Correlation of clinical features with hs-CRP in TRD patients

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Received May 14, 2018; Accepted October 10, 2018

DOI: 10.3892/etm.2018.6914

Abstract. Correlation of clinical features with hypersensitive C-reactive protein (hs-CRP) in patients with treatment-resistant depression (TRD) was investigated. The severity of disease in 103 TRD patients and 103 non-TRD patients was evaluated using the Hamilton Depression Scale (HAMD)-17. The levels of hs-CRP in both groups were detected via immunofluorescence. Clinical features and differences in hs-CRP before and after treatment in both groups were analyzed, and correlation of baseline hs-CRP level with clinical features of TRD patients was also analyzed. Moreover, the relationship between hs-CRP and occurrence of TRD was analyzed using logistic regression analysis, and the diagnostic value of hs-CRP in TRD was evaluated using the receiver operating characteristic (ROC) curve. The onset age in the TRD group was lower than that in the non-TRD group, the education in the TRD group was shorter than that in the non-TRD group, the total course of disease in the TRD group was longer than that in the non-TRD group, and both baseline and post-treatment hs-CRP level in the TRD group (12.05±5.79 and 9.02±3.71 mg/l) were higher than those in the non-TRD group (7.85±2.85 and 6.10±2.74 mg/l) ($p<0.05$). The HAMD score ($r=0.338$, $p=0.031$), anxiety/somatization factor score ($r=0.465$, $p=0.015$) and sleep disorder ($r=0.387$, $p=0.029$) of TRD patients were positively correlated with the hs-CRP level, but the onset age ($r=-0.59$, $p=0.009$) was negatively correlated with the hs-CRP level. Logistic regression analysis revealed that the baseline hs-CRP was included into the TRD regression equation [odds ratio (OR) =2.834, 95% confidence interval (CI) =1.723-4.886], and the area under the ROC curve was 0.893 ($p<0.05$, 95% CI=0.852-0.933). In the TRD group, the course of TRD in patients was longer, the onset of disease was earlier and the educational level was lower than that in the non-TRD group. Therefore, the level of hs-CRP can serve as a reference for the diagnosis of TRD.

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Key words: treatment-resistant depression, hypersensitive C-reactive protein, clinical features

Introduction

Depression is a chronic disease with a high recurrence rate, seriously affecting people's lives and health (1). The treatment with antidepressants has no or poor therapeutic effect on approximately 20-30% patients with depression, so depression will progress into treatment-resistant depression (TRD) (2). The burden of disease against TRD patients is 40% higher than that against non-TRD patients (3). Certain progress has been made in identifying biomarkers of clinical symptoms and affective disorder of TRD, and therapeutic response to antidepressants (4). Increasingly more studies have manifested that inflammatory factors are involved in the occurrence and development of depression, but reliable biomarkers for the early identification of TRD have not been found yet. In this study, hypersensitive C-reactive protein (hs-CRP), a clinically-available factor, was selected to investigate the possibility of inflammatory factors serving as biomarkers of TRD, so as to realize early diagnosis and symptomatic treatment.

Materials and methods

Objects. Depression patients treated in the Department of Psychiatry, Dongfang People's Hospital Affiliated to Xuzhou Medical University (Xuzhou, China) from May 2012 to December 2016 were enrolled according to the following inclusion criteria: i) patients aged 18-60 years. ii) Patients who met the diagnostic criteria of depressive episode in the 10th edition of International Classification of Diseases (ICD)-10, and had used two or more kinds of different antidepressants in full dose for a full course of treatment (>6 weeks of drug treatment at the therapeutic dose). Depression patients with no or little therapeutic effect were enrolled into the TRD group, while those not meeting the TRD criteria were enrolled into the non-TRD group. iii) Patients with the Hamilton Depression Scale (HAMD) score of 17 points or above. iv) Patients who

did not take psychotropic drugs within 2 weeks before enrollment.

Exclusion criteria: i) patients with secondary depression due to organic disease or other mental diseases. ii) Patients with a history of head trauma, nervous system disease or mental disorder caused by psychoactive substances and various non-addictive substances. iii) Patients with different physical or immunosuppressive diseases. iv) Pregnant or lactating women; or v) patients who took various antibiotics or immunosuppressive agents within half a year before admission.

Patients in the above two groups signed the informed consent, and this study was approved by the Ethics Committee of Dongfang People's Hospital Affiliated to Xuzhou Medical University (approval no. 2014ZL004).

In the TRD group, there were a total of 103 patients, including 48 males and 55 females aged 25-55 years with an average of 37.60±5.92 years, and the education was 5-18 years with an average of 9.51± 2.93 years. In the non-TRD group, there were a total of 103 patients, including 45 males and 58 females aged 22-55 years with an average of 38.34±7.18 years, and the education year was 8-16 years with an average of 10.71±3.39 years. Sex (p=0.674) and age (p=0.423) were matched between the TRD and non-TRD groups, and there were no statistically significant differences.

Table I. Comparison of demographic and clinical data between TRD and non-TRD patients.

Variables	TRD	Non-TRD	t/χ^2	P-value
Baseline				
Age	37.60±5.92	38.3±7.18	0.804	0.422
Education year[a]	9.51±2.93	10.72±3.39	2.728	0.007
hs-CRP[a]	12.05±5.79	7.85±2.85	6.569	0.001
BMI	21.2±2.56	21.01±2.01	0.727	0.468
Total course of disease[a]	9.1±4.9	5.51±2.92	6.387	0.001
Onset age[a]	25.56±3.21	29.10±5.44	5.678	0.001
HAMD	28.67±5.71	29.95±5.33	1.666	0.097
Sex	48/55	45/58	0.176	0.674
Family history	20/103	18/103	0.089	0.766
After treatment				
HAMD	9.07±2.73	8.41±2.41	1.87	0.063
hs-CRP[a]	9.02±3.71	6.10±2.74	6.443	0.001

[a]P<0.05. TRD, treatment-resistant depression; hs-CRP, hypersensitive C-reactive protein; BMI, body mass index; HAMD, Hamilton Depression Scale.

Scale assessment. At 1 day after admission and at 6 weeks after treatment, the severity of depression in patients was evaluated using HAMD-17 by two physicians in the Department of Psychiatry who had received strict assessment training (K=0.83). The total HAMD score and the scores of five factors were calculated, respectively, the latter of which included sleep disorder (item 4, 5 and 6), retardation (item 1, 7, 8 and 14), anxiety/somatization (item 10, 11, 12, 13, 15 and 17), weight (item 16) and cognitive disorder (item 2, 3 and 9).

Specimen collection and storage. At 2 days after admission and at 6 weeks after treatment, 5 ml fasting venous blood was drawn from each patient using the ethylene diamine tetraacetic acid (EDTA) anti-coagulant tube at 08:00 in the morning, and the blood specimen was centrifuged at 1,474 x g and 4˚C for 15 min within 1 h after blood collection. After the serum was separated, it was stored in a refrigerator at -70˚C for the detection of hs-CRP.

Determination of hs-CRP. The level of hs-CRP in patients was detected via immunofluorescence using the immunofluorescence detector and its supporting reagents (Skyverse, Ltd., Shenzhen, China). The operation was performed by laboratory staff according to the operation specifications.

Determination of body mass index (BMI). The weight and height of patients were measured at admission, and the weight of patients in both groups was measured again after 6 weeks. BMIs of patients in both groups before and after treatment were calculated according to the formula: BMI = weight (kg)/height $(m)^2$.

Drug therapy. TRD patients were treated with venlafaxine sustained-release tablets (trade name: Bolexin sustained-release tablets) at an initial dose of 37.5 mg/day, and the dose was increased to 75 mg/day after 4 days and then gradually increased to 75 mg/bid according to the clinical reaction of patients (225 mg/day at the most). The non-TRD patients were treated with fluoxetine (trade name: Prozac) at an initial dose of 20 mg/day (80 mg/day at the most). Lorazepam was used to improve the sleep of patients (6 mg/qn at the most) for 6 weeks.

Statistical analysis. Statistical Product and Service Solutions (SPSS) 22.0 software package (IBM Corp., Armonk, NY, USA) was used for data analysis. Measurement data were presented as means ± SD, the independent-samples t-test was used for the comparison between the two groups, and Spearman's correlation analysis was used for the correlation analysis. χ^2 test was performed for enumeration data. The diagnostic effect of hs-CRP on the TRD patients was evaluated using the receiver operating characteristic (ROC) curve, and the value of hs-CRP in the diagnosis of TRD was investigated via binary logistic regression analysis. P<0.05 suggested that the difference was statistically significant.

Results

Comparison of demographic and clinical data of patients between the two groups. There were no significant differences in age, sex, BMI, HAMD score and family history between the two groups of patients (p>0.05). The education in the TRD group (9.51±2.93 years) was shorter than that in the non-TRD group (10.72±3.39 years), both baseline and post-treatment hs-CRP level in the TRD group (12.05±5.79 and 9.02±3.71 mg/l) were higher than those in the non-TRD group (7.85±2.85 and 6.10±2.74 mg/l), and there was a significant difference in the hs-CRP level (9.02±3.71 mg/l) between the TRD group after treatment and the non-TRD group before treatment (7.85±2.85 mg/l) (t=2.827, p=0.005) (Table I).

Table II. Correlation of baseline hs-CRP level with clinical features of TRD patients.

Variables	Pearson's correlation coefficient (r)	P-value
Total HAMD score[a]	0.338	0.031
Anxiety/somatization[a]	0.465	0.015
Sleep disorder[a]	0.387	0.029
Weight	-0.083	0.168
Cognitive disorder	0.264	0.133
Retardation	0.261	0.077
Age	-0.156	0.076
Education year	-0.23	0.067
BMI	0.07	0.315
Total course of disease	0.135	0.054
Onset age[a]	-0.59	0.009

[a]P<0.05. hs-CRP, hypersensitive C-reactive protein; TRD, treatment-resistant depression; HAMD, Hamilton Depression Scale; BMI, body mass index.

Correlation analyses of baseline hs-CRP level with clinical features of TRD patients. The HAMD score (r=0.338, p=0.031), anxiety/somatization factor score (r=0.465, p=0.015) and sleep disorder (r=0.387, p=0.029) of the TRD patients were positively correlated with the hs-CRP level, but the onset age (r=-0.59, p=0.009) was negatively correlated with the hs-CRP level (Table II).

Logistic regression analyses of correlation of clinical factors with TRD risk. Logistic regression analyses manifested that HAMD and hs-CRP were included into the regression equation [β=0.087, SE=0.035, p=0.012, odds ratio (OR) = 1.091, 95% confidence interval (CI) = 1.019-1.269; β=0.223, SE=0.052, p=0.001, OR=2.834, 95% CI=1.723-4.886), indicating that hs-CRP is a risk factor for TRD (Table III).

Diagnostic effect of hs-CRP on TRD. The larger the area under the ROC curve, the better the diagnostic effect. The sensitivity and specificity of hs-CRP in the diagnosis of TRD are shown in Fig. 1, and the area under the ROC curve was 0.893 (p=0.001, 95% CI=0.852-0.933), indicating that hs-CRP has high accuracy in the diagnosis of TRD. The level of hs-CRP of 10.5 mg/l was the best critical value for the diagnosis of TRD with sensitivity of 0.922 and specificity of 0.721 (Fig. 1).

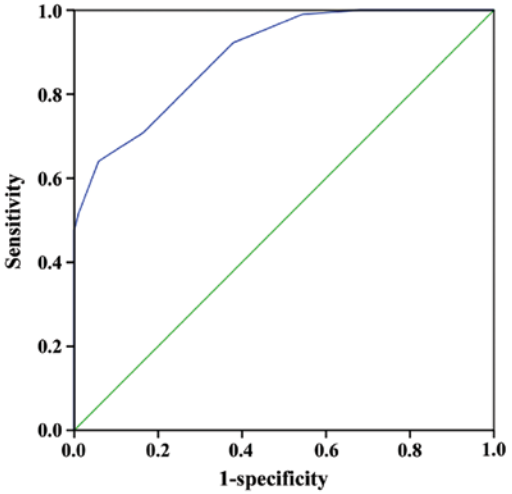

Figure 1. ROC curve of hs-CRP in the diagnosis of TRD. ROC, receiver operating characteristic; hs-CRP, hypersensitive C-reactive protein; TRD, treatment-resistant depression.

Discussion

Results of this study manifested that the total course of disease of the TRD patients was longer than that of the non-TRD patients, and the onset age was lower than that of the non-TRD patients before treatment. Conway *et al* (5) found that the course of disease of TRD patients is longer, suggesting that the disease of such patients is more likely to be chronic. According to the study of Juruena *et al* (6), it was also confirmed that the longer the single course of TRD in patients is, the worse the recovery of social function will be. Moreover, Vandoolaeghe *et al* (7) also found that the onset age of the TRD patients is lower. The above conclusions are consistent with results in this study, suggesting that the samples selected in this study have certain homogeneity with those selected by other clinical research organizations. In addition, this study demonstrated that the education of the TRD patients was shorter than that of the non-TRD patients, suggesting that the cognitive function of TRD patients may be poorer than that of non-TRD patients, which is consistent with the study result of Bodnar *et al* (8). Besides, Kiosses *et al* (9) showed that various cognitive impairments occur in TRD patients, indirectly proving the results of this study.

Research has displayed that both under- and overweight affect the correlation between hs-CRP and depression (10). According to a meta-analysis of a cross-sectional study, the correlation between depression and hs-CRP is significantly reduced after BMI is matched, but this correlation has not been determined yet in the longitudinal study after BMI is matched. To reduce the influence of BMI on the correlation between them, two groups of patients with no significant difference in BMI were selected in this study.

In recent years, studies on the correlation of depression with inflammatory factors have emphasized the immune activation in depression patients, and a variety of cytokines are produced, including interleukin (IL)-1, IL-6, tumor necrosis factor-α (TNF-α) and interferon-β (IFN-β), after immune activation. Matrisciano *et al* (11) revealed that IL-2, IL-6 and TNF-γ levels in patients with first-episode depression are significantly higher than those in the normal control group. Maes (12) also proposed the depression immune response hypothesis that depression is related to the activation of immune system, which is a kind of psychoneural immune disorder, and the peripheral immune activation, through releasing pro-inflammatory cytokines, leads to the changes in various behavior, neuroendocrine and neurobiochemistry related to the depression. In this study, it was also manifested that the hs-CRP levels were increased before and after treatment in depression patients, and it was higher in the TRD

Table III. Logistic regression analyses.

Variables	β	SE	Wald	P-value	Exp (β)	95% CI
HAMD[a]	0.087	0.035	6.271	0.012	1.091	1.019-1.269
Total course of disease	0.343	0.068	25.333	0.001	1.71	0.621-3.811
Onset age	0.242	0.047	26.102	0.001	1.274	0.561-2.398
Family history	0.035	0.466	0.006	0.94	1.036	0.415-2.581
Education year	0.09	0.061	2.227	0.136	1.094	0.972-1.231
hs-CRP[a]	0.223	0.052	18.235	0.001	2.834	1.723-4.886
Constant	0.526	1.826	9.168	0.002	0.004	

[a]P<0.05. CI, confidence interval; HAMD, Hamilton Depression Scale; hs-CRP, hypersensitive C-reactive protein.

patients than that in the non-TRD patients, suggesting that the immune activation in TRD patients is stronger, and the hs-CRP level is still increased (normal level of hs-CRP: 0-5 mg/l) after clinical symptoms are greatly improved. The above conclusion demonstrates that hs-CRP is associated with depressive state, and also may possibly be used as a specific factor of depression. According to clinical research, the levels of hs-CRP, IL-1, IL-6, IFN-γ and TNF-α are increased in the blood of depression patients (13), which is possibly related to the excessive activation of hypothalamic-pituitary-adrenal (HPA) axis. The IL-6 level in the plasma is higher in patients receiving ineffective treatment with selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) compared with that in patients receiving effective treatment (14). The increased levels of inflammatory factors upregulate the levels of 5-HT transporters and dopamine transporter, reduce neurogenesis, long-term potentiation (LTP) and 5-HT activity, increase excitotoxicity, activate HPA axis, improve release of glucocorticoids, regulate neuronal activity, lead to cognitive impairment (15).

The hs-CRP concentration in the blood can reflect the efficacy of antidepressants. The higher the concentration of hs-CRP is, the higher the inflammatory level and the stronger the response to drugs will be (16). Gene polymorphisms of inflammatory factors are also related to the sensitivity of patients to antidepressants (17), and the rs2279115C allele of B lymphocyte anti-apoptotic protein 2 is significantly associated with the response of male patients with depression to antidepressants (18). Some studies have shown that different clinical manifestations of depression will also affect the correlations of inflammatory factors with depression (19,20), and the relationship of hs-CRP with depression accompanied by somatic symptoms is higher than that with depression patients accompanied by other clinical symptoms (21,22). This study also displayed that the anxiety/somatization score in TRD patients had a significant correlation with the baseline hs-CRP level. In addition, it was found that there was an obvious correlation between sleep disorder score and baseline hs-CRP level. The possible reason is that the long-term sleep disorder can result in neuroendocrine and immune system dysfunction, thus increasing the hs-CRP level. Moreover, results of this study manifested that there was a significant negative correlation between onset age and baseline hs-CRP level in TRD patients, indicating that the lower the onset age is, the more severe the inflammatory factor system disorder will be. Chang *et al* (23) revealed that hs-CRP can act as an effective biomarker for affective disorders. Another study manifested that hs-CRP has remarkable correlations with the severity and unique subtypes of depression patients, especially in female patients (24). The increased hs-CRP level in some depression patients indicates that the hs-CRP level can be used as a predictor of antidepression effect. According to a prospective study, depression patients with the hs-CRP level of <1 mg/l have good response to escitalopram, an SSRI, while those with the hs-CRP level of >1 mg/l have good response to tricyclic drugs (25). Moreover, can the difference in the baseline hs-CRP level between TRD and non-TRD patients be used as a marker to distinguish them? In this study, the baseline hs-CRP level in the TRD patients was significantly higher than that in the non-TRD patients, and the same was true after treatment, displaying a large difference between them. In other words, there was little overlap between the the low hs-CRP level in TRD patients after treatment and the high baseline hs-CRP level in the non-TRD patients, so hs-CRP could serve as a biomarker of TRD in this study. In addition, logistic regression analyses and ROC curve in this study illustrated that hs-CRP was associated with TRD, and it was concluded that 10.5 mg/l hs-CRP was the best critical value for the diagnosis of TRD with sensitivity of 0.922 and specificity of 0.721, indicating that the diagnostic possibility of TRD is larger when the level of hs-CRP is >10.5 mg/l, with the diagnostic coincidence rate of 0.893. Therefore, hs-CRP is more likely to be a reference index for distinguishing TRD from non-TRD, which has important reference value for early identification and individualized treatment of TRD patients.

In conclusion, the educational level was lower, the first-onset age was lower, and both baseline and post-treatment hs-CRP level after treatment were higher in the TRD group than those in the non-TRD patients, so hs-CRP can serve as one of the diagnostic bases of TRD. However, the follow-up time was short and the sample size was small in this study, so the follow-up time should be extended and the sample size should be expanded to further reveal the correlation between hs-CRP and TRD.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

JQ and HZ were responsible for scale assessment and drug therapy. DG and LQ were responsible for the collection and analysis of patient data. JQ, XZ and HZ determined hs-CRP and BMI. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Dongfang People's Hospital Affiliated to Xuzhou Medical University (Xuzhou, China). Patients who participated in this study had complete clinical data. Signed informed consents were obtained from the patients or guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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