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Research report

Serum haptoglobin in Chinese patients with Alzheimer's disease and mild cognitive impairment: A case-control study

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ABSTRACT

Background: Serum level of Haptoglobin (Hp) maybe associated with Alzheimer's disease (AD) and mild cognitive impairment (MCI).
Objective: To investigate associations between serum Hp and AD, as well as between Hp and MCI.
Methods: Serum levels of Hp were measured and analyzed for 51 patients with AD, 139 patients with MCI and their healthy controls matched with sex and age. All study subjects were from a survey among residents aged 60 years and over in a community located in the southwest suburb of Shanghai.
Results: Serum levels of Hp were observed significantly higher in AD and MCI cases than controls (both $p < 0.0001$). A significant positive correlation was found between Hp and Activities of Daily Living (ADL) score ($r_s = 0.430$, $p = 0.007$), as well as between Hp and Clinical Dementia Rating (CDR) score ($r_s = 0.359$, $p = 0.027$) in all AD patients. According to the receiver operating characteristic (ROC) curve analysis, the optimal cut-off point for Hp was found to be 67.50 μg/ml (sensitivity, 0.902; specificity, 0.745) in AD patients, and 44.76 μg/ml (sensitivity, 0.986; specificity, 0.403) in MCI patients.
Conclusion: Elevated serum levels of Hp were observed in AD and MCI patients than controls. In addition, Hp may correlate with the severity of AD.

1. Introduction

With the number and proportion of elderly increasing rapidly in the world, especially in China, dementia has become one of the main causes of disability and decreased quality of life.

AD, the most common cause of dementia among elderly (Cummings and Cole, 2002), is a progressive neurodegenerative disorder that gradually robs the patient of cognitive function and eventually causes death (Sillen et al., 2008). Key pathological hallmarks of the disease are deposition of senile plaques resulting from the extracellular deposit of amyloid-β(Aβ) protein and the intracellular neurofibrillary tangles caused by the aggregation of hyper-phosphorylated tau protein (Agopian and Guo, 2012; Selkoe, 2001; Claeysen et al., 2012).

MCI is proposed to be an early phase of cognitive decline that precedes dementia (Ganguli et al., 2004; Morris et al., 2001), and a pathology-based condition with a high rate of progression to AD (Panza et al., 2005). One longitudinal study showed that people with MCI were 6.7 times more likely to develop AD than cognitively normal individuals (Boyle et al., 2006). Rates of annual conversion from MCI to dementia are reported to be 56% in a follow-up period of 4 years (Rountree et al., 2007). Thus, MCI may be a useful model as a prodromal phase of AD to test putative biomarkers for their efficacy in early disease detection (Song et al., 2009).

Though the etiology of AD is still not clearly known, the impact of inflammation on the etiopathogenesis of AD has been comprehensively studied (Rogers et al., 1996; Ferretti et al., 2012; Trollor et al., 2010). Haptoglobin (Hp), as an acute-phase protein produced by liver, exhibits several functional properties including antioxidant and anti-inflammatory activities (Sadrzadeh and Bozorgmehr, 2004; Arredouani et al., 2005). Several studies have observed an elevated Hp level among AD patients, compared to healthy controls (Song et al., 2015; Zhang et al., 2004; German et al., 2007a). But it still remains to be elucidated whether it represents a risk factor for the initiation of AD and if it can be utilized as a biomarker for MCI and AD.

The current study aimed at analyzing associations between serum Hp level and AD or MCI, investigating correlations between Hp and

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relevant parameters, and exploring the feasibility of Hp as a biomarker for AD.

2. Materials and methods

2.1. Study subjects

Data of our study were obtained from a population-based epidemiological study on cognitive impairment and dementia among elderly started from 2011 (Cheng et al., 2014). Subjects in the study were local residents aged 60 years and over from a community of Sheshan town in Songjiang district, located in the Southwest suburb of Shanghai. Face-to-face interviews, data collection and relevant investigations were conducted by trained medical staff.

Clinical diagnoses of probable AD and MCI were made by senior neurologists according to the revised diagnostic guidelines for AD from the National Institute on Aging-Alzheimer's Association criteria (McKhann et al., 2011) and the Petersen criteria (Petersen et al., 2001). We used the Chinese version of Mini-Mental Status Examination (C-MMSE), which was initially modified by Katzman et al. (1998), to identify subjects with cognitive impairment. Activities of daily living (ADL), the Chinese version of the Cornell Scale for Depression in Dementia (CSDD), the Clinical Dementia Rating (CDR) Scale and the Hachinski Ischemic Scale were also administered to all subjects with cognitive impairment to measure the severity of dementia and to exclude subjects with dementia not likely due to AD. The ADL scale used in our study was originated from Lawton and Brody (Lawton and Brody, 1969), including 14 items of functional assessment. However, we made the scores as following: 1. Able to complete the task independently and without difficulty; 2. Can complete the task, but with some difficulty; 3. Need some help from other people to complete the task; and 4. Unable to complete the task at all.

Subjects of the control group were healthy residents enrolled from the same community and matched with AD or MCI cases, respectively, for sex and age (± 3 years). Subjects with recent or ongoing infections, malignant diseases and other serious illnesses, or taking corticosteroids or immunosuppressive drugs, were excluded from the study. In addition, our cases were identified from a population survey in the community and none of them had the treatment for cognitive impairment with acetylcholinesterase inhibitors.

This study was approved by the Ethics Committee of the Ruijin Hospital, Shanghai Jiao Tong University. Informed consent was obtained from each participant.

2.2. Haptoglobin detections

Venous blood samples (3–5 ml for each sample) were collected from all cases and controls. The blood samples were centrifuged for 10 min at 3000 r/min at 4 °C. The serum was subsequently removed and stored at −80 °C until the biochemical assays. Serum levels of Hp were measured in all subjects on the same day by Human Haptoglobin (Hp) ELISA Kit (Shanghai Jianglai Industrial Limited By Share Ltd, China). Purified Human Hp antibody was used to coat microtiter plate wells and make solid-phase antibody. Then Hp was added into wells. After Hp combined with labeled Hp antibody and became antibody-antigen-enzyme-antibody complex, it was washed completely and TMB substrate solution was added. TMB substrate becomes blue when being enzyme-catalyzed. Reaction was terminated by the addition of a sulfuric acid solution and the color change is measured spectrophotometrically at a wavelength of 450 nm. The concentration of Hp in the samples is then determined by comparing the O.D. of the samples to the standard curve. The minimum detectable concentration was 10 μg/ml.

2.3. Statistical analysis

All analyses were performed using SPSS statistical software, version 22.0.

Student's *t*-test was applied for continuous variables follow a normal distribution, and comparisons of categorical variables were made using the Chi-square tests. Since serum concentration of Hp did not follow a Gaussian distribution, the nonparametric Wilcoxon signed rank sum test (related samples) was used to compare the concentrations between patients and their corresponding controls, and Kruskal-Wallis test (independent samples) was applied to compare the level of Hp among three groups. The Spearsman rank correlation test was used to ascertain associations between the concentration of Hp and each score of C-MMSE, ADL, CSDD and CDR. A receiver operating characteristic (ROC) curve was applied to analyze the Hp level specific to the AD and MCI groups. In addition, the area under the ROC curve (AUC), cut-off value determined by the maximum Youden index (Sensitivity + Specificity − 1), sensitivity and specificity were calculated.

Two-tailed p values less than 0.05 were considered statistically significant.

3. Results

3.1. Demographic characteristics

In our study, there were 51 AD patients and 51 controls, as well as 139 MCI patients and 139 controls. Demographic characteristics of the cases and controls are summarized in Table 1. There were no significant differences in age or gender distribution between cases and controls.

The AD group had a C-MMSE score indicating severe cognitive deterioration (15.8 ± 5.2), whereas MCI subjects had mild cognitive impairment (20.7 ± 5.3). C-MMSE scores for both AD and MCI cases

Table 1
Comparisons of characteristics between cases and controls for AD and MCI.

Characteristic	AD			MCI		
	Cases	Controls	p	Cases	Controls	p
Number of subjects	51	51	–	139	139	–
Males, n (%)	15 (29.4)	15 (29.4)	–	44 (31.7)	44 (31.7)	–
Mean age (SD), years	79.1 (6.1)	78.8 (5.5)	0.760	75.0 (6.3)	75.3 (6.7)	0.727
Smoking, n (%)	4 (7.8)	5 (9.8)	0.530	20 (14.4)	19 (13.7)	0.985
Alcohol drinking, n (%)	1 (2.0)	4 (7.8)	0.203	15 (10.8)	12 (8.6)	0.831
Education level n (%)			0.006			< 0.0001
Without formal education (< 1 year)	30 (58.8)	20 (39.2)		2 (1.4)	35 (25.2)	
Primary school (1–6 years)	13 (25.5)	27 (52.9)		128 (92.1)	88 (63.3)	
Middle school or higher (> 6 years)	0 (0.0)	4 (7.8)		9 (6.5)	16 (11.5)	
C-MMSE score, mean (SD)	15.8 (5.2)	22.2 (3.7)	< **0.0001**	20.7 (5.3)	23.4 (3.8)	< **0.0001**

AD, Alzheimer's disease; MCI, Mild Cognitive Impairment; C-MMSE, Chinese version of Mini-Mental State Examination.
P values in bold indicate statistical significance.

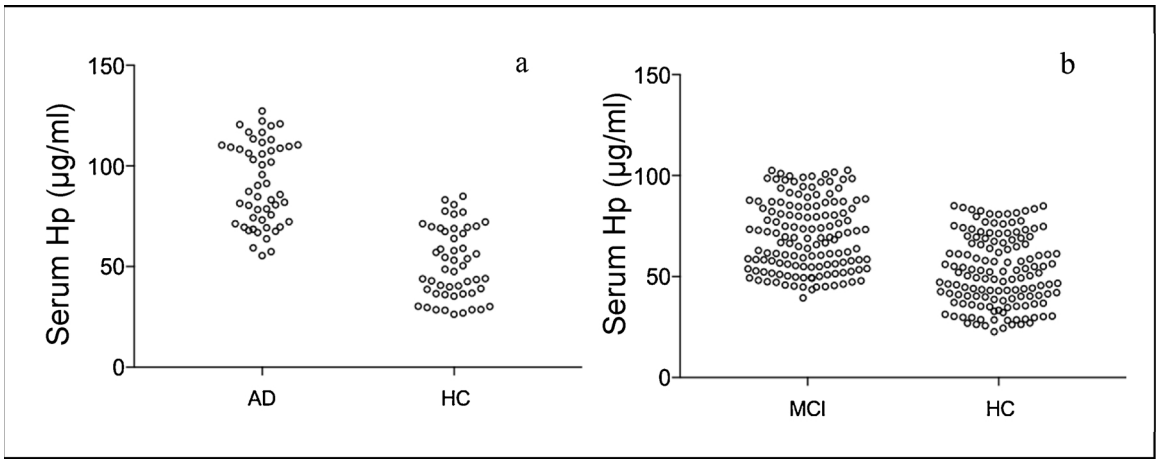

Fig. 1. Serum level of haptoglobin (Hp) in AD and MCI cases, compared to their healthy controls (HC).

were significantly lower than their controls (22.2 ± 3.7 and 23.4 ± 3.8, both $p < 0.0001$), respectively.

3.2. Serum level of haptoglobin

Serum concentrations of Hp were observed significantly higher ($p < 0.0001$) in AD and MCI cases than their controls (Fig. 1). When analyzed by sex, significantly higher concentrations were found in both male and female patients compared with healthy controls ($p < 0.001$) (Table 2).

3.3. Associations between haptoglobin and relevant parameters

A significant positive correlation was found between Hp level and ADL score ($r_s = 0.430$, $p = 0.007$) in all AD patients (Fig. 2), and a similar positive correlation was also observed between Hp level and CDR score ($r_s = 0.359$, $p = 0.027$). While a negative correlation was identified between Hp level and C-MMSE score only in female AD patients ($r_s = -0.346$, $p = 0.045$).

In addition, no statistically significant correlations between Hp level and relevant parameters were observed in MCI cases (Table 3).

3.4. ROC curve analysis

The usefulness of the serum Hp level for detecting AD and MCI was assessed by the ROC curve analysis. For AD, the AUC was 0.921 ($p < 0.001$, 95% CI = 0.873–0.969), at an optimal cut-off of 67.50 μg/ml, the sensitivity of the Hp test was 0.902 with respect to the AD patients, and the specificity was 0.745 with respect to the controls. In the case of MCI versus controls, the AUC was 0.758 ($p < 0.001$, 95% CI = 0.703–0.813), with a cut-off value of 44.76 (sensitivity, 0.986; specificity, 0.403) (Fig. 3).

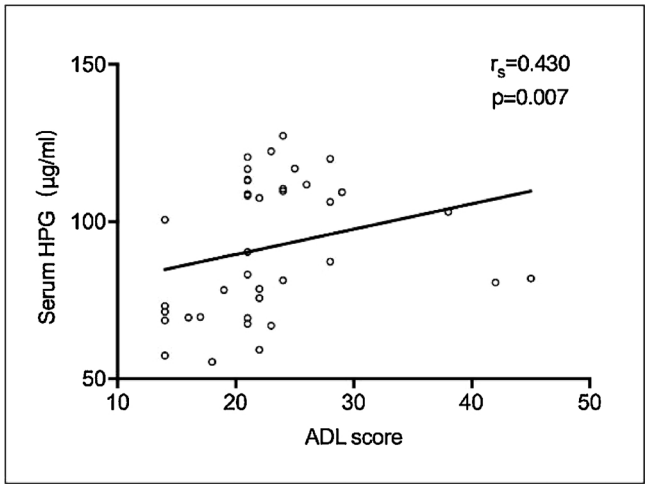

Fig. 2. Correlation between serum Hp and ADL score in all AD patients.

4. Discussion

AD is a progressive dementing disorder, which is usually preceded by a prodromal phase, amnestic MCI. Since a definite diagnosis of AD can only be made by postmortem neuropathological examinations, the identification of AD biomarkers with less invasive and more sensitive diagnosis is urgently needed. After Akiyama, et al. (2000) first reported that AD brains displayed characteristics of inflammatory processes, many efforts have been made to look for biomarkers regarding the

Table 2
Serum levels of haptoglobin (Hp) in AD and MCI cases, compared with their controls.

Serum Hp, μg/ml	Males			Females			Total		
	Cases	Controls	P	Cases	Controls	p	Cases	Controls	p
AD, n	15	15		36	36		51	51	
Mean (SD)	86.0 (18.7)	57.7 (15.6)		93.3 (21.0)	48.8 (17.6)		91.1 (20.5)	51.4 (17.4)	
Median	81.4	58.7	**0.003**	103.2	43.9	**< 0.0001**	87.3	48.7	**< 0.0001**
Interquartile range	73.2–10.6	40.5–72.2		71.6–111.4	31.6–67.2		72.3–109.7	36.5–69.0	
MCI, n	44	44		95	95		139	139	
Mean (SD)	74.0(17.5)	55.0 (17.8)		68.8 (17.3)	51.3 (17.1)		70.4 (17.5)	52.5 (17.3)	
Median	73.3	54.8	**< 0.0001**	66.8	48.7	**< 0.0001**	69.5	50.5	**< 0.0001**
Interquartile range	58.8–89.1	39.4–71.1		54.0–83.7	37.2–66.5		55.0–85.3	38.7–67.5	

P values in bold indicate statistical significance.

Table 3
Correlations between Hp and various parameters for AD and MCI cases.

Parameter	Males		Females		Total	
	r_s[a]	p	r_s[a]	p	r_s[a]	p
AD, n	15		36		51	
Hp vs. C-MMSE	0.014	0.964	−0.346	**0.045**	−0.261	0.076
Hp vs. ADL	0.284	0.371	0.387	0.044	0.430	**0.007**
Hp vs. CSDD	−0.315	0.064	0.179	0.381	−0.032	0.851
Hp vs. CDR	0.215	0.502	0.344	0.085	0.359	**0.027**
MCI, n	44		95		139	
Hp vs. C-MMSE	−0.061	0.695	0.105	0.321	0.067	0.439
Hp vs. ADL	0.203	0.198	−0.141	0.188	−0.055	0.531
Hp vs. CSDD	−0.083	0.603	−0.116	0.281	−0.120	0.172
Hp vs. CDR	0.038	0.811	−0.203	0.054	−0.144	0.099

P values in bold indicate statistical significance.
[a] Spearman correlation coefficient.

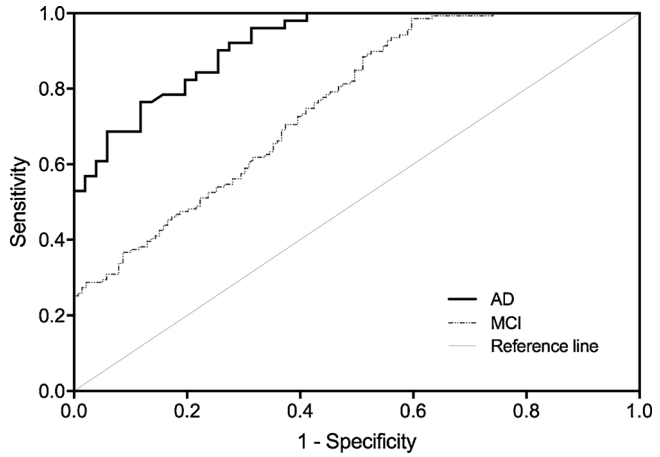

Fig. 3. Receiver operating characteristic (ROC) curves of the serum haptoglobin (Hp) level for predicting Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI).

inflammation mechanism.

Cocciolo et al. (2012) found that a trend toward decreased expression was evident for apolipoprotein A1, serotransferrin, b2-glycoprotein, Hp b chain, and fibrinogen a chain, whereas A2M increased in AD patients compared to controls. These proteins seem to be significantly differentially expressed only in AD patients, whereas no significant variations were evidenced in MCI cases. However, decreased expressions of fibrinogen a chain and Hp b chain were observed in MCI cases, compared with controls.

Hp, an acute-phase protein that binds extracorpuscular free hemoglobin, functioning as an antioxidant as well as a potent immunosuppressor of lymphocyte function and modulates the helper T-cell type 1 and type 2 (Th1/Th2) balance within the body (Sadrzadeh and Bozorgmehr, 2004). It is usually found to be induced and released in the periphery blood as a marker of inflammation (Bowman and Kurosky, 1982). A study used novel mass spectrometry (MS)-based techniques found elevated Hp in AD patients compared to controls (German et al., 2007b). Similar results were obtained by Wang et al. (2015) with utilizing magnetic nanobeads by capillary electrophoretic immunoassay with laser-induced florenscence detection. In accordance with previous reports, the elevated serum Hp level detected in AD and MCI cases in the current study may reflect an increase of inflammatory response, indicating the chronic inflammation at brain levels. In addition, our study showed a further increased Hp level in AD vs MCI, suggesting that the progressive increase could be related to the progression of the disease.

In our result, the serum Hp level was positively correlated with the ADL and CDR scores in AD patients, and negatively correlated with the C-MMSE score in female AD patients. In 2006, Marshall, et al., reported a significantly positive correlation between ADL score and a greater overall pathologic burden by practicing brain autopsy on twenty-two patients with definite AD (Marshall et al., 2006), demonstrating that functional status, reflected by measures of ADL, deteriorates as AD progresses (higher scores indicate severer disability). CDR is a clinical dementia staging instrument for assessing an individual's cognitive and functional performance (Morris, 1993). These two scores, as well as C-MMSE, may indicate the severity of AD to a large extent. Hence, our results may be interpreted that the higher the level of Hp, the severer the AD can be.

Previous reports documented that Hp has the ability to both suppress amyloid fibril formation and protect neuroblastoma cells from Aβ-induced toxicity by forming stable and soluble high molecular weight complexes with misfolded proteins (Yerbury et al., 2009; Yerbury and Wilson, 2010). Hp, along with other extracellular chapterones such as clusterin, play an important role as an element of a system of protein folding quality control in defending human body against Aβ toxicity and inappropriate aggregation of some proteins, which can be either amorphous or amyloid in character (Yerbury and Wilson, 2010; Yerbury et al., 2005). Under a pathologic circumstance when this system of defense is overwhelmed, it may be less able to protect cells from Aβ-induced toxicity and less efficient to promote Aβ1-42 uptake in macrophage-like cells. As a result, amyloid deposits aggregate and lead to the pathogenesis of impaired cognitive function. At the same time, excessive unbinding chapterones may be released into the peripheral blood, resulting in an increased serum Hp level.

Despite significantly increased serum Hp levels were observed in AD and MCI cases from our study, it is far to take the serum Hp level as an AD-specific biomarker, as our result failed to fully meet the current consensus criteria proposed by the National Institute on Aging (NIA) (Frank et al., 2003). In our study, Hp had a relatively high sensitivity (> 90%) and a relatively low specificity (< 75%) for identifying patients with AD. This may be related to our small sample size, especially the scant of male cases, which is a limitation for the power of our results. In addition, whether biomarkers with different pathophysiological backgrounds can give an additive prognostic value for AD and MCI remains to be established. Therefore, it should be cautious to evaluate and interpret our results in investigating the pathogenesis of AD and disease progression, and exploring the potential to develop disease-modifying treatments for AD based on modulating peripheral level of Hp.

In summary, significantly higher serum levels of Hp were observed in AD and MCI cases. In addition, the serum level of Hp may be correlated to the severity of AD. However, more studies with larger sample sizes, especially longitudinal investigations, are needed, in order to fully elucidate the disease pathogenesis and identify plasma biomarkers for AD and MCI.

Conflict of interest

The authors have no conflict of interest to report.

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