Higher inflammation and cerebral white matter injury associated cognitive deficit in asthmatic patients with depression

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Research

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Abstract

Background

Depression is a common co-morbidity in asthma, worsening asthma control and impairing patient's quality of life. Previous studies have reported a higher risk of cognitive deficit in depression. However, few research has focused on the cognitive status of asthmatic patients with depression. Evidence showed that inflammation may play an important role in both asthma and depression. Moreover, cerebral white matter injury, which could be induced by inflammation, has been associated with depression. The present study aimed to assess the cognitive function and explore the potential mechanism in patients with asthma, depression and comorbidity.

Methods

We admitted four groups: Asthma comorbid Depression group (A + D, n = 26), Depression group (D, n = 25), Asthma group (A, n = 33) and Normal controls (N, n = 28). Cognitive function was assessed by Montreal Cognitive Assessment (MoCA). Various inflammatory cytokines were measured, including interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), high-mobility group box 1(HMGB1) and Netrin-1. Cerebral white matter injury was assessed by serum myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG), and their correlations with cognitive performance were calculated.

Results

A + D group showed the highest incidence of cognitive deficit with specific affected cognitive domain. Compared to N group, serum levels of IL-6, HMGB1, Netrin-1, MBP and MOG were significantly elevated in A + D group. MOG level was negatively correlated with MoCA score.

Conclusion

Patients with comorbid condition presented more definite, severe cognitive deficit and higher level of inflammatory cytokines. Cerebral white matter injury may account for the cognitive deficit in these patients and MOG could be a potential biomarker of this process.

Introduction

Asthma is a common chronic disease characterized by bronchial hypersensitivity and airway inflammation, resulting in reversible airflow obstruction. A total of 334 million people worldwide suffer from this disorder, causing huge burden on society and individuals.[1] Evidence has shown that patients with asthma had 1.52 times higher risk of developing depression as compared with those not having

asthma, and depressive patients had an increased risk for asthma (OR 3.2) as compared with those not having depression.[2] The comorbidity of asthma and depression is associated with poorer symptom control, impairing patient's quality of life.[3]

Depression, affecting people's thoughts, emotions, interpersonal relationships and work efficiency, is one of the most common mental disorders and increasingly recognized as a global public health and social problem.[4] Recently, more attention has been payed to the relationship between depression and cognition. Depression has been considered as an important modifiable risk factor of dementia[5] and to predict conversion from any-type of mild cognitive impairment to all-cause dementia.[6] However, few research has focused on the cognitive status of asthmatic patients with depression.

The pathogenetic mechanism of asthma is persistent airway inflammation,[7] typically referring, but not limited to, atopic response with Th2-predominant inflammation (related to secretion of IL-4, IL-5 and IL-13).[8] Meanwhile, systemic inflammation with neutrophilic airway inflammation was increased in patients with asthma, characterized by increased levels of inflammatory markers such as C-reactive protein (CRP), interleukin- (IL-) 6, IL-1β, tumor necrosis factor- (TNF-) α, and leptin.[9] Inflammation also plays a key role in depression. Accumulative studies have described higher level of inflammatory cytokines in depressive patients.[10–12] Moreover, treatment with anti-inflammatory agents such as selective Cox2 inhibitors and TNF Antagonist has been shown to improve symptoms in depressive patients.[13] In recent years, some new inflammatory cytokines have been investigated in depression. Our prior research observed that high-mobility group box 1 (HMGB1), along with traditional inflammatory cytokines such as IL-1β, TNF-α, was elevated in depressive mice.[14] HMGB1, remaining at a high level 24 hours after inflammatory activation and recognized as a late inflammatory mediator,[15] has been reported to induce depressive behaviors in mice through neuroinflammation.[16] Netrin-1, a new anti-inflammatory factor that plays a critical role in restraining inflammatory respond, was found to promote the proliferation and differentiation of oligodendrocyte precursor cells in favor of myelin recovery, resulting in the repair of cerebral white matter.[17] Given the critical role of inflammation in both asthma and depression, we aimed to seek evidence that inflammation might also involve in the underlying process of cognitive deficit in the comorbid condition, and to explore the difference of inflammatory cytokines in patients with comorbidity, with asthma and with depression alone.

Immunity diseases targeting white matter, such as multiple sclerosis, have high incidence of depression as well as cognitive deficit.[18] Great rates of cerebral white matter integrity abnormality on diffusion tensor imaging (DTI) has been reported in depression.[19] Our previous research also showed that the serum levels of phospholipid were significantly elevated in patients with post-stroke cognitive deficit, indicating white matter injury.[20] We further demonstrated its underlying mechanism that white matter and oligodendrocyte changes driven by inflammatory reaction were associated with depression subsequent to cerebral ischemia.[21] Similar results have been observed in other animal models by other researchers.[22]

These observations developed into a hypothesis that cerebral white matter damage may contribute to the cognitive deficit in asthmatic patients with depression.

Therefore, the present study aimed to assess the cognitive function in patients with asthma and depression comorbidity and to explore the role of inflammation and cerebral white matter injury in their cognitive deficit. Furthermore, we expected to screen for potential biomarker of cognitive deficit in the comorbid condition and provide effective targets for further treatment.

Methods

1. *Subjects*

We recruited four groups from different sources. 26 patients with Asthma comorbid Depression (A+D) and 33 Asthma (A) patients from Respiratory Department, 25 Depression (D) patients from Psychological Department, Changhai Hospital, Shanghai, China. Age, sex and education matched healthy control subjects (N) were recruited from various free health camps for general population. All asthma patients (i.e. A+D and A group) received comparable routine treatment including glucocorticoid intake with low dose (<5mg/d).

Depression diagnosis was established according to the Diagnostic and statistical manual of mental disorders, 5th edition (DSM-V) criteria,[23] as assessed by the Structured Clinical Interview for DSM-V. The standard global initiative for asthma (GINA) diagnostic criteria[24] was adopted for including the asthma participants. The exclusion criteria included: (1) severe cardiac, hepatic and renal failure, (2) systemic diseases such as malignant tumors or other neurological diseases leading to brain structural lesions, (3) history of applying psychotic drugs, (4) unable to complete the neuropsychological tests or unwilling to participate the research. The study protocol was approved by the local Institutional Research Ethic Committee and performed in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). All participants were all provided written informed consent prior to participation.

2. *Methods*

2.1 Cognitive assessment

A standard Case Report Form was used to register demographic and medical data. Cognition was evaluated using Montreal Cognitive Assessment (MoCA). Data was normalized referring to the age and education matched norms and cognitive deficit was determined by a score of 26 or lower.

2.2 Inflammatory cytokines and white matter related indexes

Blood samples were collected, centrifuged at 3000 rpm for 15 minutes, and stored at -80℃ until thaw for further analysis. Serum levels of inflammatory cytokines (i.e.IL-1β, IL-6, TNF-α, HMGB1 and Netrin-1) as well as cerebral white matter related indexes (i.e. MBP and MOG) were assayed using a sandwich enzyme-linked immunosorbent assay (ELISA, SHANGHAI WESTANGBIOTECHINC). All measurements were carried out at the same time in the same laboratory and strictly in accordance with the reagent box standard process.

2.3 Statistical analysis

Group comparisons were performed with chi-square test for numeration data (i.e. gender, hypertension, diabetes, smoking and drinking) and with analysis of variance (ANOVA) for measurement data (i.e. cognition score, inflammatory cytokines and white matter related indexes), respectively. Bonferroni test was used as a post hoc test to examine the differences between groups when a significant difference across four sample means being revealed. In addition, Spearman correlation was applied to test the association between MoCA score and cerebral white matter related indexes.

Results

1. *Demographic Data*

Table 1 presents the demographic data for four groups, including age, education, BMI index, gender, hypertension, diabetes, smoking and drinking. No significant differences was found between groups.

2. *Cognition Evaluation*

Cognitive deficit was observed in 13, 15 and 19 patients in D, A and A+D groups respectively, indicating the highest incidence of impaired cognition (73.08%) and the lowest score in A+D group. The subtests of various cognitive domains in MoCA scale revealed significant difference between the four groups ($F_{Naming(4,107)}$=4.018, p=0.009; $F_{Attention(4,107)}$=5.826, p=0.001; $F_{Language(4,107)}$=8.503, p=<0.001; $F_{Abstract(4,107)}$= 12.238, p=<0.001; $F_{Memory(4,107)}$= 2.489, p=0.064; $F_{Orientation(4,107)}$=9.942, p=<0.001; $F_{Visuoexecutive\ (4,107)}$= 4.036, p=0.009(Table1). The post-hoc analyses showed that, compared with N group, A+D group performed worse in MoCA score (p<0.001), attention (p<0.001), language (p=0.006), abstract (p=0.007), orientation (p=0.001) and visuospatial executive function (p=0.023). In contrast to D group, performance of A+D group was better on naming (P=0.036) while poorer on language (p<0.001) and orientation (p=0.006). Compared to A group, A+D group showed significantly lower score on language (p<0.001) and abstract (p=0.004).

3. *Inflammatory cytokines*

Variance analysis showed significant differences in IL-6, HMGB1 and Netrin-1 between four groups ($F_{IL-1\beta(4,107)}$=0.791, p=0.502; $F_{IL-6(4,107)}$=9.630, p<0.001; $F_{TNF-a(4,107)}$=0.161, p=0.922; $F_{HMGB1(4,107)}$=4.495, p=0.005; $F_{Netrin1(4,107)}$=13.258, p<0.001). The post-hoc analyses showed that IL-6 increased significantly

in A+D group compared to N ($p<0.001$), D ($p=0.44$) and A group ($p=0.0027$). Similar results were observed for HMGB1, which was significantly elevated in A+D group than in N group ($p=0.041$). In contrast to N and A group, A+D group showed significantly increased Netrin-1 level ($p=0.04$, $p<0.001$) (Figure 1).

4. *Cerebral white matter related indexes*

As show in Figure 2, ANOVA results showed a significant between-groups difference in MBP and MOG ($F_{MBP(4,107)}=9.743$, $p<0.001$; $F_{MOG(4,107)}=13.714$, $p<0.001$). Post-hoc analyses revealed that MBP was significantly higher in A+D group than N ($p=0.0214$) and A group ($p<0.001$). MOG significantly enhanced in A+D group compared with the other three groups ($p<0.001$).

5. *Correlation related to MoCA score*

In order to screen a sensitive biomarker of cognitive deficit in depression, we conducted the Spearman correlation analysis within the A+D group between MoCA score and the peripheral serum indexes with significant between-group variance (i.e. IL-6, HMGB1, Netrin-1, MBP and MOG). We observed a negative correlation between MoCA score and MOG ($r=-0.476$, $P=0.014$, Figure 3), indicating that white matter injury revealed by elevated MOG could imply the cognitive deficit in patient with comorbidity. However, significant correlation was unfound between inflammatory indexes and cognition.

Discussion

The present study demonstrated impaired cognitive performance as well as elevated inflammatory cytokines (IL-6, HMGB1, Netrin-1) in patients with asthma and depression comorbidity. Moreover, we found a significant elevation in white matter lesion related indexes (MBP, MOG), one of which negatively correlated with cognitive performance. These findings provided important evidence on potential mechanism of cognitive deficit in asthmatic patients with depression.

Existing studies have recognized cognitive burden in patients with asthma.[25] Specifically, asthma has a strong effect, not only on broader capacities involving academic achievement and global intellect, but also on particular cognitive domain including processing speed, executive function, attention, visuospatial functioning, language, learning, and memory.[26] However, there is few research on cognition in patients with asthma and depression comorbidity. Our preliminary investigation showed that the A + D patients presented higher incidence of cognition deficit compared to patients with single asthma or depression and healthy controls. The particular vulnerable cognition domains included attention, language, abstract, orientation, visuospatial and executive function. The vulnerability of specific cognitive domains remains to be verified with more delicate neuropsychological assessments and its underlying mechanism remains to be explored.

Alterations in the immune systems are very likely to contribute to the increased risk of co-occurrence of asthma and depression.[27] One study reported that the CRP level was elevated in children and adolescents with both diseases.[28] Another study on gene expression of blood CD4 + T cells from comorbid patients

showed that the main active pathways in depressive asthma are IL-6 and CRP signalling.[29] In our study, the acute inflammatory mediator IL-6 was elevated significantly in A + D group. This finding is partly in accordance with a previous Meta-analysis illustrating that concentrations of cytokines such as IL-1, IL-4, IL-6, TNF-α were higher in depressive patients than non-depressive controls.[2] Furthermore, we discovered a significant increase in HMGB1 and Netrin-1 of A + D patients. HMGB1 has been shown to involve in the diseases characterized by chronic inflammation, especially in pulmonary pathology,[30] and elevate in the depressive animal models established with chronic stress.[31] Considering asthma comorbid with depression could be a chronic inflammatory reaction, it would be reasonable to find increased HMGB1 in patients with both diseases. As a new anti-inflammatory factor, Netrin-1 express in both acute and chronic inflammatory response. Considerable studies have demonstrated that Netrin-1 was consumed in acute inflammation such as acute lung injury or pancreatitis, thus playing protective role by restraining inflammatory damage.[32–33] Interestingly, we also found elevated Netrin-1 in asthma patients with depression. A possible explanation is that the chronic inflammatory respond in A + D group may induce a simultaneous process of compensatory protective reaction. Therefore, IL-6, HMGB1 and Netrin-1 may be sensitive indexes to reflect the activation of multiple inflammatory pathway in comorbid asthma and depression.

As cerebral white matter related index maintaining the structure and function of myelin in central nervous system, MBP and MOG have been reported to increase significantly in the peripheral blood of depressive individuals.[34–35] To our knowledge, it is still lack of data on the alterations in white matter related markers in asthma patients. Our study showed that both MBP and MOG increased significantly in patients with asthma and depression comorbidity, similarly to the findings in patients with depression. The relationship between inflammation and white matter has been largely explored. Our previous work[36] as well as other researches[37] have demonstrated that systemic inflammation could alter the development of the white matter by blocking the maturation process of oligodendrocytes through changing the coordinated expression of several transcription factors. Given the above empirical evidence, our results on elevated MBP and MOG may suggest an important pathophysiological alteration in asthma and depression comorbidity, that is, the white matter damage.

Furthermore, our study showed that cognitive deficit was negatively correlated with MOG, indicating that white matter lesion may result in cognitive alteration in asthmatic patients with depression. This result was consistent with previous imaging study showing a negative correlation between cognition, depressive syndrome and white matter hyperintensities.[38] A recent DTI study further showed that MOG correlated positively with white matter damage in depression.[35] Despite a minor component of myelin sheath (0.01–0.05% of the membrane protein) compared to MBP (30% of the membrane protein),[39] MOG has been exclusively expressed in oligodendrocytes in central nervous system (CNS),[40] while MBP was found to additionally express in peripheral nervous system and cells of the immune system.[41] We assume that MOG may be a more specific index than MBP to reflect CNS myelin injury in brain, therefore could be a more sensitive biomarker of cognitive deficit in asthma patients with comorbid depression.

The present study has some limitations. Firstly, this is a cross-sectional study therefore is unable to determine a causal relationship between cognitive deficits and inflammation or white matter injury. It would be of greater value to elucidate whether cognitive performance changes over time. Nevertheless, we observed a phenomena which could give a clue on this relationship and further research would be encouraged to conduct its potential mechanism. Secondly, we performed only MoCA as assessment tool of cognition, which is routinely a screen test for mild cognitive deficit. Complete and detailed neuropsychological assessments are encouraged such as Wechsler Intelligence Scale and other cognition battery tests which evaluate multiple cognitive domains. Thirdly, we provided evidence on white matter injuries by means of serum markers but lack of structural or functional image findings. More researches using advanced neuroimaging technic are needed to explore the unique characteristics of white matter injury in asthma and depression comorbid condition.

In conclusion, the present study identified high incidence of cognitive deficit and inflammatory cytokine levels in patients with asthma and depression comorbidity. Cerebral white matter injuries characterized by increased levels of MOG could be a potential biomarker of this process.

Conclusions

This study provided new evidence on cognitive deficit in patients with asthma and depression comorbidity. To our knowledge, this is the first study that tested the inflammatory mechanism and cerebral white matter injury in patients with comorbid condition. These patients presented more definite and severe cognitive deficit and higher level of inflammatory cytokines. Cerebral white matter injury may account for the cognitive deficit in these patients and MOG could be a potential biomarker of this process.

Abbreviations

A+D: Asthma comorbid Depression; D: Depression; A: Asthma; N: Normal Controls; MoCA: Montreal Cognitive Assessment; IL-1β: Interleukin-1β; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor-α; HMGB1: High-Mobility Group Box 1; MBP: Myelin Basic Protein; MOG: Myelin Oligodendrocyte Glycoprotein; DTI: Diffusion Tensor Imaging; DSM-V: Diagnostic and Statistical Manual of mental disorders, 5th edition; CNS: Central Nervous System

Declarations

Ethics approval and consent to participate

The study protocol was approved by the local Institutional Research Ethic Committee and performed in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). All participants were all provided written informed consent prior to participation.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Competing interests

The authors declare that there are no conflicts of interest.

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Authors' contributions

Conception and design: Xiaoying Bi and Yan Shang; Data analysis and interpretation: Yue Lu and Cunxiu Fan; Drafting the manuscript for intellectual content: Yue Lu and Shu Zhou; Revision of the manuscript: Yue Lu and Shu Zhou. The authors read and approved the final manuscript.

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Tables

Table1 Demographic data and cognitive performance in N, D, A and A+D group

riables	N (n=28)	D (n=25)	A (n=33)	A+D (n=26)	F or χ^2	p value
raphic data						
ars)	50.86(1.43)	48.36(2.96)	47.72(2.31)	55.65(2.28)	2.419	0.070
(female/all)	15/28	15/25	15/33	18/26	4.240	0.236
on(Years)	12.64(0.41)	12.12(0.75)	12.12(0.54)	10.50(0.67)	2.338	0.078
/m^2)	24.53(0.66)	22.18(0.64)	22.75(0.50)	23.28(0.72)	2.502	0.063
ension	3/28	7/25	4/33	5/26	3.582	0.310
s	0/28	3/25	0/33	1/26	7.119	0.057
g	10/28	5/25	10/33	4/26	7.525	0.058
g	2/28	2/25	1/33	2/26	0.845	0.872
ve performance						
	27.67(0.26)	24.32(0.66)	24.55(0.68)	23.85(0.61)	7.495	<0.001*
ing	3.00(0.00)	2.40(0.18)	2.64(0.12)	2.77(0.43)	4.018	0.009*
ıtion	6.00(0.00)	5.52(0.13)	5.64(0.12)	5.35(0.56)	5.826	0.001*
uage	2.79(0.08)	2.88(0.07)	2.97(0.03)	2.50(0.10)	8.503	<0.001*
act	1.67(0.10)	0.84(0.17)	0.64(0.13)	1.15(0.09)	12.238	<0.001*
ory	3.50(0.20)	2.92(0.19)	2.70(0.26)	2.73(0.22)	2.489	0.064
ıtation	5.92(0.06)	5.92(0.06)	5.24(0.16)	5.35(0.10)	9.942	<0.001*
executive	4.63(0.20)	3.48(0.34)	3.81(0.18)	3.85(0.20)	4.036	0.009*

Results are shown as mean(χ^2SD); or as frequencies.

Figures

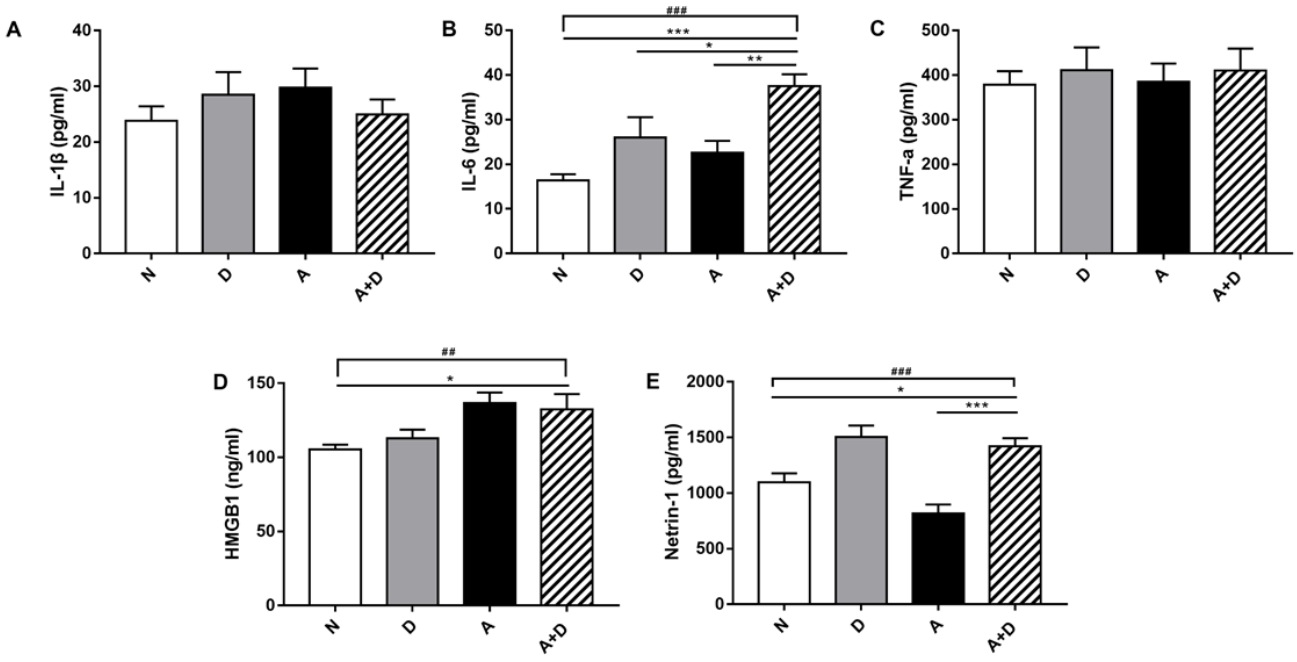

Figure 1

Inflammatory cytokines in four groups. (A) IL-1β, (B) IL-6, (C) TNF-α, (D) HMGB1 and (E) Netrin-1 in Normal control (N), Depression (D), Asthma (A) and Asthma comorbid Depression (A+D) group. ## p<0.01, ### p<0.001, for group comparisons; * p<0.05, **p<0.01, *** p<0.001, for post-hoc analysis.

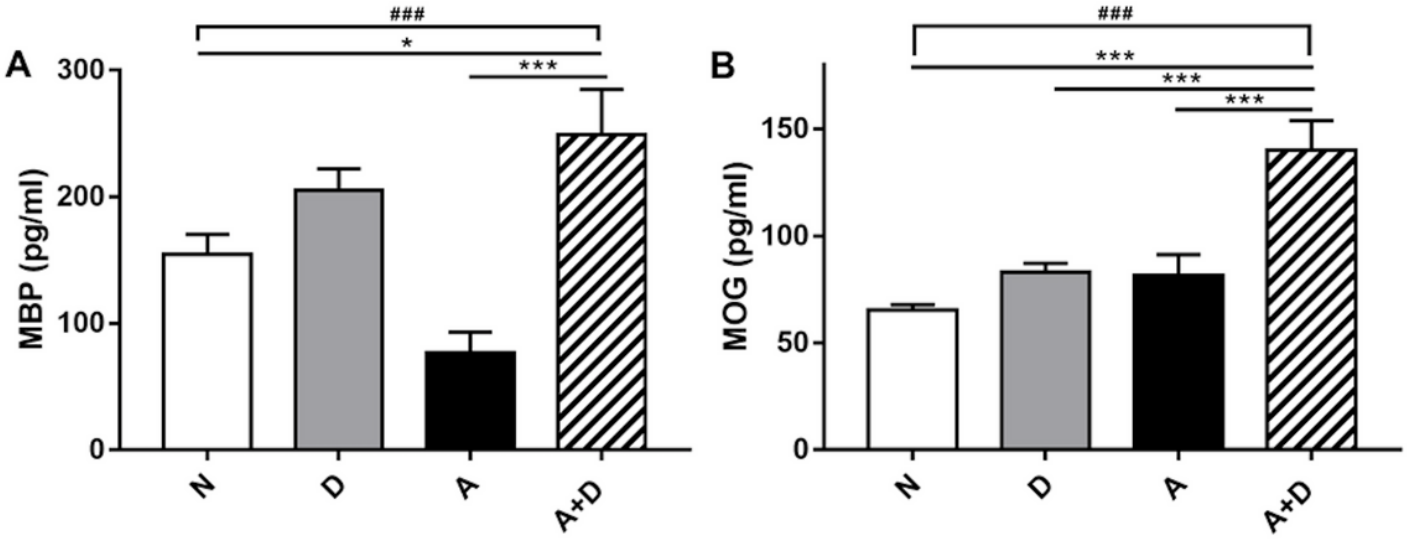

Figure 2

Cerebral white matter related indexes in four groups. (A) MBP and (B) MOG in Normal control (N), Depression (D), Asthma (A) and Asthma comorbid Depression (A+D) group. ## p<0.01, ### p<0.001, for group comparisons; * p<0.05, **p<0.01, *** p<0.001, for post-hoc analysis.

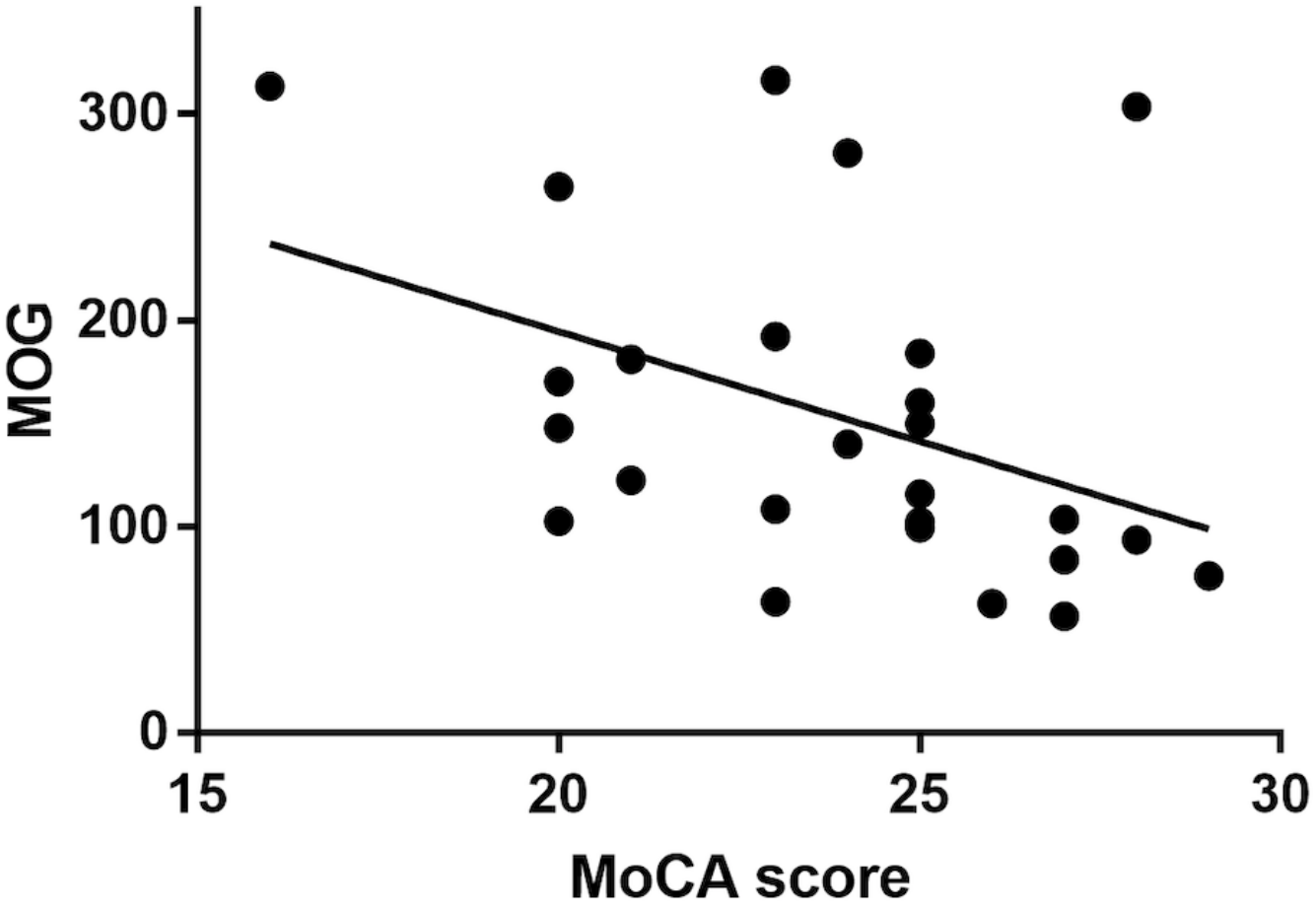

Figure 3

Correlation between MoCA score and MOG in the A+D group by Spearman analysis.