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Original Article

Diagnosis of TCM symptoms and analysis of risk factors of mild cognitive impairment in patients with type 2 diabetes mellitus

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Abstract: Objective: To explore the diagnosis of traditional Chinese medicine (TCM) syndrome and analyze the risk factors of mild cognitive impairment (MCI) in patients with type 2 diabetes mellitus (T2DM). Methods: 141 T2DM patients, who were hospitalized in department of endocrinology of our hospital from February 2020 to December 2020, were chosen as research subjects. The patients were divided into an observation group (n=65, T2DM with MCI) and a control group (n=76, T2DM with normal cognitive function) according to the Montreal Cognitive Assessment (MoCA) score and diagnostic criteria of MCI. Pearson correlation analysis was used to study the correlation between MoCA score and influencing factors, and multiple logistic regression analyses were applied to analyze the risk factors of T2DM patients. Results: Deficiency of kidney essence (34/65, 52.31%) and phlegm obstructing orifices (16/65, 2.62%) were common in T2DM patients with MCI. The observation group had apparently lower MoCA scores than the control group (23.46±3.12 points vs. 27.39±2.56 points, t=8.2150, P=0.0000). According to the results of multivariate logistic regression analysis, age, course of diabetes, homocysteine (HCY) and glycosylated hemoglobin (HbAlc) were the independent risk factors of MCI, and the education level was a protective factor. Conclusion: Mental deficiency and phlegm obstruction are common in T2DM patients complicated with MCI. The factors such as age, diabetes course, education degree, HCY and HbAlc are closely related to MCI. The occurrence of MCI in T2DM patients can be prevented by improving the education degree of patients, effective control of blood glucose and reduction of HCY level.

Keywords: Type 2 diabetes mellitus, mild cognitive impairment, diagnosis of traditional Chinese medicine (TCM) syndrome, risk factors

Introduction

Type 2 diabetes mellitus (T2DM) is a non-infectious metabolic and chronic disease that seriously threatens human life. The major clinical manifestation is the elevated blood glucose caused by deficiency of insulin secretion [1]. According to related studies, the occurrence and progression of diabetes are caused by a variety of factors, including metabolic disorders caused by changes in environmental factors, genetic factors, and abnormal glucose metabolism associated with age [2, 3]. According to WTO statistics, by year 2000, the number of elderly patients with T2DM in the world reached 175 million. With the accelerated aging process, the rapid growth of urban population, and the changes in lifestyle and dietary habits, the incidence of T2DM is increasing year by year. It is estimated that the number of T2DM patients worldwide will reach 300 million by 2030 [4]. Mild cognitive impairment (MCI) is an intermedi-

ate state between normal aging and mild Alzheimer's disease. It is clinically manifested as mild memory impairment or other cognitive dysfunction, which has been diagnosed as dementia [5, 6]. According to statistics, the prevalence of MCI in the elderly over 65 years old is 25%, while that in the elderly over 85 years old rises to around 65% [7, 8], indicating a high morbidity rate among the elderly groups. The end-stage manifestation of the progression of MCI is dementia, and about 10-15% of MCI patients progress to dementia every year, causing huge burden to the society and families [9]. Clinical studies have manifested that T2DM is intimately associated with MCI and is the independent risk factor of its occurrence [10, 11]. Therefore, strengthening the prevention and treatment of T2DM complicated by MCI has become a major issue. The advantages of treatment and intervention in traditional Chinese medicine (TCM) are embodied in "preventive treatment of disease" and "early treatment and prevention of pathological changes". However, the study of MCI in T2DM patients is still in its early stage. This study analyzed the TCM classification of T2DM patients with MCI through the TCM syndrome diagnosis and treatment, and the risk factors of T2DM with MCI by Pearson correlation analysis and multivariate logistic regression, with a goal to provide clinical basis for reducing MCI incidence.

Materials and methods

General materials

A total of 141 cases of T2DM patients, who were hospitalized in the department of endocrinology of our hospital from February 2020 to December 2020, were included as the research subjects, and their clinical data were retrospectively analyzed. The patients were divided into an observation group (n=65, T2DM with MCI) and a control group (n=76, T2DM with normal cognitive function) according to the Montreal Cognitive Assessment (MoCA) score and diagnostic criteria of MCI. The study was carried out under the approval of the ethics committee of our hospital (No. 20200205).

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients met the WTO diagnostic criteria of T2DM [12]; (2) Patients with a course of T2DM exceeding 6 months; (3) Patients with normal binaural hearing, binocular vision or corrected vision and consciousness, and can successfully complete the questionnaire survey and psychological assessment; (4) Patients had complete clinical data and signed the informed consent.

Exclusion criteria: (1) Patients with acute complications of diabetes within 1 month; (2) Patients with severe complications of liver, kidney or cardiovascular system; (3) Patients with mental disorders or mental diseases; (4) Patients with communication disorders that affect the assessment of cognitive function; (5) Those with long-term application of glucocorticoids, sedative and hypnotic drugs; (6) Patients with neurological diseases that cause dementia, such as Parkinson disease, brain tumors, epilepsy, severe trauma, etc.

Diagnostic criteria of MCI in patients with T2DM

The diagnosis of MCI in Western medicine referred to the diagnostic criteria in *2018 Chinese Guidelines for the Diagnosis and Treatment of Dementia and Cognitive Impairment* (5) [13], and the diagnosis of TCM referred to the diagnostic criteria of syndromes in *Guiding Principles for Clinical Research of Mild Cognitive Impairment (Draft)* [14]. The criteria were divided into the following five categories, and patients with two or more primary symptoms and secondary symptoms were diagnosed with MCI. (1) Syndrome of deficiency of kidney essence. The main symptoms were the decline of memory, tired and sleepy, and soreness of waist and knees. The secondary symptoms were mental retardation, dull expression, tinnitus, auditory hallucination, easy panic, weight-bearing gait, difficulty in walking, flushing cheeks and incontinence. Patients with kidney-yang deficiency were accompanied by pale tongue, thin tongue fur and weak/thin pulse, and those with kidney-yin deficiency had red tongue, less moss and narrow/quickened pulse. (2) Syndrome of phlegm obstructing orifices. The main symptoms were the decreased memory, abdominal distension, heavy head as wrapped and salivation, and the secondary symptoms included reticence, dullness, obesity, heavy limbs, slow movement, and nausea and vomiturition. Those with turbid phlegm and fever were lethargic or restless, with pale tongue and white greasy fur, fat tongue, and

Table 1. Distribution of TCM syndromes in T2DM patients with MCI

Symptomatic type	Number of cases	Proportion
Deficiency of kidney essence	34	52.31
Phlegm obstructing orifices	16	24.62
Deficiency of heart and spleen	6	9.23
Deficiency of heart and liver Yin syndrome	2	3.08
Qi stagnation and blood stasis	7	10.77

slippery pulse, and patients with phlegm fever had red tongue with yellow greasy fur, and slippery pulse. (3) Deficiency of heart and spleen. The main symptoms included the decreased memory, fatigue and somnolence, and pale complexion. The secondary symptoms were melancholy, apathy, palpitations, shortness of breath, yellow complexion, cold limbs, loss of appetite, pale tongue with thin white coating, and weak pulse. (4) Deficiency of heart and liver Yin syndrome. The primary symptoms included mental decline, palpitations, insomnia and moodiness, and the secondary symptoms were dim eyes, irritability, deafness and tinnitus, tight limbs, red tongue with little fur, and week pulse. (5) Syndrome of Qi stagnation and blood stasis. The main symptoms were decreased memory, dark lips, cyanose in nails, and head tingling, and the secondary symptoms were reluctant or restless, silent expression, nonsense, slurred speech, dry skin, pale complexion, low fever in afternoons, palpitation and insomnia, dark purple tongue or ecchymosis, dark purple veins under tongue, and astringent/late pulse.

Methods

The cognitive function of all patients was evaluated by Montreal Cognitive Assessment (MoCA), including attention calculation (6 points), orientation (6 points), delayed recall (5 points), visual-spatial and executive function (5 points), naming (3 points), language (3 points), and abstract thinking (2 points) [15]. The total score of the assessment was 30 points, and the higher scores indicated better cognitive function. Combined with the diagnostic criteria of MCI, those with MoCA score of 20-26 were divided into the observation group, and those with MoCA score ≥26 were divided into the control group, and syndromes of MCI in T2DM patients were summarized accordingly. The two groups of patients underwent physical examination, and their basic information of age, gender, course of diabetes, education, and complications, etc. were recorded in detail. The unified measurement tool was applied to measure the height and weight of patients. Their body mass index (BMI) was calculated, and the diastolic blood pressure (DBP), systolic blood pressure (SBP), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), homocysteine (HCY) and glycosylated hemoglobin (HbAlc) were detected accordingly. In addition, the connected factors that may affect the MCI of T2DM patients were also analyzed and screened out.

Statistical method

The statistical analysis of the research was conducted by Spss19.0. The measurement data were expressed by ($\bar{x}\pm$sd), and the comparison between groups was done by *t*-test of independent samples. The enumeration data were expressed by percentage, and the results were compared by χ^2 test. *P<0.05* was regarded as the statistically significant difference. In addition, we applied Pearson correlation analysis to study the correlation between MOCA score and various influencing factors, and multivariate logistic regression analysis was applied to confirm the independent risk factors for MCI in T2DM patients. The test level α=0.05, and *P<0.05* was deemed as statistically significant difference.

Results

Distribution of TCM syndrome types in observation group

In T2DM patients with MCI, the syndrome of deficiency of kidney essence (34/65, 52.31%) was the most common, followed by phlegm turbid obstruction of orifices (16/65, 24.62%). The syndrome of stagnation of Qi and blood (7/65, 10.77%) and deficiency of both heart and spleen (6/65, 9.23%) were relatively rare, while the syndrome of heart liver yin deficiency (26/65, 3.08%) was most rare (**Table 1**).

Comparison of MoCA scores

The scores of attention calculation, orientation, delayed recall, visual-spatial and execu-

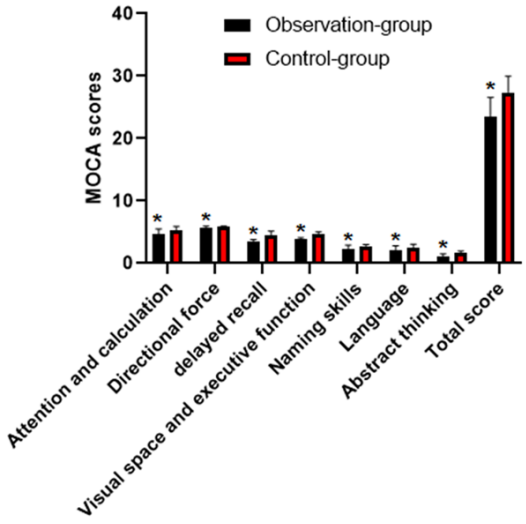

Figure 1. Comparison of MOCA scores between the two groups of patients. Note: compare with control group, *P<0.05.

tive function, naming, language, abstract thinking and total MoCA in observation group were remarkably lower than those in control group, and the difference was statistically significant (23.46±3.12 points vs. 27.09±2.56 points, *t*=7.5879, *P*=0.0000) (**Figure 1**).

Comparison of general clinical data

There was no significant difference in general clinical data such as gender, age and BNI between the two groups (P>0.05). The course of disease in observation group was significantly longer than that in control group, and the difference was statistically significant (12.54±5.23 years vs. 8.47±3.84 years, t=5.3142, P=0.0000). The education level of the observation group was dramatically lower than that of the control group (9.29±3.62 years vs. 12.15±3.54 years, t=4.7325, *P*=0.0000) (**Table 2**).

Comparison of complications

There was no significant difference between the two groups in terms of family disease history, or the complications such as coronary heart disease, diabetic nephropathy, and diabetic peripheral neuropathy (*P>0.05*) (**Table 3**).

Comparison of inspection indexes between the two groups

There was no significant difference in the level of DBP, SBP, TG, TC, LDL-C and HDL-C between the two groups (*P>0.05*); The HCY level of observation group was obviously higher than that of control group (15.87±2.38 vs. 14.62±2.57, *t*=2.9782, *P*=0.0034), and the HbAlc in observation group was higher than that in control group (10.12±2.12 vs. 7.95±2.35, *t*=5.7162, *P*=0.0000) (**Table 4**).

Pearson correlation analysis of MOCA score and various influencing factors

The correlations between MoCA score and the related factors such as age, course of disease, education level, HCY and HbAlc were analyzed by Pearson in observation group. It was found that MoCA score was negatively correlated with age, course of disease, HCY and HbAlc (*P<0.05*), and positively correlated with education level (*P<0.05*) (**Table 5**).

Multivariate logistic regression analysis of MoCA score and connected factors

The multivariate logistic regression analysis showed that age, diabetic course, HCY and HbAlc were independent risk factors for MCI in T2DM patients. Patients with older age, longer course of diabetes and higher HCY and HbAlc levels had greater risk of cognitive impairment, while the educational level was a protective factor for MCI in T2DM patients. The higher educational level resulted in the lower risk of cognitive dysfunction (**Table 6**).

Discussion

Kidney essence deficiency and phlegm obstructing orifices are common basic symptoms of MCI in T2DM patients. Traditional Chinese medicine believes that kidney is the congenital foundation that contains essence and marrow of the body. Kidney essence is the material basis of brain function, and its relationship with brain function is mainly reflected in the transformation of kidney essence into brain marrow. Kidney essence, derived from innate essence of parents and refined essence of water and grain produced by the acquired essence, affects the physiological function of brain. The deficiency of kidney essence will lead to the abnormal transport of water and grain, the brain cannot be supported, and cognitive dysfunction thus occurs [16]. Phlegm turbidity is also an important factor of MCI in T2DM patients. The kidney dominates the transportation and excretion of body fluid, and the transpi-

Table 2. Comparison of general clinical data between the two groups

Items	Observation group (n=65)	Control group (n=76)	χ^2/t	*P*
Gender (M/F, cases)	38/27	41/35	0.2898	0.5903
Age ($\bar{x}$±sd, yd)	65.87±5.37	62.25±5.71	3.8565	0.0002
BMI ($\bar{x}$±sd, kg/m^2)	25.26±3.77	24.89±3.46	0.6073	0.5446
Course of diabetes ($\bar{x}$±sd, years)	12.54±5.23	8.47±3.84	5.3142	<0.0001
Education level ($\bar{x}$±sd, years)	9.29±3.62	12.15±3.54	4.7325	<0.0001

Table 3. Complications in the two groups

Items	Observation group (n=65)	Control group (n=76)	χ^2	*P*
Family history of diabetes (yes/no, number of cases)	24/41	25/51	0.2507	0.6166
Coronary heart disease (Y/N, cases)	18/47	16/60	0.8441	0.3582
Hypertension (Y/N, cases)	31/34	30/46	0.9641	0.3262
Diabetic nephropathy (Y/N, cases)	27/38	29/47	0.1672	0.6826
Diabetic peripheral neuropathy (Y/N, cases)	52/7	70/6	0.6015	0.4380

Table 4. Comparison of inspection indexes between two groups of patients ($\bar{x}$±sd)

Items	Observation group (n=65)	Control group (n=76)	t	*P*
DBP (mmHg)	73.71±2.56	72.95±2.45	1.7985	0.0743
SBP (mmHg)	139.11±7.25	138.28±7.52	0.6642	0.5077
TG (mmol/L)	1.81±0.28	1.78±0.25	0.6720	0.5027
TC (mmol/L)	4.73±0.62	4.62±0.44	1.2273	0.2218
LDL-C (mmol/L)	2.82±0.43	2.69±0.48	1.6813	0.0949
HDL-C (mmol/L)	1.33±0.26	1.24±0.31	1.8493	0.0665
HCY	15.87±2.38	14.62±2.57	2.9782	0.0034
HbAlc	10.12±2.12	7.95±2.35	5.7162	<0.0001

Table 5. Pearson correlation analysis of MoCA score and connected factors

Indicators	r	*P*
Age	-0.284	0.0219
Course of diabetes	-0.313	0.0111
Education level	0.347	0.0046
HCY	-0.419	0.0005
HbAlc	-0.434	0.0003

ration and gasification of kidney can help the small intestine to "distinguish the turbidities", the stomach to "transform the essence of water and grain into Qi, blood and body fluid needed by human body", and the lung to "dredge and regulate of the body fluid". However, patients with deficiency of kidney essence have abnormal transpiration and gasification, their Qi cannot nourish the body normally, and the mutual formation of phlegm and blood stasis obscures the brain orifice, therefore leading to the cognitive impairment [17].

Epidemiological studies have shown that T2DM is an independent risk factor for the occurrence of MCI. It increases not only the risk of MCI, but also the disease progression [18, 19]. Therefore, the exploration and analysis of MCI risk factors in T2DM patients are conducive for applying targeted clinical interventions to prevent or delay the occurrence of MCI and improve patients' living quality of life. At present, the primary methods for the diagnosis and evaluation of MCI is through the quantitative and standardized neuropsychological tests, in which MoCA is the widely used scale as MCI screening tools [20, 21]. This study compared the MoCA scores of T2DM patients with and without MCI, and the results showed that MoCA score in T2DM patients with MCI was remarkably lower than those without MCI, with each aspect included in the scale at a low level.

In the study of risk factors, age, the course of diabetes, HCY and HbAlc were the independent risk factors for T2DM with MCI. Foreign studies have reported that T2DM cognitive dysfunction will aggravate with age [22]. The results of this study, which are consistent with the above research results, indicated that the age is neg-

Table 6. Multivariate logistic regression analysis of MoCA score and the connected factors

Factor	β	S.E	wald χ^2	*P*	OR	95% CI
Age	0.614	0.131	21.968	<0.001	1.848	1.429-2.389
Course of diabetes	0.459	0.137	11.225	0.001	1.582	1.210-2.070
Education level	-0.464	0.142	10.677	0.001	0.629	0.476-0.831
HCY	0.438	0.155	7.985	0.005	1.550	1.144-2.100
HbAlc	0.513	0.162	10.028	0.002	1.670	1.216-2.295

atively correlated with the MoCA score in patients with T2DM, and is an independent risk factor for the occurrence of MCI. The reason may be that brain function naturally deteriorates with age, and T2DM patients are subjected to factors that lead to brain damage, thus increasing the risk of MCI [23]. It has been reported that the incidence of cerebrovascular injury and brain atrophy increases with the progression of diabetes [24]. The results of this study showed that MoCA score was negatively correlated with the course of diabetes. This indicates that the longer the course of diabetes, the lower the MoCA score and the more severe the brain dysfunction of patients, which finding is consistent with that of a previous study [25]. HbAlc reflects the blood glucose control of T2DM patients in the past 3 months. Studies have found that good HbAlc control will contribute to the improvement of cognitive function [26, 27]. In this study, the score of MoCA is negatively correlated with HbAlc, and the latter is an independent risk factor of MCI for T2DM patients. The worse control of HbAlc level results in greater risk of cognitive impairment, which is consistent with research conclusion of other scholars. The reason is that the high HbAlc level indicates the unsatisfactory recent control of blood glucose in patients, and the long-term high glucose may impose toxic effects on central nervous system. In addition, high glucose status can also cause mitochondrial dysfunction and promote nerve cell apoptosis, which leads to cognitive dysfunction. HCY, which is a vascular injury-responsive amino acid, can directly damage the nerve cells with cognitive functions, thus causing the occurrence of cognitive dysfunction [28]. It is discovered in this research that HCY level in observation group was dramatically higher than that in control group, and multivariate logistic regression analysis showed that HCY level was an independent risk factor of MCI. Besides, according to the finds of the study, MoCA score was positively correlated with educational level, which proves that high educational level can reduce the risk of MCI, and T2DM patients with high educational level will have a reduced MCI risk. The reason is related to the stimulation of brain during education receiving process. The brain structure, neurobiological structure, and multiple synaptic connections undergo complex changes in the learning process, which enhance the compensatory ability of brain aging and thereby reduce the risk of MCI [29]. Therefore, we need to encourage people with diabetes to think, act and communicate more to reduce the risk of cognitive impairment. At present, the pathogenesis of cognitive dysfunction caused by T2DM is not fully clarified, and it is generally considered that mild cognitive dysfunction in T2DM patients may be related to the factors of course of disease, diabetes complications, blood glucose control and mental behavior abnormalities. There was no correlation between diabetes comorbidities and MoCA score in this study, which may be due to the small number of people selected in this study. In addition, there may be some commonalities between the cases from a single center, and deviations may exist in the results. Therefore, we look forward to further studying with multi-centers and large samples to support the results of this study. In this study, there was no significant difference in the levels of DBP, SBP, TG, TC, LDL-C and HDL-C between the two groups, which were considered not related to type 2 diabetes mellitus with mild cognitive impairment. Although some scholars believe that abnormal blood lipid and blood pressure may have a certain impact on cognitive function, in this study, it seems that blood lipid and blood pressure have little impact on cognitive function. At the same time, considering that this study only included patients with mild cognitive impairment, it is likely that blood lipid and blood pressure have not shown a significant impact on cognitive function. This needs to be confirmed by further research.

In summary, mental deficiency and phlegm obstruction are common in T2DM patients complicated with MCI. The factors such as age, diabetes course, education degree, HCY and HbAlc are closely related to cognitive impairment. The occurrence of MCI in T2DM patients can be prevented by improving the education degree of patients, effective control of blood glucose and reduction of HCY level.

Disclosure of conflict of interest

None.

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