Plasma fibrinogen is associated with cognitive decline and risk for dementia in patients with mild cognitive impairment

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Introduction

Fibrinogen is the precursor of fibrin and the major coagulation protein in blood by mass. Elevated levels of plasma fibrinogen may increase blood viscosity, reduce blood flow, predispose to thrombosis and enhance platelet activation (1). These impacts put patients with hyperfibrinogenaemia at increased risk for cardiovascular diseases (2,3), and consequently, vascular dementia (VaD) (4). On the other hand, plasma fibrinogen is a non-specific biomarker for inflammatory conditions (5). There are increasing evidences for a role of inflammation in dementia pathology (6). Several inflammatory markers in circulation, such as d-dimer and C-reactive protein have been associated with cognitive decline and risk for dementia (7,8). A recent population-based cohort study indicated that plasma fibrinogen is associated with increased risk for VaD as well as Alzheimer disease (9).

Most studies of relationship between inflammatory markers and risk for dementia were population based or longitudinal observation of cognitively normal elderly people (9–12). The value of these markers in predicting outcomes of mild cognitive impairment (MCI), a prodrome for dementia, have not been investigated so far. Detecting potential influence factors for cognitive changes in patients with MCI is of great clinical importance. Because a large proportion of MCI patients will develop dementia in a few years, if some interventions which are capable of decelerating or stopping cognitive decline initiated promptly, onset of dementia may be delayed or even prevented (13). This study, for the first time, evaluated the association between plasma fibrinogen level and cognitive decline in a cohort of Chinese elderly patients with MCI.

SUMMARY

This study was aimed to investigate the relationship between plasma fibrinogen level and risk for cognitive decline and dementia in patients with mild cognitive impairment (MCI). Elderly patients with suspected cognitive impairment were screened and evaluated periodically. One hundred and eighty-five patients who met the criteria for MCI were enrolled. Blood coagulation functions and plasma fibrinogen levels were measured at baseline. Hyperfibrinogenaemia was defined as plasma fibrinogen ≥3.0 g/l. Global cognitive function was assessed serially with Mini-Mental State Examination (MMSE). The enrolled patients were followed for 2 years to observe if dementia was developed. There were 185 patients diagnosed as MCI, of which 17 (9.2%) deceased, 15 (8.1%) lost to follow-up, and 68 (36.8%) developed dementia during follow-up. Mean of MMSE score of the enrolled patients declined significantly during follow-up (22.0 ± 3.0 vs. 18.1 ± 5.8, p < 0.001). Patients with hyperfibrinogenaemia at baseline had greater MMSE decrement during follow-up than patients with normal fibrinogen level (−5.4 ± 5.4 vs. −3.5 ± 4.5, p < 0.05). Linear regression indicated that plasma fibrinogen level was associated with cognitive decline (R = 0.17, p < 0.05). Patients with hyperfibrinogenaemia had an increased risk for dementia and vascular dementia compared with patients with normal level of plasma fibrinogen (log rank test, p < 0.05). There was a trend that hyperfibrinogenaemia also increased risk for dementia of Alzheimer’s type (p = 0.061). It can be concluded that plasma fibrinogen level may be associated with cognitive decline, and hyperfibrinogenaemia may increase risk for dementia in patients with MCI.

What’s known

• Hyperfibrinogenaemia increase risk for dementia.

What’s new

• Hyperfibrinogenaemia increase risk for dementia conversion in MCI patients.
Methods

Subjects were patients in Jinling Hospital, which is affiliated to Nanjing University (Nanjing, China). All patients with suspected cognitive impairment who visited the hospital during 1 July, 2002 and 30 June, 2004 were assessed serially for the eligibility of participation. Patients were enrolled and followed once they met the criteria for MCI. Diagnosis of MCI was made if the patient: (i) complained memory decline; (ii) had normal activities of daily living; (iii) did not reach the criteria of dementia; and (iv) had mild quantitative abnormalities of cognitive impairment identified by Mini-Mental State Examination (MMSE), with cut-off points adjusted by age and educational level. The cut-off points were set as mean subtracting one standard deviation of general population of the equivalent age and educational level (14). Other inclusion criteria included Chinese-speaking and aged 45 years or older. Subjects with pre-existing tumour, uncontrolled seizures and recent infectious central nerve system diseases were excluded. The protocol for this study was approved by Institutional Review Boards of Jinling Hospital.

Cognitive status was assessed at baseline utilising the 30-point Chinese-version MMSE (15). The screened patients underwent a complete neurological and neuropsychological evaluation. Other systemic investigations performed at baseline included brain computerised topography (CT) or magnetic resonance imaging (MRI), chest X-ray photography, complete blood cell count, blood biochemical analysis, serum antitreponemiasis, anti-HIV antibody titre and urinalysis. Hamilton Depression Rating Scale was performed for detecting possible confounds because of depression (16). Baseline data of all laboratory variables were used for statistical analyses. Risk factors for cerebrovascular disease (CVD) recorded at baseline included hypertension, diabetes mellitus (DM), hyperlipidaemia, atrial fibrillation (AF), history of smoking and alcohol drinking and previous CVD.

Blood samples were collected at baseline and stored at ~80 °C until determination. Plasma fibrinogen and blood coagulation functions were measured in the central laboratory of Jinling Hospital according to international standards. Fibrinogen was measured by determining the coagulation time of prediluted citrated plasma in the presence of a large amount of thrombin.

After enrollment, subjects were scheduled for regular clinical visits and had their cognitive functions evaluated at 3–6 monthly intervals. Patients or their caregivers were asked to have an extra clinical visit if they observe any cognitive change during the intervals. After each visit, assessment results, which included medical information, test performances, neuroimaging results as well as clinical impressions, were weighed comprehensively by a team of neurologists to judge if the patients developed dementia. Dementia was diagnosed according to the American Psychiatric Association’s criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (17). The diagnosis of dementia required evidence of cognitive deficit on the neuropsychological test and interference of daily life. Dementia of Alzheimer’s type (DAT) was made according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA) (18). VaD was diagnosed according to the criteria of National Institute of Neurological Disorders and Stroke /Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINCDS/AIRENS) (19).

Statistical analysis was performed utilising SPSS® 10.0 software (Statistical Product and Service Solutions Inc., Chicago, IL, USA). Unadjusted statistical analyses were performed using chi-squared analysis for dichotomous results. Means of parameter data were compared with one-way ANOVA or t-test. The relationship between cognitive changes and plasma fibrinogen levels was estimated with linear regression. The cumulative risks of dementia by presence or absence of hyperfibrinogenaemia were estimated with the Kaplan–Meier analysis. The 2-year dementia conversion ratios in MCI patients with different fibrinogen levels were compared with log rank test.

Results

There were 185 patients were diagnosed as MCI and enrolled in the present study. Among them, 17 (9.2%) deceased, 15 (8.1%) lost to be follow and 68 (36.8%) developed dementia during 2-year follow-up. Baseline characteristics of the enrolled patients according to their progression to dementia during follow-up were showed in Table 1. Patients who developed dementia were older than those who did not at the time of MCI diagnosis (p < 0.05). No significant differences were detected between demented and non-demented patients for educational levels. Prevalences of hypertension, DM and hyperlipidaemia at baseline were much similar regardless whether they progressed to dementia in follow-up. No significant differences were detected concerning history of AF, CVD and smoking at baseline between demented and non-demented patients. Patients who
developed dementia had significantly lower MMSE scores at baseline compared with those who did not develop dementia. There were 48 (25.9%) patients defined with hyperfibrinogenaemia (plasma fibrinogen ≥3 g/l). Among the 185 MCI patients, 157 (84.9%) had CT scan and 128 (69.2%) had MRI scan.

The global cognitive function of MCI patients evaluated by MMSE declined significantly during the 2-year follow-up (22.0 ± 3.0 vs. 18.1 ± 5.8, p < 0.001). Mean of MMSE changes from baseline to the last assessment was 3.9 ± 4.7. MMSE scores of patients with hyperfibrinogenaemia decreased significantly more than those of patients with normal fibrinogen levels (5.4 ± 5.4 vs. 3.5 ± 4.8, p < 0.05). Utilising decrement during follow-up and baseline MMSE score, the percentage of cognitive decline was determined in each individual. The relationship between cognitive declines and plasma fibrinogen levels were estimated with linear regression (Figure 1). There was a slighter but significant positive correlativity between percentages of cognitive decline and plasma fibrinogen levels (R = 0.17, p < 0.05).

Impacts of hyperfibrinogenaemia on the transition of MCI to dementia, VaD and DAT were evaluated with the Kaplan–Meier analysis. Twenty (41.7%) patients with hyperfibrinogenaemia and 48 (35.0%) patients with normal plasma fibrinogen developed dementia during follow-up. Patients with hyperfibrinogenaemia had a higher dementia transitional ratio at the end of 2-year follow-up than patients with normal plasma fibrinogen (log rank test, p < 0.05, Figure 2). Twelve (25.0%) patients with hyperfibrinogenaemia and 29 (21.2%) patients with normal plasma fibrinogen developed DAT during follow-up. There was a trend that patients with hyperfibrinogenaemia had a higher DAT transitional ratio at the end of 2-year follow-up than patients with normal plasma fibrinogen, but the difference did not reach the significant level (log rank test, p = 0.61, Figure 2).

Table 1 Characteristics of participants when mild cognitive impairment was diagnosed

| Characteristics          | Demented during follow-up |
|--------------------------|---------------------------|
|                          | Yes (n = 68)              | No (n = 117) | p-value |
| Age, mean (SD), years    | 71.6 (7.2)                | 69.2 (7.5)  | 0.022   |
| Female gender, n (%)     | 16 (23.5)                 | 30 (25.6)   | 0.749   |
| Education, mean (SD), years | 4.7 (2.2)       | 5.2 (2.5)   | 0.186   |
| Hypertension, n (%)      | 34 (50.0)                 | 45 (38.5)   | 0.126   |
| DM, n (%)                | 23 (33.8)                 | 40 (34.2)   | 0.960   |
| Hyperlipidaemia, n (%)   | 25 (36.8)                 | 54 (46.2)   | 0.213   |
| History of AF, n (%)     | 9 (13.2)                  | 20 (17.1)   | 0.486   |
| History of CVD, n (%)    | 21 (30.9)                 | 31 (26.5)   | 0.522   |
| Smoking, n (%)           | 33 (48.5)                 | 56 (47.9)   | 0.930   |
| Alcohol intake, n (%)    | 27 (39.7)                 | 44 (37.6)   | 0.777   |
| MMSE score, mean (SD)    | 20.1 (2.8)                | 23.0 (2.7)  | <0.001  |

Non-parameters were compared with chi-squared test. Parameters were compared with independent t-test. AF, atrial fibrillation; CVD, cerebrovascular diseases; DM, diabetic mellitus; MMSE, Mini-Mental State Examination; SD, standard deviation.

Figure 1 Relationship between plasma fibrinogen level at the time of mild cognitive impairment diagnosis and cognitive decline during follow-up. Percentage of cognitive decline for an individual was calculated as Mini-Mental State Examination decrement during follow-up divided by baseline score, and then multiple 100%
Discussion

Based on a cohort of Chinese elderly patients with MCI, this study confirmed that plasma fibrinogen level is associated with cognitive decline and risk for dementia in MCI patients. Patients with higher levels of plasma fibrinogen had great cognitive decrements during follow-up. Hyperfibrinogenaemia increased the risk for dementia and VaD in MCI patients.

Mild cognitive impairment is a syndrome defined as cognitive decline greater than expected for an individual’s age and educational level but that does not interfere notably with activities of daily life (20). Some people with MCI may remain stable or return to normal over years, but more than half progress to dementia within 5 years (13). MCI was thus regarded as a risk state for dementia, and its identification could lead to secondary prevention by controlling modifiable risk factors (21,22). Aiming at probing the potential risk factors for MCI transition, this study assessed the influence of plasma fibrinogen level on the outcomes of MCI.

The present study observed an increased risk for VaD in MCI patients with hyperfibrinogenaemia. This result is supported by several previous studies which showed fibrinogen was associated with increased risk for ischaemic CVD (2,3,23,24). Many patients with ischaemic stroke had increased levels of plasma fibrinogen, and fibrinogen level was related to stroke severity and prognosis (25,26). High fibrinogen is associated with atheroma genesis and progression of atherosclerosis (27,28). These findings can explain the higher ratio of VaD in patients with hyperfibrinogenaemia by increasing the risk for CVD. On the other hand, hyperfibrinogenaemia has been correlated with white matter lesions (29), leukoaraiosis (30), silent infarction (31) and cerebral hypoperfusion (32,33), all of which were further related to cognitive decline and VaD (34,35). These cascade effects may put patients with hyperfibrinogenaemia at increased risk for VaD even in the absence of overt CVD. In a case–control study, Stott et al. (4) had showed raised levels of plasma fibrinogen in patients with ischaemic stroke and VaD.

A trend of increased risk for DAT in MCI patients with hyperfibrinogenaemia was detected in the present study, but the difference did not reach significant level. Relationship between plasma fibrinogen level and Alzheimer disease has been scarcely studies. The role of plasma fibrinogen in the pathogenesis of dementia is not known (9,36). In a cohort study, Gupta et al. (37) found that plasma fibrinogen levels were higher in patients with dementia than in control group but the values did not reach statistical significance. Borroni et al. (38) also failed to find a significant difference for plasma fibrinogen levels between patients with Alzheimer disease and age-matched control subjects. But recent published data from Rotterdam Study, which is a population-based prospective study with large number of subjects, indicated that high fibrinogen levels were associated with an increased risk of both VaD and Alzheimer disease (9). This study did not associate high plasma fibrinogen level with increased risk of DAT. 

Figure 2 Kaplan–Meier analysis evaluated transitional ratios to dementia (top), vascular dementia (middle) and dementia of Alzheimer’s type (bottom) in mild cognitive impairment patients with and without hyperfibrinogenaemia
result however should be considered with regarding to the relatively small sample size and short follow-up time.

Several drugs which can decrease plasma fibrinogen are clinically available in present time, such as ancord and batroxobin, which have been evaluated with favourable safety and efficacy and now have been widely used in treating acute ischaemic stroke (39,40). Considering the results of present study as well as other studies, a clinical trial assessing the feasibility of these drugs in delaying or preventing dementia, especially in MCI patients with hyperfibrinogenemia, is warranted.

There are several limitations in the present study which should be addressed. This is not a population-based study, which may harbour bias in patient selection. A predominant portion of the screened and enrolled patients in our study were male elderly patients. This disproportion of gender distribution may decrease the feasibility of generalising the results to other patient populations. Patients were screened and followed at 3–6 monthly intervals in this study. These relatively long intervals may generate a time lag between diagnosis and actual MCI or dementia onset.

**Conclusion**

In conclusion, plasma fibrinogen level may be predictive for cognitive decline and risk for dementia in MCI patients. Hyperfibrinogenemia may be associated with increased risk for dementia and VaD in MCI patients. Whether hyperfibrinogenemia is a causative factor or an epiphenomenon for cognitive decline in MCI patients needs further study.

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