Changes in Serum Amyloid A (SAA) and 8-OHdG in Patients with Senile Early Cognitive Impairment

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: This study assessed variations in SAA and 8-OHdG in patients with senile early cognitive impairment (CI).

Material/Methods: The subjects were divided into 3 groups: 121 patients with mild cognitive impairment (MCI), 131 with Alzheimer's disease (AD), and 100 healthy persons that underwent physical examinations during the same period (Control). These groups were evaluated by MMSE and MoCA, and the SAA and 8-OHdG levels in these groups were tested using ELISA sandwich technique.

Results: The AD group had significantly higher TG and ApoB levels, followed by the MCI and Control groups, respectively (P<0.05). The MCI group had the highest HDL-C level significantly, while the Control group had the lowest (P<0.05). The Control (normal) group had significantly higher MoCA and MMSE scores, followed by the MCI group and the AD group (P<0.05). The Control (normal) group had significantly lower SAA and 8-OHdG levels, followed by the MCI group and the AD group (P<0.05). The MoCA and MMSE scores and serum 8-OHdG and serum SAA levels in the 3 groups were negatively correlated, but their SAA and 8-OHdG levels were positively correlated.

Conclusions: SAA and 8-OHdG in the MCI and AD groups were highly expressed but had an inverse correlation with cognitive function scores (hereafter referred to as CFs scores). They can also be applied as test indicators of MCI. We also detected an apparent link between SAA and 8-OHdG.

MeSH Keywords: **Alzheimer Disease • Amyloid beta-Peptides • Serum Amyloid A Protein**

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Background

With economic advances and population aging in China, the incidence of CI, particularly that of MCI, in the elderly is continuously increasing [1], with an incidence rate of approximately 3–42% [2]. MCI represents a status between normal aging and dementia and may develop into AD at a rate between 2% and 31% [3,4]. Further, MCI is an irreversible process that dramatically affects patients' health status and quality of life (QOL) and also imposes a heavy burden on family and society [5]. Nonetheless, proper measures can prevent and delay the progression, and preventing the progression from MCI to dementia is immensely important [6]. Therefore, early identification of cognitive impairment and adoption of corresponding actions are necessary.

SAA, which is a highly sensitive protein produced by the body in response to acute reactions [7], functions as a marker in diagnosis and prognosis of numerous diseases. SAA is created in the liver and exhibits a relatively weak tolerance to inflammatory reactions in the body; in fact, it sharply increases in acute and chronic inflammation [8]. SAA is also associated with cognitive impairment [9]. Meanwhile, 8-OHdG, which is an oxidized derivative of guanine base, is used to evaluate the oxidative stress level [10]. The increase of urine 8-OHdG is significantly correlated with acute ischemic stroke [11]. However, few studies have been conducted to verify the possible role of SAA and 8-OHdG as test factors for early cognitive impairment and their correlation in elderly patients with MCI.

The present study focused on the expression of SAA and 8-OHdG in patients with senile early cognitive impairment, and assessed the correlation among SAA, 8-OHdG, and cognitive functions and between SAA and 8-OHdG.

Material and Methods

General materials

The MCI group included 112 patients admitted to our hospital due to early CI, consisting of 48 males and 73 females, with an average age of 67.21±1.89 years and an average BMI of 23.12±3.78 kg/m^2. Among them, 38 concurrently had diabetes and 65 had hypertension. The AD group included 113 patients with AD, consisting of 44 men and 69 women, with a mean age of 67.31±1.76 years, and a mean BMI of 24.01±4.04 kg/m^2. Among these, 32 concurrently had diabetes and 57 had hypertension. Meanwhile, 100 healthy persons who underwent physical examinations in our hospital were enrolled in the Control group, consisting of 37 males and 63 females with an average age of 67.48±1.83 years and an average BMI of 23.97±3.89 kg/m^2. Among them, 33 patients were concurrently suffering from diabetes and 53 from hypertension.

We enrolled patients (60~85 years) with detailed clinical data and excellent compliance and no health-risk behaviors, with similar educational status above primary school, with the provision that they were accompanied by family members upon admission.

We excluded patients with a previous history of mental illness or cognitive impairment, craniocerebral trauma, excessive drinking or drug dependence, severe organic lesions, or treated with antidepressant drugs or drugs to improve cognition.

The study was approved by the Ethics Committee of Sichuan Provincial People's Hospital, and all subjects signed the informed consent form.

Serum test

We extracted 3 ml of blood from the veins of patients in the 3 groups after fasting and then stored the blood in vacuum blood collection tubes. Thereafter, these blood samples were centrifuged at 3000 rpm for 5 min at 4°C and stored them frozen at –80°C for future use. We measured the levels of folic acid, B12, TG, TC, ApoA1, ApoB, HDL-C, and LDL-C using the Catalyst One automated biochemical analyzer (Silksmodel Biotechnology Co., Beijing, China). SAA and 8-OHdG levels were determined using a BS-1101 ELISA analyzer (Linmao Technology Co., Beijing, China) by ELISA sandwich technique. Test kits of SAA and 8-OHdG were obtained from Shanghai Zhenyu Biotechnology Co. (product no. CSB-E12058h-1 and CEA660Ge-1, respectively). Control wells were set up following the same steps but without the addition of ELISA reagent and sample. Some wells were filled with 10 µl of sample and 40 µl of diluents, and others were filled with 50 µl of Control agent of different concentrations. To all wells, except the control wells, we added 50 µl of ELISA reagent and cultivated them at 37°C for 60 min before washing. Then, we added 50 µl of substrates A and B individually to each well and kept them at 37°C away from light for 15 min to develop colors. We then added 50 µl of stop buffer into each well, but this was set to zero in the control wells. The OD at 450 nm in 25 min was determined to calculate serum SAA and 8-OHdG contents.

Observation indicators

The cognitive functions and IQ of patients from the AD, MCI, and Control groups were assessed by Montreal cognitive assessment (MoCA) [12] and (Mini-Mental state examination (MMSE) [13], with 30 being the highest possible score. Higher scores indicate better cognitive functions.

Table 1. Comparison of general clinical materials among the 3 groups (x±SD)/n [%].

	MCI group (n=121)	AD group (n=113)	Control group (n=100)	F/χ^2	P
Sex				0.17	0.92
M	48 (39.67)	44 (38.94)	37 (37.00)		
F	73 (60.33)	69 (61.06)	63 (63.00)		
Mean age (years)	67.21±1.89	67.31±1.76	67.48±1.83	0.60	0.55
BMI (kg/m²)	23.12±3.78	24.01±4.04	23.97±3.89	1.93	0.15
History of smoking				3.31	0.19
Y	52 (42.98)	49 (43.36)	54 (54.00)		
N	69 (57.02)	64 (56.64)	46 (46.00)		
Year of education (years)	8.97±4.01	9.21±3.77	9.31±3.27	0.25	0.78
Complications					
Diabetes	38 (31.40)	32 (28.32)	33 (33.00)	0.60	0.74
Hypertension	65 (53.72)	57 (50.44)	53 (53.00)	0.35	0.84

Table 2. Comparison of nutritional markers and blood fat levels in the 3 groups (x±SD).

	MCI group (n=121)	AD group (n=113)	Control group (n=100)	F/χ^2	P
Folic acid (ng/ml)	8.17±4.31	7.98±4.21	68.97±3.76	1.71	0.18
B12 (pg/ml)	582.13±376.91	498.47±234.12*#	641.12±361.22	5.12	0.01
TG (mmol/L)	1.26±0.61	1.34±0.76	1.18±0.41	1.79	0.17
TC (mmol/L)	4.97±1.04*	5.43±1.12*#	4.43±0.98	24.03	<0.05
ApoA1 (mmol/L)	1.37±0.71	1.45±0.89	1.27±0.45	1.68	0.19
ApoB (mmol/L)	1.34±0.51*	1.52±0.63*#	1.02±0.34	25.64	<0.05
HDL-C (mmol/L)	1.67±0.66*	1.31±0.58*#	2.01±0.95	24.07	<0.05
LDL-C (mmol/L)	2.78±1.19	2.92±1.27	2.61±1.21	1.70	0.18

* P<0.05 as compared with the Control group; # P<0.05 as compared with the MCI group.

The nutritional markers and blood fat levels and the SAA and 8-OHdG levels in the AD, MCI, and Control groups were observed and compared. The correlations between the SAA and 8-OHdG levels and MoCA and MMSE scores in all 3 groups were also analyzed.

Statistical analysis

Statistical analysis was conducted using SPSS 2.0 (IBM Corp, Armonk, NY, USA). Nominal data were expressed as [n(%)] and subjected to chi-squared testing to assess between-group differences. Measurement data were expressed in $\bar{\chi}$±SD, designated as F, and subjected to independent-samples *t* test between groups or LSD-*t* in the same group for post-analysis. Moreover, bivariate correlation was analyzed using Pearson correlation coefficient. P<0.05 indicates a statistically significant difference.

## Results

Comparison of general clinical materials

We compared the general clinical materials of patients in the 3 groups according to sex, age, BMI, history of smoking, year of education, and complications (P>0.05, Table 1).

Differences in nutritional markers (NMs) and blood fat levels in the 3 groups

No marked differences in folacin, TG, ApoA1, or LDL-C levels were detected (P>0.05), and the AD group had the lowest B_{12} level (P<0.05). The AD group had the highest TC and ApoB levels, and the Control group had the lowest (P<0.05). The MCI group had the highest HDL-C level and the Control group had the lowest level (P<0.05). Results are presented in Table 2.
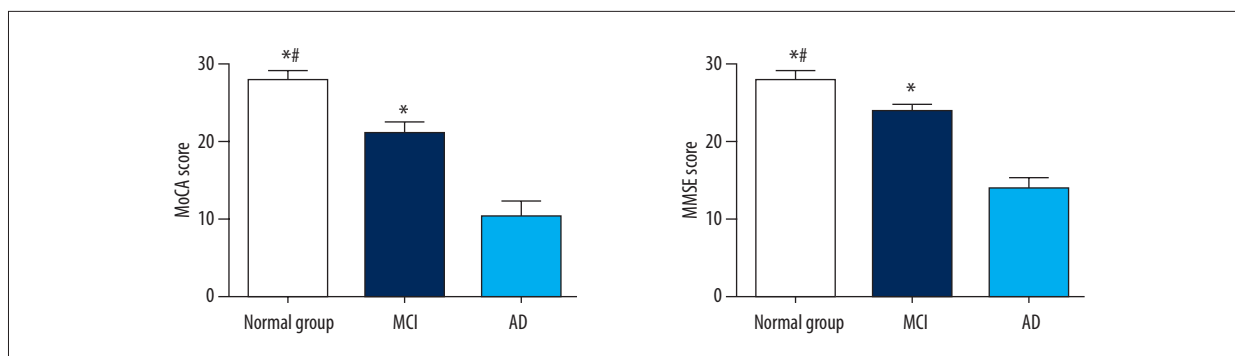
Figure 1. Comparison of the scores of cognitive functions among the 3 groups. The Control (normal) group had the highest MoCA and MMSE scores, followed by the MCI group and then the AD group (P<0.05).
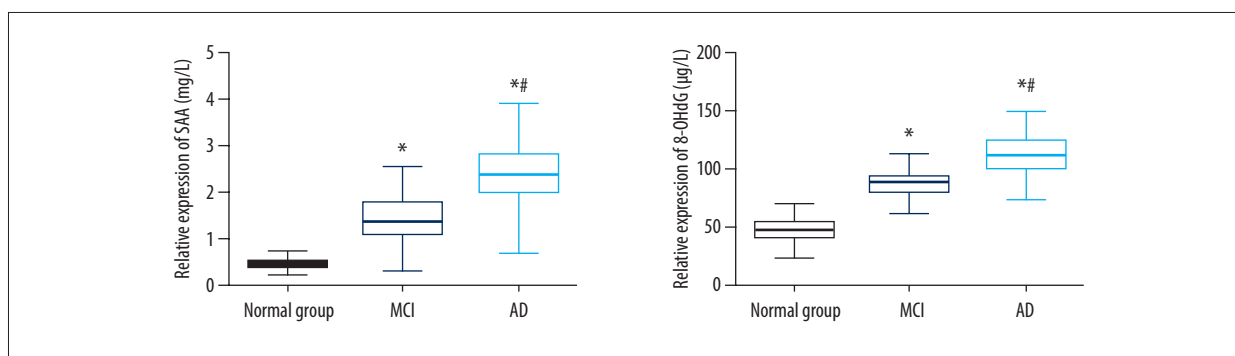
Figure 2. Comparison of SAA and 8-OHdG among the 3 groups. The Control (normal) group had the lowest SAA and 8-OHdG levels, followed by the MCI group and then the AD group (P<0.05).

Comparison of cognitive function scores among the 3 groups

The MoCA and MMSE scores of the 3 groups were statistically analyzed. We found that the Control group had the highest scores and the AD group had the lowest scores (P<0.05, Figure 1).

SAA and 8-OHdG levels

The SAA and 8-OHdG levels in the 3 groups were investigated and the results showed that the Control and AD groups had the lowest and highest levels, respectively (P<0.05, Figure 2).

Relationship between SAA and 8-OHdG levels and CFs scores

Relationship between SAA and 8-OHdG levels and MoCA scores in the 3 groups

Pearson analysis showed an obvious inverse relationship between MoCA score and SAA level in all 3 groups (r=–0.6481, –0.7572, –0.7724; P<0.05) and between MoCA score and serum 8-OHdG level (r=–0.6078, –0.7925, –0.6865; P<0.05, Figure 3).

Relationship between SAA and 8-OHdG levels and MMSE scores in the 3 groups

Pearson analysis showed a marked inverse relationship between MMSE score and SAA level in all 3 groups (r=–0.7097, –0.7441, –0.7591; P<0.05) and between the MMSE score and serum 8-OHdG level (r=–0.5806, –0.7826, –0.6650; P<0.05, Figure 4).

Correlation between SAA and 8-OHdG levels in the 3 groups

Pearson analysis indicated a significant negative correlation in the 3 groups between SAA and 8-OHdG levels (r=0.6679, 0.7774, 0.6778; P<0.05, Figure 5).

Discussion

As China emerges as an aging society, the mental status and QOL of the elderly population have become a serious concern. Patients with MCI will experience deficiencies in self-management [14]. Clinically, MMSE and MoCA are extensively applied to evaluate cognitive impairment [15]. To date, various factors related to MCI have been found. These factors include the systematic disease caused by an immune dysfunction or metabolic disorder, mental illness and depression, and
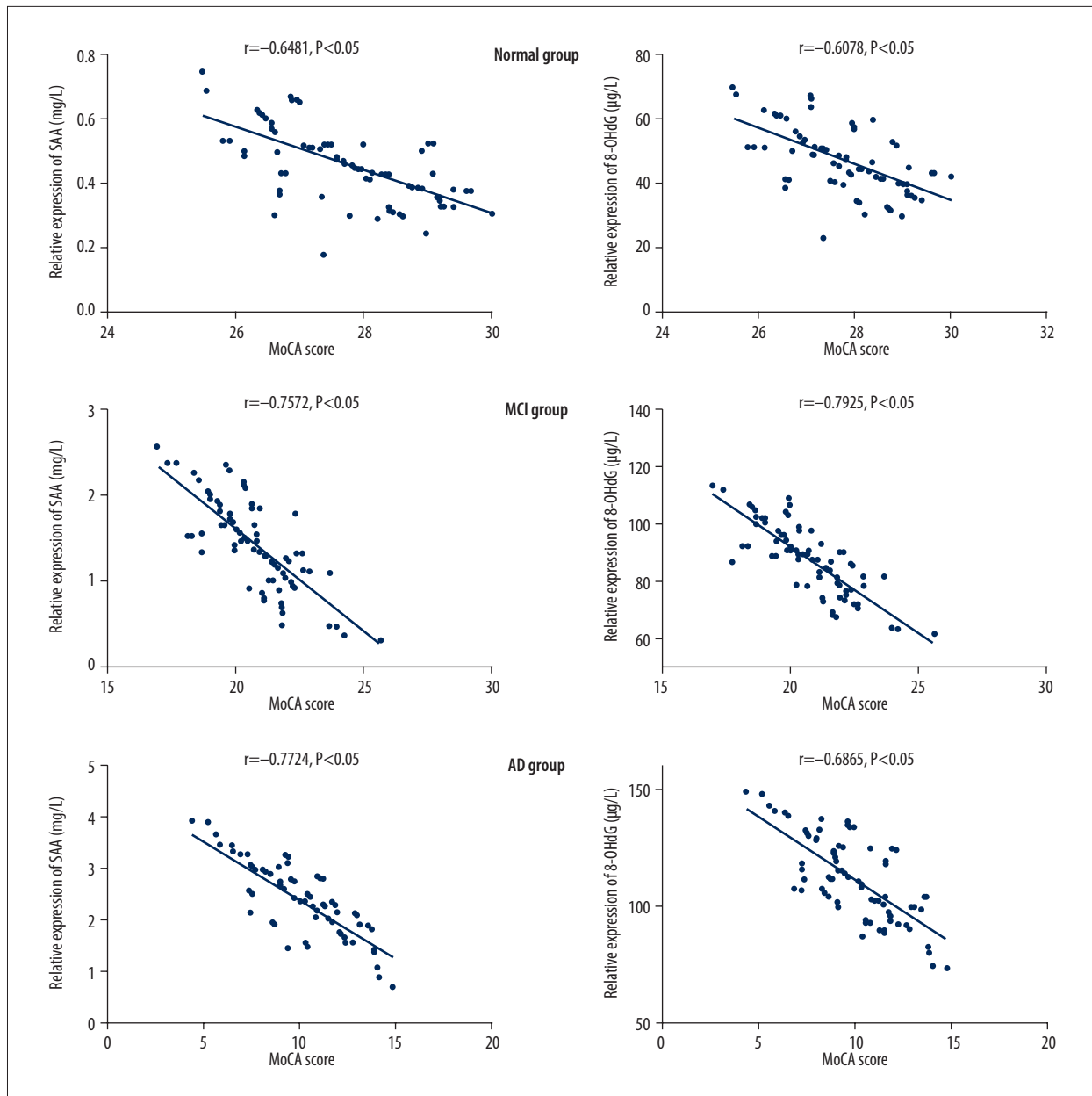
Figure 3. Relationship among MoCA Scores, SAA level, and 8-OHdG level in 3 groups. Pearson analysis displayed a significant inverse relationship between MoCA score and SAA level (r=−0.6481, −0.7572, −0.7724; P<0.05) and between the MoCA score and serum 8-OHdG level (r=−0.6078, −0.7925, −0.6865; P<0.05) in the 3 groups.

damaged brain tissue caused by trauma or vascular lesion, all resulting in abnormal CNS. As an early manifestation of AD, senile MCI requires complicated clinical scoring and tests to differentiate it from AD, a process with considerable subjectivity and increased difficulties in case of similar behavioral expressions [16,17]. Therefore, early identification and treatment of MCI have important effects in delaying MCI, improving patient QOL, and reducing progression to AD.

SAA may aggregate abnormally under the stimulation of chronic cerebral inflammation and change the morphology of microglia via a series of pathways by increasing its activity to induce the abnormal expression of interleukin and TNF, thereby resulting in brain damage [18]. SAA also inhibits the counter-transport of cholesterol and activity of transferase, reduces the HDL level, affects the body's lipid metabolism, and worsens the damage of brain tissues [19]. Furthermore, the metabolism of SAA can cause a synergistic action with MCP-1, which accelerates the progression of brain tissue damage [20]. 8-OHdG
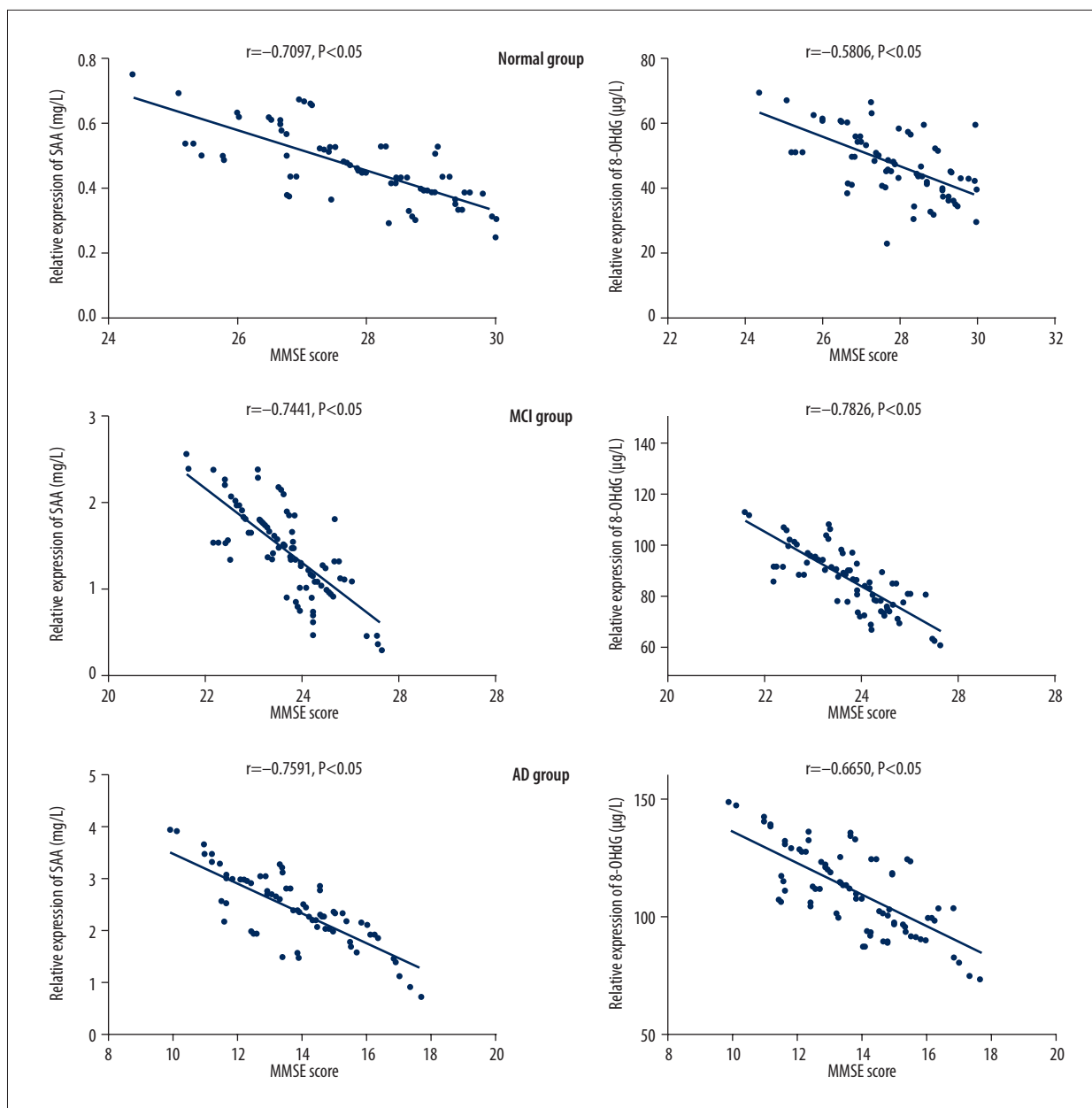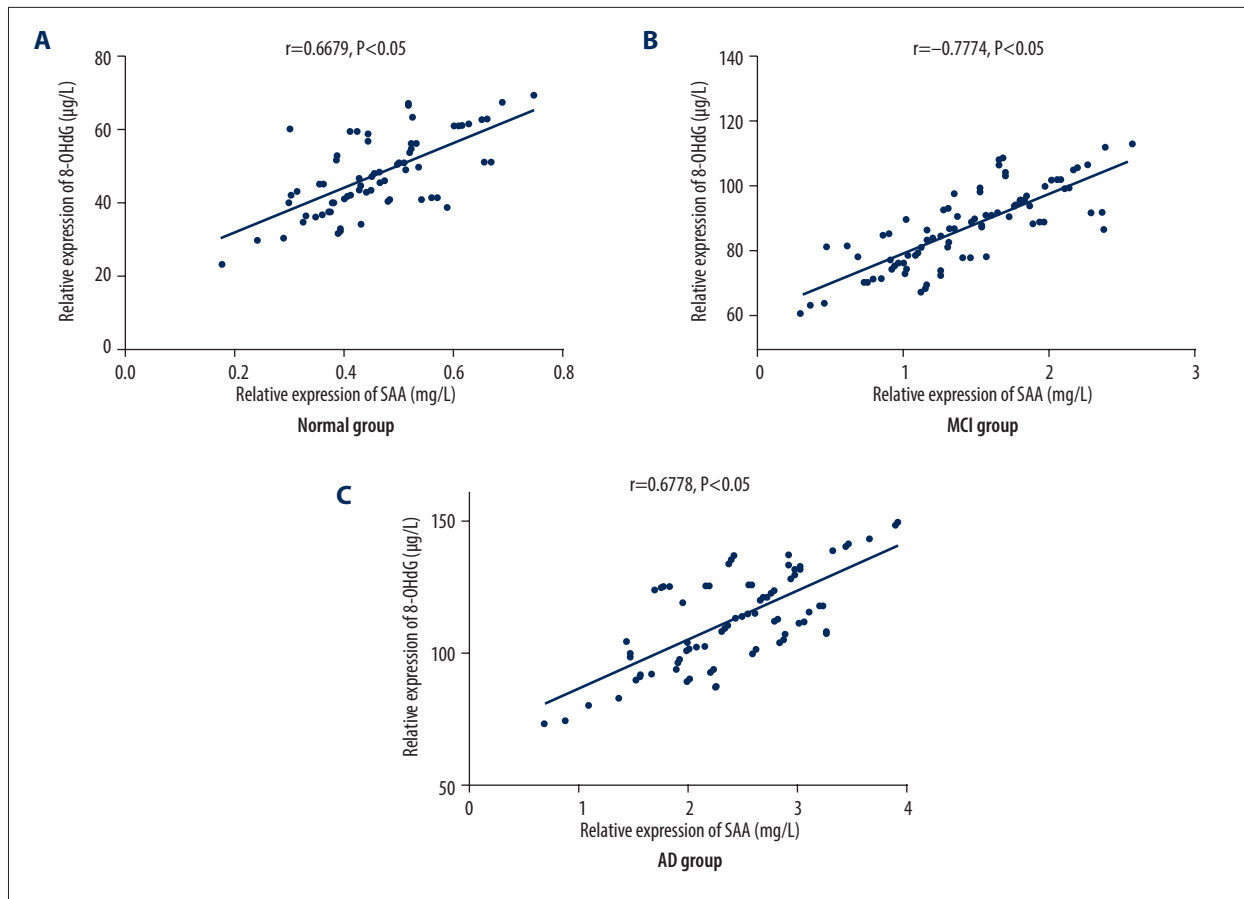
Figure 4. Correlation between serum SAA and 8-OHdG levels and MMSE scores in the 3 groups. Pearson analysis indicated a significant negative correlation between MMSE score and SAA level (r=−0.7097, −0.7441, −0.7591; P<0.05) and between the MMSE score and serum 8-OHdG level (r=−0.5806, −0.7826, −0.6650; P<0.05) in the 3 groups.

is a new indicator used to assess the oxidative damage and oxidation state of DNA [10]. 8-OHdG is an oxidized derivative of deoxyguanosine and is one of the major products of DNA oxidation; it is produced by attacking the carbon atom at position 8 in the guanine base of the DNA molecule with singlet oxygen and hydroxy radical. Then, it separates from the DNA chain via various processes, such as nucleotidyl excision and base excision repair with the help of 8-oxoguanine DNA glycosylase as its self-protection mechanism, and it is eventually discharged from the body through urine in a free form [21].

Further, AD patients, tend to have higher serum 8-OHdG levels than healthy persons, suggesting that DNA oxidative damage is linked to the occurrence and progression of AD, and the extent of damage of cognitive functions is also closely related to 8-OHdG [22].

Although the expression level of NMs in various CI diseases lacks sufficient evidence, some studies supported the correlation between the expression of NMs and cognitive functions [23]. The present study determined the levels of NMs in

Figure 5. Pearson analysis displayed a significant positive relation between SAA and 8-OHdG levels in the Control group (**A**) (r=0.6679, P<0.05), an apparent positive correlation between SAA and 8-OHdG levels in the MCI group (**B**) (r=0.7774, P<0.05), and a significant positive correlation between the SAA and 8-OHdG levels in the AD group (**C**) (r=0.6778, P<0.05).

patients and showed that the AD group had a notably higher B12 level than other groups (P<0.05), similar to the findings of Hu et al. [24]. Hence, low B12 level possibly increases the risk of AD through an unknown mechanism. Moreover, the AD group had significantly higher TC and ApoB levels (P<0.05) but had a significantly lower HDL-C level than the MCI and Control groups (P<0.05). According to a study by Zha et al. [24] on changes in hemorheological and blood fat indicators in patients with MCI and AD, use of periodic hemorheology and blood fat tests were useful in early prevention and treatment of MCI and AD. Their findings indicated a correlation between the development of MCI and AD and the levels of TC, ApoB, and HDL-C; the SC level may also rise, thereby damaging the capillary endothelial cells and cerebral artery functions and subsequently increasing the risks of developing MCI and AD. Similar studies have reported that the MCI and AD groups had significantly higher MoCA and MMSE scores than the Control group (P<0.05), and these scores were valuable in MCI diagnosis [25,26]. In the present study, MoCA and MMSE scores of the 3 groups were collected and assessed, and the results showed that the Control group had significantly higher levels

than the MCI group, with the AD group having the lowest levels (P<0.05). Levels of 8-OHdG in brains of LAD and MCI patients tend to be high [27]. Further, the SAA level in severe TBI patients with multiple injuries was higher than that in patients with mild or moderate brain injuries [28]. The present study assessed the SAA and 8-OHdG levels in the 3 groups and found that the Control group had significantly lower levels, followed by the AD and MCI groups (P<0.05); therefore, SAA and 8-OHdG are good indicators in MCI diagnosis. However, the relationship between SAA and nerve functions is unclear. Ge et al. [19] found a clear inverse relationship between SAA level and CFs scores in patients with COPD, which is inconsistent with the conclusion from some cross-sectional studies that no link exists between SAA level and MMSE score [29]. The correlation coefficient analysis in the present study showed a significant negative correlation between SAA, cognitive functions, and IQ; however, the correlation diminishes as CFs scores rise. Liu et al. [30] found that the serum 8-OHdG level was inversely related to MMSE score in CI patients after cerebral apoplexy, while several reports indicated that the relationship between MoCA scores and 8-OHdG level in PD patients

was negligible [31]. The present study showed that SAA and 8-OHdG levels can reflect the development of CI in the elderly. Therefore, passive immunization with reduced concentrations of SAA and 8-OHdG may improve cognitive function, but this conclusion still needs further verification. In addition, serum SAA and 8-OHdG levels can also reflect cognitive impairment, which helps clinicians to detect cognitive dysfunction early so that therapy can be given in a timely manner. In the present study, the significant negative correlation between the serum 8-OHdG levels and scores of cognitive functions and IQ and between SAA and 8-OHdG levels was supported through correlation coefficient analysis and Pearson analysis, respectively. Hence, our findings revealed their interaction and offer a new direction for future study. However, to date, the correlation between SAA and 8-OHdG has remained rarely studied; thus, more tests are needed for confirmation. It has been shown that SAA and 8-OHdG levels are disordered in a variety of senile diseases [32,33], SAA can participate in the regulation of inflammatory response [34], and 8-OHdG can affect the level of oxidative stress in the body [35]; therefore, the specificity of SAA and 8-OHdG as diagnostic or prognostic markers for elderly patients with cognitive dysfunction may be affected. Whether SAA and 8-OHdG are specific indicators of cognitive dysfunction remains to be determined.

The present study assessed the expression levels of SAA and 8-OHdG in 3 groups, and then investigated the function and relationship of SAA and 8-OHdG with MCI. However, the specific mechanism and thresholds of SAA and 8-OHdG in MCI are unclear, and further studies are required to identify its possibility as a prognostic monitoring index and to reduce the expression of SAA and 8-OHdG in MCI. There were also differences in nutrition markers among the 3 groups, and whether they are confounding factors for SAA and 8-OHdG needs to be confirmed.

Conclusions

Briefly, SAA and 8-OHdG in the MCI and AD groups were markedly expressed. They were also negatively correlated with CFs scores, and they can be applied as the test indicators of MCI. Furthermore, a significant correlation was observed between SAA and 8-OHdG.

Conflict of interests

None.

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