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Relation Analysis between IL-6 Levels and Cognitive Function in Depression Sick Persons Co-morbid with Type 2 Diabetes

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Abstract: *Objective: To explore the relation between hs-CRP, IL-6 levels and cognitive function in depression sick persons co-morbid with type 2 diabetes. Methods: 200 sick persons with first-episode depression who were hospitalized at Kailuan Mental Health Center from May 2019 to May 2021 were selected. According to whether were co-morbid with type 2 diabetes, they were divided into 100 sick persons with depression co-morbid with type 2 diabetes (observation group) and 100 sick persons with depression alone (control group). The baseline data, HAMD-24 item scores, serum hs-CRP and IL-6 levels, cognitive function and the relation between hs-CRP and IL-6 and total MoCA score and each factor and total HAMD-24 score in the observation group were compared between the two groups, and the difference was considered statistically significant at P<0.05. Results: There was a statistical difference in the total HAMD-24 score between the 2 groups of sick persons (P<0.05). The serum hs-CRP and IL-6 levels of sick persons in the observation group were significantly higher than those in the control group (P<0.05). Delayed memory, abstract thinking, attention, memory, visuospatial ability, orientation scores and total MoCA scores were lower in the observation group than in the control group (P<0.05). There was a highly significant negative relation (P<0.01) between serum hs-CRP and IL-6 and delayed memory, attention, memory, visuospatial ability, and total MoCA score in the observation group; and a highly significant positive relation (P<0.01) with total HAMD score. Conclusion: Serum hs-CRP and IL-6 levels were higher in depression sick persons co-morbid with type 2 diabetes than in those with depression alone, and there was a relation between serum hs-CRP and IL-6 levels and depression levels as well as cognitive function.*

Keywords: *Depression, Type 2 diabetes, Inflammation, Cognitive function*

1. Introduction

Depression is one of the most common disabling psychological illness. According to relevant statistics from the World Health Organization, more than 350 million people worldwide ill with depression [1]. Among them, cognitive dysfunction is the core diagnostic feature of depression and causes significant impairment in the daily functioning of sick persons. However, cognitive impairment in depression is often independent of depressive symptom clusters and can persist even when depressed mood largely resolves[2]. Diabetes mellitus (DM) is a global epidemic, with an estimated 400 million people worldwide living with the disease [3].The damage caused by diabetes is mainly due to complications resulting from poor long-term glycemic control, including kidney disease, hypertension, infections and diabetic foot[4]. In addition, diabetes often leads to cognitive impairment, reduced learning and memory, decreased comprehension and judgment, and even dementia [4].

Depression and type 2 diabetes have a high comorbidity rate, and the risk of developing diabetes in depressed sick persons is 1.6 times higher than in the normal population[5]. comorbidity depression with type 2 diabetes may be a combination of factors that may involve changes in neuroendocrinology, multiple neurotransmitter systems, immune activation, oxidative stress, and neurotrophic factors, but the exact pathogenesis is unclear. Inflammation is believed to be a potential common mechanism for depression and certain diseases related to chronic inflammation, such as cognitive deficits in diabetes[6].Numerous studies have shown that depressed sick persons, as well as sick persons with type 2 diabetes, tend to have elevated concentrations of pro-inflammatory cytokines such as C-reactive protein (CRP) and interleukin 6 (IL-6)[7,8]. Whether cognitive dysfunction is getting severe and plasma pro-

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inflammatory cytokine concentrations are higher after comorbidity of depression with type 2 diabetes has not been reported nationally or internationally. The study aims to investigate the serum hs-CRP and IL-6 levels in sick persons with depression co-morbid type 2 diabetes, the impairment characteristics of cognitive function, and also to analyze the relation between plasma hs-CRP and IL-6 concentrations and cognitive function levels, to further investigate the biological mechanisms of depression co-morbid type 2 diabetes, and to contribute to the intervention of cognitive dysfunction in sick persons with depression co-morbid type 2 diabetes.

2. Materials and Methods

2.1 Participants

200 sick persons with depression who were seen and hospitalized at Kailuan Mental Health Center from May 2019 to May 2021 were selected. Inclusion criteria: ① sick persons with first-episode depression who meet the diagnostic criteria for depression in the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).② 24-item version of the Hamilton Depression Scale (HAMD)[9] total score ≧ 20; ③ Age 18-65 years; ④ Education: junior high school and above. Exclusion criteria: ① Those with other combined psychiatric diseases, cerebrovascular diseases, acute infectious diseases, autoimmune diseases. ② Treatment with antidepressants, antipsychotics, immunomodulators, hormonal drugs, MECT, rTMS, etc. within 6 months prior to enrollment; ③ Pregnant and lactating women. The sick persons were divided into 100 cases in the depression co-morbid type 2 diabetes group (observation group) and 100 cases in the depression alone group (control group) according to whether they had co-morbid type 2 diabetes. there was no significant difference in the baseline data between the 2 groups (P>0.05), and there was a statistically significant difference in the total HAMD-24 score (P<0.05). See Table 1.

Table 1: Comparison of gender, age, education level, and total HAMD-24 score between the two groups ($x \pm s$)

Groups	Gender (male/female)	Age (years)	Education (years)	HAMD-24 score (score)
Observation group	41/59	34.51±13.5	10.11±4.21	29.34±2.03
Control group	47/53	35.5±12.12	9.85±4.01	26.46±2.13
t	0.731	-0.55	0.45	9.82
P	0.393	0.59	0.66	<0.01

2.2 Serum hs-CRP and IL-6 Detection

Serum hs-CRP was detected by immunoturbidimetric method in two groups of sick persons. serum IL-6 level was detected by ELISA method, and the kits were purchased from Shenzhen New Industry Biomedical Engineering Co.

2.3 Assessment of Cognitive Function

Sick persons' cognitive function was tested by the Montreal Cognitive Assessment (MoCA) scale, an assessment tool for rapid screening of mild cognitive impairment. It assesses many different cognitive domains, including attention, executive function, memory, language, visual structural function, abstract thinking, computation, and orientation. The total score for this scale is 30 points. If the subject has less than 12 years of education, 1 point should be added to correct for bias. A total score of ≥ 26 indicates normal cognitive function, otherwise cognitive impairment. A total score ≥ 26 indicates normal cognitive function, otherwise cognitive impairment. The reliability coefficient of the scale was 0.760.

2.4 Statistical Treatment

SPSS23.0 was applied for data analysis, and the data of the respondents were continuous numerical variables, and the measurement data were expressed as mean ± standard deviation, and the t-test of two independent examples was used for comparison between groups, and the difference was considered statistically significant at P<0.05. The relations between hs-CRP and IL-6 and delayed memory, attention,

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memory, visuospatial ability, abstract thinking, verbal fluency, orientation, naming, MoCA scale total score, and HAMD-24 total score in each group were analyzed by Pearson relation relation.

3. Results

3.1 Comparison of hs-CRP and IL-6 Levels in the Observation Group and the Control Group

The hs-CRP and IL-6 levels of sick persons in the observation group were significantly higher than those in the control group, and the differences were statistically significant (P<0.05). See Table 2.

Table 2: Comparison of hs-CRP and IL-6 levels in the observation and control groups ($x \pm s$)

Groups	hs-CRP(mg/L)	IL-6(ng/L)
Observation group	5.56±1.55	38.91±4.75
Control group	4.34±1.26	31.45±5.63
t	6.06	10.15
P	<0.01	<0.01

3.2 Comparison of MoCA Scores between the Observation Group and the Control Group

Delayed memory, abstract thinking, attention, memory, visuospatial ability, orientation scores and total MoCA scores were lower in the observation group than in the control group (P<0.05), but there was no statistical difference in verbal fluency and naming scores (P>0.05). See Table 3.

Table 3: Comparison of MoCA scores in the observation and control groups (score, $x \pm s$)

Groups	Delayed memory	Abstract thinking	Attention	Memory	Visual space execution ability	Language fluency	Orientation	Naming	Total score
Observation group	2.58±0.87	0.8±0.34	4.84±0.57	4.01±0.35	2.38±1.25	2.72±0.31	3.77±1.26	2.38±0.39	22.65±3.13
Control group	3.7±0.63	1.02±0.37	5.96±0.42	4.44±0.59	4.63±0.49	2.77±0.37	4.43±0.49	2.41±0.43	28.82±0.55
t	-10.44	-4.38	-15.97	-6.4	-16.69	-1.05	-4.91	-0.53	-19.39
P	<0.01	<0.01	<0.01	<0.01	<0.01	0.3	<0.01	0.6	0

3.3 Relation Analysis of hs-CRP and IL-6 with MoCA Score and HAMD-24 Total Score in the Observation Group

Table 4: relation analysis of hs-CRP and IL-6 with MoCA score and HAMD-24 total score in the observation group

Indexes		hs-CRP (mg/L)		IL-6 (ng/L)	
		r	P	r	P
HAMD-24 score (score)		0.871	0.000	0.679	0.000
MoCA score (score)	Delayed memory	-0.730	0.000	-0.683	0.000
	Abstract thinking	-0.012	0.905	-0.090	0.375
	Attention	-0.587	0.000	-0.564	0.000
	Memory	-0.684	0.000	-0.666	0.000
	Visual space execution ability	-0.690	0.000	-0.713	0.000
	Language fluency	0.056	0.583	0.069	0.493
	Orientation	-0.140	0.166	-0.091	0.366
	Naming	0.033	0.745	0.132	0.19
	Total score	-0.881	0.000	-0.644	0.000

The relation analysis of hsCRP, IL-6, delayed memory, abstract thinking, attention, memory, visuospatial ability, verbal fluency, orientation, naming, MoCA total score, and HAMD total score in the observation group showed that:There was a highly significant negative relation (P<0.01) between hs-CRP and IL-6 and delayed memory, attention, memory, visuospatial ability, and total MoCA score with relation coefficients of 0.735, 0.671, 0.783, 0.792, and 0.709, respectively, and no relation with abstract thinking, verbal fluency, orientation, and naming; and a highly significant positive relation with total HAMD score (P<0.01) with a relation coefficient of 0.656. See Table 4.

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4. Discussion

Our findings show that HAMD scores as well as serum hs-CRP and IL-6 levels are significantly higher in sick persons with co-morbid type 2 diabetes mellitus than in sick persons with depression alone, and there is a positive relation between hs-CRP and IL-6 levels and HAMD scores in sick persons with co-morbid type 2 diabetes mellitus, suggesting that depression co-morbid type 2 diabetes mellitus can increase inflammation as well as has with levels in sick persons. Recent studies have shown that depression is a high risk factor for type 2 diabetes and vice versa, and it has been hypothesized that common biological pathways, one of which is inflammation, may underlie the association between depression and diabetes [10].Numerous prospective studies have shown that high levels of inflammatory markers predict the prevalence of type 2 diabetes as well as depression [11]. The association between diabetes and inflammation involves multiple mechanisms, including altered glucose uptake by adipose tissue, and an indirect mechanism involving increased levels of free fatty acids that block insulin signaling pathways [12].Depression not only enhances the production of inflammatory cytokines, but also increases the level of inflammation by producing cytokines that activate sympathetic as well as macrophage-ergic receptors[13][14]. In a participating cohort of 5166 sick persons, baseline inflammation marker (CRP and IL-6) levels were associated with subsequent risk of depression during follow-up [15]. However, this relation was not found in sick persons who was illed with type 2 diabetes. A recent meta-analysis showed that the relative risk of developing type 2 diabetes was 1.26 (95% CI 1.16-1.37) for each 1 mg/L increase in CRP levels [16]. Hood et al. did not find a significant association between depression and inflammation in diabetic sick persons, which is inconsistent with our results [17]. These inconsistent results can be explained, at least in part, by different study designs, different hypotheses being investigated, including different confounding factors, and the difficulties inherent in obtaining epidemiological measures of patient status (e.g., depression and cardiovascular disease status) at the time of data acquisition.

Our findings also show a relation between serum hs-CRP and IL-6 levels and HAMD scores and cognitive domains such as delayed memory, attention, memory, and visuospatial ability in sick persons with depression co-morbid diabetes, suggesting that hs-CRP and IL-6 levels in sick persons with depressive co-morbid diabetes are associated with the severity of depression as well as cognitive function. One hypothesis regarding the link between depression, cognitive impairment and diabetes is that all these conditions share some common findings: reduced hippocampal volume, altered cerebral vasculature and neurotransmitter deficits. All these changes are individually associated with chronic inflammation[18]. Studies have found higher levels of pro-inflammatory cytokines in depressed sick persons, suggesting that the inflammatory response plays a crucial role in the pathophysiology of depression [19]. Circulating inflammatory marker levels are elevated in sick persons with type 2 diabetes compared to the non-diabetic population. Thus, inflammatory mediators may play a role in the accelerated development of cognitive impairment in diabetic sick persons either through direct effects on the brain or by influencing the development of vascular disease. Another study has shown that inflammatory changes in cognitive impairment in depression co-morbidities in diabetic sick persons are associated with the activation of macrophages [20]. Two possible pathways for inflammatory cytokines to enter the CNS and have behavioral effects include signal transduction from peripheral nerves, including the vagus, to the CNS, where microglia are activated to produce cytokines [21].Another pathway involves saturating cytokine transporters, allowing many cytokines to cross the blood-brain barrier directly. Once cytokine signals cross the blood-brain barrier, they interact with multiple brain mechanisms to induce cognitive impairment [21].

In conclusion, this study shows that there is a superimposed effect of type 2 diabetes and depression compared to depressed sick persons alone, resulting in more severe cognitive dysfunction and higher levels of serum pro-inflammatory cytokines hs-CRP and IL-6. And there is a relation between hs-CRP and IL-6 levels and depression levels as well as cognitive function in depressed sick persons with co-morbid type 2 diabetes mellitus. The results of this study are valuable to further explore the biological mechanisms of cognitive dysfunction in depression co-morbid type 2 diabetic sick persons, to provide precise interventions for cognitive impairment in depression co-morbid type 2 diabetic sick persons.

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