml, with a corresponding clinical sensitivity of 0.623 (95% CI: 0.553–0.690), a specificity of 0.626 (95% CI: 0.552–0.695) and an AUC of 0.705. The ROC curve is plotted with the black dashed line in Fig. 2(a). The cutoff concentration of plasma $A\beta_{1-42}$ for differentiating PD patients from NCs was 16.17 pg/ml, with a sensitivity of 0.585 (95% CI: 0.514–0.652), a specificity of 0.578 (95% CI: 0.503–0.649) and an AUC of 0.614. The ROC curve is plotted with the gray dashed line in Fig. 2(a). Using plasma α-synuclein to discriminate PD patients from NCs, the cutoff concentration was 0.0916 pg/ml. The clinical sensitivity, specificity and AUC were 0.802 (95% CI: 0.741–0.854), 0.733 (95% CI: 0.663–0.795) and 0.872, respectively. The ROC curve is plotted in black in Fig. 2(a). Compared to Tau and $A\beta_{1-42}$, plasma α-synuclein showed greater potential for differentiating PD patients from NCs. This result is consistent with the pathogenesis of Parkinson's disease, which is an α-synucleinopathy.

The cutoff concentrations, clinical sensitivity, specificity and AUC for discriminating PDD patients from PD-NC patients using plasma biomarkers were investigated. Since there was no significant difference in plasma $A\beta_{1-42}$ levels between PDD patients and PD-NC patients, $A\beta_{1-42}$ was excluded. Plasma Tau showed a cutoff concentration of 21.22 pg/ml for differentiating PDD patients from PD-NC patients, with a corresponding sensitivity of 0.684 (95% CI: 0.569–0.784), a specificity of 0.508 (95% CI: 0.418–0.597) and an AUC of 0.591. The ROC curve is plotted with the dashed line in Fig. 2(b). The solid line in Fig. 2(b) denotes the ROC curve for discriminating PDD patients from PD-NC patients using plasma α-synuclein levels. The cutoff concentration was 0.577 pg/ml. The sensitivity was 0.747 (95% CI: 0.636–0.838), the specificity was 0.750 (95% CI: 0.666–0.822), and the AUC was 0.735. Thus, α-synuclein is a dominant factor for determining progression to dementia in PD patients.

The results in Fig. 2 reveal that the AUCs of plasma $A\beta_{1-42}$, Tau and α-synuclein for discriminating PD patients from NCs were 0.614, 0.704 and 0.872, respectively. The AUCs of plasma Tau and α-synuclein for discriminating PDD patients from PD-NC patients were 0.591 and 0.735, respectively. This seems to suggest that Tau and α-synuclein are strongly associated with the incidence of PD. Moreover, α-synuclein was the dominant factor contributing to the progression of dementia in PD patients. It is worth investigating the correlation between plasma α-synuclein levels and cognition using scores on tests such as the MMSE. Such correlations for plasma $A\beta_{1-42}$ and Tau were also examined.

As listed in Table 3, all of these biomarkers were negatively and moderately correlated with the MMSE score. Notably, plasma Tau showed a relatively strong correlation ($r = -0.259$, $p = 0.0009$) with the MMSE scores compared to α-synuclein ($r = -0.204$, $p = 0.0092$) and $A\beta_{1-42}$ ($r = -0.252$, $p = 0.0012$). However, α-synuclein showed a relatively weak correlation with the MMSE scores. Although α-synuclein is the dominant factor related to dementia in PD patients, Tau

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but not α-synuclein is related to the severity of cognitive impairment in PD patients. This seems to imply that certain proteins act as triggers for dementia, while other proteins may reflect functional deterioration in PD.

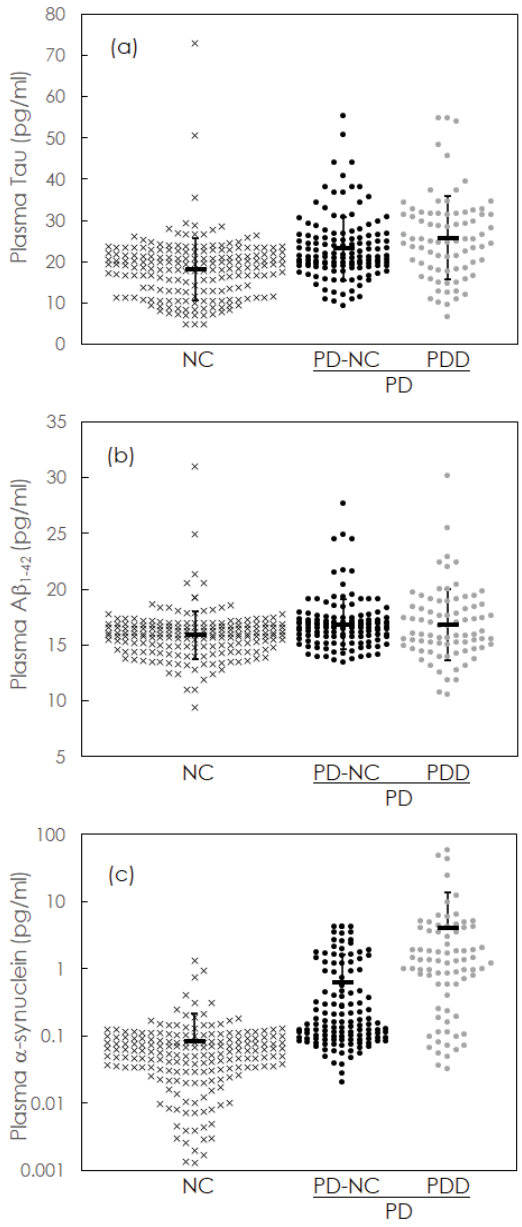

Figure 1: Dot plot of plasma (a) Tau (b) $A\beta_{1-42}$ and (c) α-synuclein concentrations in the NC (×), PD-NC (•) and PDD (•) groups.

Discussion

The understanding of brain-derived Tau, $A\beta_{1-42}$ and α-synuclein levels in the peripheral blood of PD patients is limited. Due to the development of ultrasensitive assay technologies [31-33], studies on plasma biomarkers of brain-derived Tau, $A\beta_{1-42}$ and α-synuclein in PD are currently attracting the interest of researchers. Examinations of plasma biomarkers in PD are continuously reported [34-39,42-44]. One interesting topic is the correlation of biomarker concentrations between blood and CSF. Many studies exploring CSF biomarkers in PD patients have been published [24,26,48,49]. Although the CSF results reported by independent research groups might not be consistent with each other, some of the previously reported findings support the observations in this study.

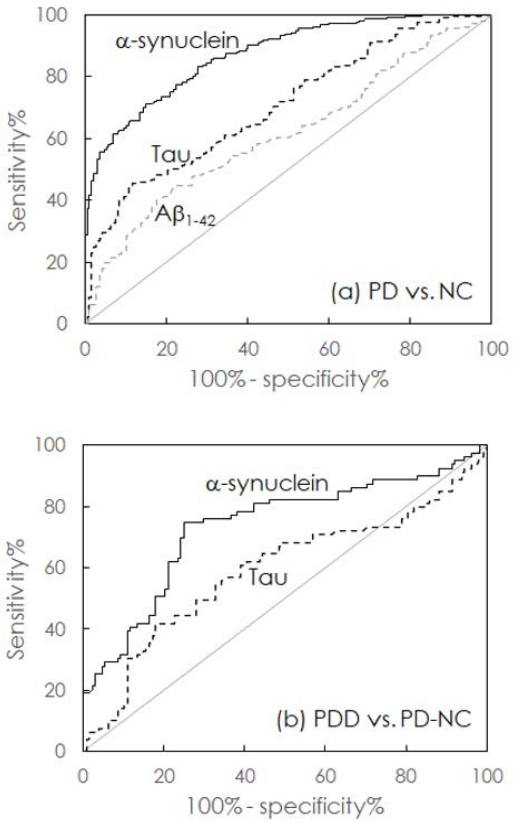

Figure 2: ROC curves for discriminating (a) PD patients from NCs using plasma Tau, Aβ1-42 and α-synuclein levels and (b) PDD patients from PD-NC patients using plasma Tau and α-synuclein levels.

Buddhala et al. reported significant differences in CSF $A\beta_{1-42}$ and α-synuclein levels between NCs and PD-NC patients [48]. This reveals that not only α-synuclein but also $A\beta_{1-42}$ play roles in PD. Similar results were also observed with plasma α-synuclein and $A\beta_{1-42}$ levels, as shown in Fig. 2(a). Stav et al. reported that various CSF biomarkers, such as $A\beta_{1-42}$, Tau and α-synuclein, have different abilities to predict regional atrophy of the brain in PD patients [50]. This finding demonstrates the different roles of biomarkers in aspects of cognitive or motor dysfunctions in PD patients. Hence, the effects of multiple nonindividual biomarkers on brain atrophy and clinical symptoms in PD patients should be considered.

Tau has been shown to promote microtubule polymerization and drive the assembly of tubulin into

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microtubules, which form the cytoskeleton of neurons and define neuronal morphology [51]. In neurodegenerative diseases, hyperphosphorylated tau inhibits microtubule assembly [52] and the free tau molecules aggregate into paired helical filaments that cause nerve death [53]. Tau is a key plasma biomarker associated with neural damage in the brain. When neurons become damaged or fibrillary, abundant tau protein is released in the brain, leading to a change in the Tau protein concentration in cerebrospinal fluid (CSF) and blood. Moreover, brain atrophy occurs regionally or globally due to neuronal damage. Thus, Tau levels in fluid are significantly correlated with brain atrophy. Lin et al. utilized IMR to assay Tau levels in plasma and used magnetic resonance imaging (MRI) to measure brain atrophy in PD patients [54]. A positive correlation between plasma Tau levels and brain atrophy in PD patients has been reported. Additionally, using IMR and MRI, Chiu et al. and Liu et al. reported a negative correlation between plasma Tau levels and brain volume in patients with amnesic mild cognitive impairment and Alzheimer's disease [55,56]. On the other hand, Chen et al.*et al.* revealed a negative correlation between plasma α-synuclein levels and brain atrophy, especially in the region of the limbic cortex [57]. These results imply that other plasma biomarkers in addition to Tau play roles in brain atrophy in PD patients. Further explorations are needed to clarify the roles of biomarkers in brain atrophy in PD patients.

Skogseth et al. revealed an association between reduced CSF α-synuclein concentrations and cognition in PD patients and suggested that pathological α-synuclein contributes to early cognitive impairment in PD patients [24]. The results support the discrimination between PDD and PD-NC using α-synuclein, as shown in Fig. 2(b). Consistent results for biomarkers between CSF and blood were not only found in this work. Schirinzi et al. reported that brain-derived Tau, $A\beta_{1\text{-}42}$ and α-synuclein may change correspondingly in both the peripheral blood and CSF of PD patients [49].

In fact, there are inconsistent results for biomarkers between blood and CSF. Yousaf et al. showed that both CSF $A\beta_{1\text{-}42}$ and Tau levels significantly differ in PD-NC and PDD patients [26]. However, the results in Figs. 1(a) and (b) show that only plasma Tau not the levels of $A\beta_{1\text{-}42,}$ significantly differed between the PDD and PD-NC groups. More explorations to correlate blood biomarkers with CSF biomarkers are needed.

Even among studies on CSF biomarkers, inconsistent changes in CSF α-synuclein levels have been found in PD patients among cohorts. Several studies have shown that CSF α-synuclein levels are lower in PD patients than in NCs [58-60]. Other studies have reported that there is no significant difference in CSF α-synuclein levels between PD patients and NCs [61,62]. These inconsistencies might be attributed to several factors, such as the CSF preparation method, assay technologies, the antibodies used in the assays, and the subjects enrolled. A standard protocol from sample preparation to data analysis should be developed to ensure consistent results among studies.

IMR assay kits and the analyzer for α-synuclein, $A\beta_{1\text{-}42}$ and Tau in human plasma have been registered with CE IVDD. Standard processes, including blood draw, plasma preparation, Good-Manufacture-Production grade reagents/calibrators/controls, assay steps and data analysis, were established. Consistent results in assaying plasma α-synuclein, $A\beta_{1\text{-}42}$ and Tau using the IMR assay among studies on PD have been reported. A definite increase in plasma α-synuclein and Tau levels in PD patients has been shown independently by many groups [34,36-38,42,63]. This reveals the importance of standardization for assays.

As listed in Table 3, plasma Tau levels were relatively strongly correlated ($r = -0.259$, $p = 0.0009$) with the MMSE scores compared to α-synuclein ($r = -0.204$, $p = 0.0092$) and $A\beta_{1\text{-}42}$ ($r = -0.252$, $p = 0.0012$) levels. In a previous study, correlations between high plasma Tau levels and cognitive evaluation scores (the MMSE and clinical dementia rating) and the severity of PD (UPDRS) were detected, further supporting the role of tau in neuronal degeneration. Similar to the case of Alzheimer's disease (AD), there is an obvious change in the $A\beta_{1\text{-}42}$ level in prodromal AD patients compared to that in NCs, followed by a nearly stable level of plasma $A\beta_{1\text{-}42}$ as the disease progresses to mild or severe AD [64]. However, Tau levels continue to increase as cognition declines in individuals with AD [52,65].

According to previous studies [38,42,43,57], in addition to the MMSE scores, plasma Tau levels are associated with executive dysfunction and regional atrophy in the brain of PD patients. Several groups have reported a negative correlation between plasma Tau levels and MMSE scores [65], between plasma Tau levels and hippocampal volume [55], and between plasma Tau levels and cortical thickness in AD patients [66]. Therefore, Tau levels are a promising index reflecting the severity of neuronal damage and cognitive impairment in neurodegenerative diseases.

With the measured concentrations in NCs, the age dependency and sex-dependent dependency of biomarker concentrations were explored. In the NC group, there were 121 female subjects and 66 male subjects. All NC subjects were either middle-aged or elderly (≥ 50 years old). The correlations between age and plasma Tau, $A\beta_{1\text{-}42}$ and α-synuclein levels were analyzed for females and males, as listed in Table 4. The Pearson's correlation coefficients were within the -0.110 to 0.114 range, and all the p values were greater than 0.05. All plasma Tau, $A\beta_{1\text{-}42}$ and α-synuclein levels were independent of age in middle-aged and elderly NCs, regardless of sex. The age independence of plasma Tau, $A\beta_{1\text{-}42}$ and α-synuclein levels in the NC group is consistent

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with previously reported results [67]. Hence, the measured concentrations of plasma Tau, $A\beta_{1-42}$ and α-synuclein do not need to be adjusted for age for discussion.

The concentrations of plasma Tau, $A\beta_{1-42}$ and α-synuclein in female and male NCs are listed separately in Table 5. There was no significant difference in age between the females (62.9 ± 6.1 years) and males (64.3 ± 6.5 years; $p > 0.05$). Among the three plasma biomarkers, only -synuclein was significantly different between females (0.0064 ± 0.054 pg/ml) and males (0.120 ± 0.213 pg/ml; $p < 0.05$). The reason for the increase in plasma α-synuclein levels in males compared to females is not clear. Further studies should be performed to clarify this difference. The fact that plasma Tau tau and A_{1-42} levels are not sex-dependent in the NC group is consistent with that reported in a previous paper [68]. Hence, the measured concentrations of plasma Tau and $A\beta_{1-42}$ do not need to be adjusted according to sex for discussion.

The correlation between the H-Y stage and plasma biomarker levels was investigated in PD patients. Because of the small sample size, PD patients with H-Y stage 5 disease were not included. The Pearson correlation coefficients (r) and p values between the plasma biomarkers and H-Y stage (0.5-4) in PD patients are listed in Table 6. For α-synuclein, $A\beta_{1-42}$ and Tau, there was no significant correlation with the H-Y stage. In addition to these three biomarkers, Lin et al. reported that the plasma level of Ser129-phosphorated α-synuclein was significantly and positively correlated with the severity of motor disorders [69].

The correlation between plasma biomarkers was analyzed. The results are listed in Table 7. In both NCs and PD patients, plasma Tau levels were significantly and moderately positively correlated with plasma $A\beta_{1-42}$ levels. Plasma Tau concentrations also showed a significant and moderately positive correlation with plasma α-synuclein concentrations in the NC group but not in the PD group. The plasma $A\beta_{1-42}$ concentration did not significantly correlate with the plasma α-synuclein concentration in the NCs or PD patients.

The results shown in Fig. 2(a) reveal that plasma $A\beta_{1-42}$ is less crucial to the incidence of PD than plasma Tau and α-synuclein are. In addition, PDD patients and PD-NC patients have equivalent levels of plasma $A\beta_{1-42}$. Thus, $A\beta_{1-42}$ does not play a key role in PD. Similar to the results of Chojdak-Łukasiewicz et al., plasma $A\beta_{1-42}$ levels cannot be used to differentiate NCs from PD patients with a disease duration of less than 5 years, as they can only discriminate NCs from PD patients with a disease duration of more than 5 years [70]. Regarding plasma Tau and α-synuclein concentrations, significant differences between PD patients and NCs and between PDD patients and PD-NCs were found, as shown in Table 1 and Figs. 2(a) and (b). This finding implies that Tau and α-synuclein are more important for the incidence of PD and dementia in PD. However, plasma Tau is not correlated with plasma α-synuclein in PD patients. This finding suggests that α-synuclein should be regarded as an independent biomarker in PD. It is possible that there are two mechanisms associated with these two biomarkers leading to PD and dementia. Therefore, not only α-synuclein but also Tau should be considered when treating PD.

In published papers, plasma biomarkers are promising for differentiating PDD patients from PN-NC patients. However, the reported results among studies are not consistent. For example, Lin et al. used IMR for assaying plasma α-synuclein and phosphorylated α-synuclein levels [34,69]. α-synuclein was found to be able to discriminate PDD from PD-NC patients, while phosphorylated α-synuclein enabled differentiation of motor disorder in PD patients. The ability to differentiate PDD from PD-NC patients using plasma α-synuclein levels was also validated by Chang et al. using IMR [63]. Syafrita et al. used enzyme-linked immunoassay (ELISA) for assaying plasma $A\beta_{1-42}$, α-synuclein and Tau in PD-NC and PDD patients [71]. It was found that plasma $A\beta_{1-42}$ levels significantly discriminate PDD from PD-NC patients, whereas plasma α-synuclein and Tau levels cannot. The results reported by Syafrita et al. are inconsistent with those of this study and Lin et al. Mizutani et al. used single molecule array (SIMOA) to quantitatively detect plasma biomarkers for predicting cognitive impairment in PD patients [72]. Plasma glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL), but not $A\beta_{1-42}$ or phosphorylated Tau (pTau181), were able to discriminate PDD patients from PD-NC patients. The feasibility of differentiating PDD patients from PD-NC patients using plasma NfL levels assayed with IMR was independently demonstrated by Chen et al. and Chen et al. [38,73]. In addition to soluble plasma biomarkers, Blommer et al. utilized electrochemiluminescence assays to quantify α-synuclein in extracellular vesicles (EVs) in human blood [74]. A significant difference in EV α-synuclein levels was detected between PD-NC and PDD patients. By using IMR, Chung et al. reported significant increases in EV $A\beta_{1-42}$ and Tau levels in PDD patients but not in PD-NC patients [44]. According to published papers, some groups have revealed the role of plasma α-synuclein in differentiating PDD from PD-NC patients, while other groups have reported the prediction of cognitive impairment in PD patients using plasma $A\beta_{1-42}$; however, other groups have proposed utilizing plasma for discriminating PDD from PD-NC patients. Among biomarkers, plasma α-synuclein is the most dominant biomarker for predicting cognitive impairment in PD patients. However, other biomarkers contribute to cognitive impairment in PD patients.

Limitations

In this study, PD patients were diagnosed mainly using the United Kingdom Parkinson's Disease Society Brain Bank

diagnostic criteria. Enrolled subjects were not examined with CSF biomarker assays. PD patients did not undergo neuroimaging examinations, namely, MRI or 18-FDG-PET, to exclude other differential diagnoses, i.e., vascular parkinsonism, or to achieve a more accurate differential diagnosis between PDD and dementia with Lewy bodies.

Conclusion

Plasma $A\beta_{1-42}$, Tau and α-synuclein levels were significantly greater in PD patients than in NCs. Further increases in plasma Tau and α-synuclein levels were found in PDD patients compared to PD-NC patients. Among these three biomarkers, α-synuclein showed relatively strong discriminating power between PD patients and NCs, as well as between PDD patients and PD-NC patients. Tau is the second most abundant protein. Tau showed a relatively strong correlation with MMSE scores. All three protein levels were found to be independent of age in the NCs aged 50 years and older. These results suggest that both Tau and α-synuclein play roles in the occurrence of PD and dementia in PD. However, Tau levels are not associated with α-synuclein levels in PD patients, which implies that Tau and α-synuclein should be regarded as independent biomarkers of PD.

Data availability

The dataset generated and analyzed in the current study is available from the corresponding author upon reasonable request.

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Author contributions

This study was designed by H.C. Liu, S.Y.Y. and W.C.L. and was executed by P.Y.C., C.H.L., M.J.C., C.J.H., P.N.W., T.F.C., F.C.Y., L.K.H. and C.H.L. S.Y.Y. prepared the manuscript. All authors approved the final manuscript.

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Competing interests

H.C. Liu is an employee of MagQu Co., Ltd. S.Y. Yang is a shareholder and an employee of MagQu Co., Ltd. The other authors report no disclosures.

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