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ORIGINAL RESEARCH

The Effect of Type 2 Diabetes Mellitus on Neuropsychological Symptoms in Chinese Early Alzheimer's Disease Population

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Objective: To explore the effect of Type 2 diabetes mellitus (T2DM) on the development of neuropsychiatric symptoms (NPS) in early Alzheimer's disease (AD).

Methods: From September 2017 to March 2019, a cross-sectional study was conducted on the clinical data of 158 early AD patients over 65 years old in the Department of Neurology of Daping Hospital. All early stage of AD patients were divided into early stage of AD with NPS group and early stage of AD without NPS group according to the presence or absence of NPS. Clinical data of age, sex, body mass index (BMI), smoking and alcohol consumption, history of hypertension, hyperlipidemia, white matter leisure (WML) and T2DM, MMSE, CDR and NPI-Q scores were collected. Multivariate logistic regression analyses were performed to examine the relationship between T2DM and NPS in early AD.

Results: Compared with the early stage of AD group without NPS, the early stage of AD group with NPS was older, the proportion of women was higher, the proportion of T2DM, hypertension, hyperlipidemia and WML was higher, and the MMSE score was lower ($P< 0.05$). T2DM was an independent risk factor for NPS in early stage of AD patients (OR 3.48, 95% CI 2.91–3.84). The incidence of T2DM in AD patients with depression, anxiety, nighttime behavioral disturbances, and appetite disturbances was significantly higher than in AD patients without these symptoms. T2DM was an independent risk factor of depression (OR 2.04, 95% CI 1.71–2.38), anxiety (OR 1.69, 95% CI 1.38–1.97), nighttime behavioral disturbances (OR 1.95, 95% CI 1.75–2.13) and appetite disturbances (OR 1.62, 95% CI 1.33–1.94) in early AD patients.

Conclusion: T2DM was an important independent risk factor for NPS in early AD, which promotes the occurrence of depression, anxiety, nighttime behavioral disturbances and appetite disturbances in early AD.

Keywords: Alzheimer's disease, type 2 diabetes, neuropsychiatric symptoms

Introduction

Alzheimer's disease (AD) is a common disease that causes dementia, and by 2050 there will be more than 100 million AD patients worldwide.[1] Cognitive decline is the core symptom of AD, but most AD patients are often accompanied by neuropsychiatric symptoms (NPS), and some patients even seek treatment at the first time because of NPS. In recent years, more attention has been paid to NPS of AD patients, but the early stage of AD patients may have different and atypical NPS, which are easily overlooked clinically. Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease mainly manifested as hyperglycemia, characterized by insulin resistance and relative reduction

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of insulin. Studies have found that T2DM often causes a variety of NPS, such as anxiety and depression which are about twice as common as normal people.[2] When AD patients are combined with T2DM, their pathological changes are aggravated and their cognitive impairment is accelerated.[3] It is not clear whether T2DM has any effect on the occurrence of NPS in the early stage of AD patients. This study provides an important clinical basis for the prevention and treatment of NPS by analyzing the risk factors associated with NPS in the early stage of AD patients.

Materials and Methods

Subjects

Continuously collected 158 early stage of AD patients who were treated at Daping Hospital from September 2017 to March 2019. Inclusion criteria: 1) age ≥ 65 years; 2) diagnosis of AD; 3) clinical dementia rating (CDR) score of 0.5 or 1; 4) completion of the Mini-mental State Examination (MMSE) and the Neuropsychiatric Inventory-Questionnaire (NPI-Q) assessment; 5) completion of laboratory inspection and imaging examination. Exclusion criteria: 1) a clear history of stroke, brain trauma, and intracranial tumors; 2) a clear history of psychosis; 3) non-AD dementia patients; 4) other neurological diseases that may affect cognition or cause NPS; 5) unfinished MMSE, CDR or NPI-Q assessment. The study was approved by the Ethics Committee of Daping Hospital of the Army Medical University (numbered: Medical Research (2018) No. 60), and all participants or guardians provided written informed consent to be included in this study, and that this study was conducted in accordance with the Declaration of Helsinki.

Clinical Data Collection

Age, gender, BMI, smoking and alcohol consumption, history of hypertension, hyperlipidemia, WML, T2DM and MMSE, CDR and NPI-Q scores were collected.

Diagnostic Criteria for AD

The diagnostic criteria for AD are based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association diagnostic criteria (NINCDS-ADRDA criteria).[4] Vascular dementia and mixed dementia were excluded using the Hachinski Ischemic Scale (HIS score ≥ 4).[5] Lewy body dementia was excluded using by the fourth edition of the Lewy Body Dementia Diagnosis and Management Consensus.[6] The use of frontotemporal dementia clinical diagnostic guidelines to exclude frontotemporal dementia.[7]

Diagnosis of the Early Stage of AD

The CDR scale was evaluated in AD patients, and the CDR score of 0.5 or 1 was defined as the early stage of AD.[8] Scoring criteria: Memory (M) is the main item and the others are the secondary items. CDR=M, if at least three secondary items scores are the same as the M scores; CDR=most secondary items score when three or more secondary items are scored higher or lower than the M score; three secondary items are scored on one side of M, two secondary items are scored on the other side of M, CDR=M; when M=0.5, if at least three other items are scored 1 or above, CDR=1; when M=0.5, the CDR cannot be 0, only 0.5 or 1.

Assessment of Cognitive Function

MMSE is used to measure cognitive function. The boundary score of MMSE was defined as <17 (illiteracy), <20 (primary school), <24 (middle school and higher). If the MMSE scale is lower or equal to the normal threshold, it will be judged as cognitive impairment, and the higher threshold is normal.[9]

Assessment of NPS

NPS were assessed based on the NPI-Q questionnaire:[10] NPI-Q consisted of 12 items (delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviors, nighttime behavioral disturbances, appetite disturbances), the insider indicates whether each symptom is present (yes or no). For each "yes" response, the person is asked to assess the severity (1–3) and frequency (1–4) of the symptoms, yielding a composite symptom domain score (frequency×severity). Frequency and severity rating scales have defined anchor points to enhance the reliability of caregiver responses.

T2DM Diagnosis and Exclusion Criteria

T2DM was based on the 2019 American Diabetes Diagnostic Criteria (fasting blood glucose ≥7.0mmol/l or OGTT 2 hr blood glucose ≥11.1mmol/l or HbAlc≥6.5%).[11] Exclude type 1 diabetes and diabetes caused by other causes such as monogenic diabetes syndrome, exocrine pancreatic disease, drugs or chemically induced diabetes.

Observation Projects and Grouping

The early stage of AD patients was divided into groups with and without NPS according to the patient's NPI-Q score. If any of the NPI-Q 12 items receives a "yes" response, the patient is considered to be accompanied by NPS. Observed whether there were differences in age, gender, BMI, smoking and alcohol consumption, etc. between the two groups, and whether there were differences in blood glucose, blood pressure, blood lipids and other indicators. To explore the relationship between T2DM and NPS in the early stage of AD patients.

Statistical Analyses

Data analysis was performed using SPSS 19.0 statistical software, and the usage rate of the count data was expressed. The chi-square test was used for comparison between the two groups. The measurement data obeying the normal distribution are represented by x±S, and the *t*-test is used for comparison between the two groups, and the non-parametric test is used without the normal distribution. Multivariate logistic regression was used to analyze the relationship between T2DM and NPS in the early stage of AD patients. The difference was statistically significant with $P<0.05$.

Results

Baseline Characteristics of Patients with Early Stage of AD

Compared with the early stage of AD group without NPS, the early stage of AD group with NPS was older, the proportion of women was higher, the proportion of T2DM, hypertension, hyperlipidemia and WML was higher, and the MMSE score was lower (P< 0.05). However, there were no significant differences in smoking history, drinking history, body mass index (BMI), and CDR scores between the two groups (P>0.05) (Table 1).

Table 1 Baseline Characteristics of the Early AD Patients with or Without NPS

Items	Early Stage of AD with NPS (N=91)	Early Stage of AD Without NPS (N=67)	P
Age, mean(SD), y	74.4±5.7	71.3±4.9	0.042
Female, No. (%)	55 (60.44)	31 (46.27)	0.039
History of smoking, No. (%)	27 (29.67)	19 (28.35)	0.559
History of drinking, No. (%)	24 (26.37)	18 (26.87)	0.632
BMI (kg/m^2, x±s)	25.3±3.9	24.6±3.1	0.147
T2DM, No. (%)	52 (57.14)	18 (26.87)	0.006
Hypertension, No. (%)	58 (63.73)	35 (52.24)	0.038
Hyperlipidemia, No. (%)	50 (54.95)	28 (41.79)	0.041
WML, No. (%)	62(68.13)	27 (40.30)	0.017
MMSE Score, mean(SD)	23.2±1.8	24.6±1.3	0.045
CDR Score, mean(SD)	0.72±0.11	0.69±0.13	0.632

Abbreviations: AD, Alzheimer's disease; T2DM, type 2 diabetes; BMI, body mass index; WML, white matter lesions; MMSE, simple mental status assessment scale; CDR, Clinical Dementia Rating; NPS, neuropsychological symptoms.

The Independent Risk Factors for NPS in Early AD Patients

In the multivariate logistic regression analysis model, after adjusting for age, gender, T2DM, hypertension, hyperlipidemia, and WML, T2DM (OR: 3.48, 95% CI: 2.91–3.84), hypertension (OR: 1.56, 95% CI: 1.31–1.89) and WML (OR: 3.13, 95% CI: 2.75–3.52) were significantly associated with the early stage of AD with NPS, and T2DM had the highest risk factor (Table 2).

The Incidence of T2DM in AD Patients with Various Psychiatric Symptoms

We also calculated the incidence of T2DM in various neuropsychiatric symptoms, and the results showed that the incidence of T2DM in AD patients with depression, anxiety, nighttime behavioral disturbances, and appetite disturbances was significantly higher than in AD patients without these symptoms (P< 0.01). The incidence of T2DM in AD patients with agitation is higher than in AD patients without agitation (P< 0.05) (Figure 1).

The Relationship Between T2DM and Various NPS in Early AD Disease

In the multi-factor logistic regression analysis model, after adjusting the relevant confounding factors, T2DM was an independent risk factor for depression (OR: 2.04, 95% CI: 1.71–2.38), anxiety (OR: 1.69, 95% CI: 1.38–1.97), nighttime behavioral disturbances (OR: 1.95, 95% CI: 1.75–2.13), and appetite disturbances (OR: 1.62, 95% CI: 1.33–1.94) in the early stage of AD patients. It was not an independent risk factor delusions, hallucinations, agitation, euphoria, apathy, disinhibition, irritability, aberrant motor behaviors (Table 3).

Discussion

This different type of non-cognitive disorder, also known as behavioral and psychological symptoms in dementia or NPS, affects approximately 90% of AD patients.[12] Previous studies have shown that with advancing cognitive

Table 2 The Independent Risk Factors for NPS in Early AD Patients (Logistic Regression Analysis)

Items	OR Unadjusted (95% CI)	P	OR Adjusted (95% CI)	P
Age	1.30 (1.06–1.72)	0.046	1.31 (1.01–1.76)	0.055
Female	1.77(1.36–2.11)	0.043	1.53 (1.30–2.01)	0.053
T2DM	3.63 (2.98–3.93)	0.007	3.48 (2.91–3.84)	0.005
Hypertension	1.61 (1.34–1.93)	0.031	1.56 (1.31–1.89)	0.038
Hyperlipidemia	1.70 (1.27–2.09)	0.039	1.64 (1.22–2.04)	0.052
WML	3.17 (2.79–3.49)	0.023	3.13 (2.75–3.52)	0.021

Note: Multivariate logistic regression analysis adjusted for age, gender, T2DM, hypertension, hyperlipidemia, WML.

Abbreviations: AD, Alzheimer's disease; T2DM, type 2 diabetes; WML, white matter lesions; NPS, neuropsychological symptoms; OR, odds ratio; 95% CI, 95% confidence interval.

decline in AD patients, neuropsychiatric symptoms include apathy, depression, agitation, and aggression, to psychosis. With the gradual decline in cognition and function in patients with AD dementia, the presence of NPS is thought to represent neurodegeneration in the nervous system.[13–16] However, different neuropsychiatric measurements and clinical definitions have blurred the true incidence and progression of NPS in AD patients. Our results showed that T2DM, hypertension and WML were significantly correlated with the development of NPS in patients with early AD, and T2DM had the highest risk of promoting the development of NPS in patients with early AD. And we also found that the incidence of T2DM in AD patients with depression, anxiety, nighttime behavioral disturbances, and appetite disturbances were significantly higher than in AD patients without these symptoms. It was further found that T2DM is an independent risk factor for anxiety, depression, nighttime behavioral disturbances and appetite disturbances in AD patients, rather than independent risk factors for delusions, hallucinations, agitation, euphoria, apathy, disinhibition, irritability, aberrant motor behaviors.

Eustace et al[13] found that the NPS symptoms of AD trend into 3 "phases": first, irritability, depression, and nighttime behavioral disturbances; then, anxiety, appetite disturbances, agitation and apathy; finally, excitement, dyskinesia, hallucinations, delusion and disinhibition. More serious non-cognitive symptoms, such as excitation, dyskinesia, hallucinations, delusions and disinhibition appear in progressive ad dementia. Our results showed that T2DM is a risk factor for anxiety, depression, nighttime behavioral disturbances and appetite disturbances in early AD patients, which is consistent with the above views. Aβ load, neuron apoptosis and glucocorticoid level rise are all the possible mechanisms of various NPS in early AD. The progressive deposition of Aβ and local neurodegeneration of subcortical structure affects the activity of limbic system and neocortex,[17] destroy the brain circuit involved in emotional response;[18] the deposition of Aβ weakens the inhibition of hippocampus on HPA axis, and increases the level of glucocorticoids.[19] The amyloid peptide of T2DM can aggregate or form a molecular hybrid with Aβ, participate in the formation of amyloid plaque, promote the abnormal modification of tau, and damage the activity of neurons;[20,21] hyperglycemia and insulin resistance increase the generation of Aβ,[22] make the dendrites at the top of neurons shrink, and reduce presynaptic vesicles.[23]

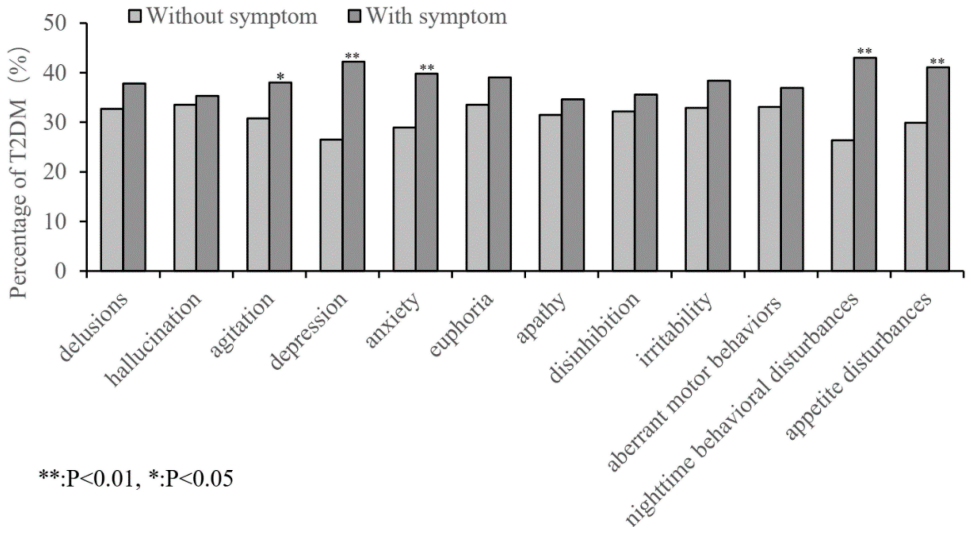

Figure 1 Incidence of T2DM in AD patients with various psychiatric symptoms.

Abbreviations: AD, Alzheimer's disease; T2DM, type 2 diabetes; NPS, neuropsychological symptoms.

Table 3 The Relationship Between T2DM and Various NPS in Early AD Disease

Items	Delusions OR (95% CI)	Hallucination-Ns OR (95% CI)	Agitation OR (95% CI)	Depression OR (95% CI)	Anxiety OR (95% CI)	Euphoria OR (95% CI)	Apathy OR (95% CI)	Disinhibition OR (95% CI)	Irritability OR (95% CI)	Aberrant Motor Behaviors OR (95% CI)	nighttime Behavioral Disturbances OR (95% CI)	Appetite Disturbances OR (95% CI)
Without T2DM	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
With T2DM	1.24 (0.93–1.47)	1.12 (0.82–1.35)	1.17 (0.91–1.42)	2.04 (1.71–2.38)	1.69 (1.38–1.97)	1.27 (0.95–1.49)	1.09 (0.89–1.30)	1.13 (0.84–1.46)	1.21 (0.96–1.49)	1.36 (0.97–1.71)	1.95 (1.75–2.13)	1.62 (1.33–1.94)

Note: Multivariate logistic regression analysis adjusted for age, gender, hypertension, hyperlipidemia.
Abbreviations: AD, Alzheimer's disease; T2DM, type 2 diabetes; NPS, neuropsychological symptoms; WML; OR, odds ratio; 95% CI, 95% confidence interval.

AD is also known as type 3 diabetes, which shows that there is a close relationship between AD and diabetes. Many studies have found that T2DM is an important risk factor for AD. A study by Barbagallo et al found that T2DM increased the risk of ad at least twice.[24] Cheng et al studied 1488 diabetic patients in New York and found that T2DM was closely related to the development of AD. Their study also found that the relationship between T2DM and AD may be mediated by pathological changes of cerebral vessels.[25] Huang et al found that after adjusting for age, patients with T2DM had a significantly higher risk of developing AD than those without T2DM.[26] Moran et al performed a brain MRI scan of 350 T2DM patients and 363 controls. They found that the volume of gray matter, white matter, and hippocampus in T2DM patients was significantly reduced compared with non-diabetic patients. It is further observed that the loss of gray matter in T2DM patients mainly occurs in medial temporal, anterior, cingulate, and medial frontal lobes.[27]

Other studies have found that T2DM can impair the non-cognitive function of CNS. The study found that 12% of patients with T2DM developed severe depression and 31% had mild or subclinical depression.[28] T2DM increased the production of inhibitory neurotransmitters in the brain,[29] active HPA axis increased the production of glucocorticoids,[30] and promoted the occurrence of depression. Studies have shown that poor glycemic control promotes depression in patients with T2DM.[31] For every 1% increase in HbA1c mean, the incidence of depressive symptoms increases by 1.31 times, and the mean HbA1c>7% is significantly associated with the number of T2DM depressive symptoms.[17] Kruse et al found that T2DM had an effect on the occurrence of NPS, especially anxiety, which was consistent with our findings. However, they also found that T2DM with HbA1c greater than 7% had no significance, while T2DM with HbA1c less than 7% had significance.[32] This is not consistent with the supposed effect of the severity of T2DM on NPS, because HbA1c is only one aspect of T2DM control, and patients who are well controlled may be severely treated with insulin, while patients who are poorly controlled may still be on diet, exercise or medication in the early stages of T2DM.

Some scholars have screened more than 2000 diabetic patients and found that 32.0% of patients exceeded the "mild to severe" anxiety score of HADS, which was significantly higher than the general population sample.[33] Trento et al studied the relationship between diabetes and cognitive function, anxiety, depression, and found that depression was associated with female not modified by diabetes duration or switching to insulin therapy.

Diabetes duration and lower schooling may affect anxiety and cognitive impairment.[34] T2DM can increase the level of serum CRP. The study found that there is a positive correlation between anxiety symptoms and high CRP level in serum, which may be one of the mechanisms of the relationship between T2DM and anxiety symptoms.[35,36]

Fasting blood glucose directly affects the expression of clock genes (related to the regulation of circadian rhythm),[37] and insulin resistance increases with time to increase somatic autonomic symptoms (such as fatigue, sleep disorders, and appetite changes).[38] The pineal gland in the brain acts as a "zeitgeber" by secreting melatonin to drive the circadian rhythm. Melatonin and insulin regulate the expression of core clock genes through feedback from various transcription factors.[39–41] Recent studies have found that mutations near the core clock gene member CRY2 are associated with elevated fasting blood glucose in humans.[42] On the other hand, studies have found that insulin resistance can increase somatic autonomic symptoms (such as fatigue, sleep disorders, and appetite changes) as the disease progresses. Our study supports the view that T2DM promotes nighttime behavioral disturbances in early AD patients.

Typical symptoms of T2DM include eating more and drinking more, highly coordinated interactions between the brain and peripheral metabolic organs are critical for the maintenance of energy and glucose homeostasis.[43] The use of diabetes drugs, such as GLP-1 and its analogues, can lead to reduced food intake. A concern about the specificity of the feeding-inhibitory actions of GLP-1 has arisen due to the idea that the decreases in food intake after treatment with GLP-1, or a synthetic analog, are attributable to visceral illness or feelings of nausea. GLP-1 is able to induce a conditioned taste aversion (CTA) under a variety of conditions, but the satiety and CTA effects appear to be nuclei-specific.[44]

This study has some limitations. First, this study was a cross-sectional study, which concluded that T2DM was associated with onset of mental symptoms in the early stage of AD patients, rather than a causal relationship. Second, in the assessment of NPI-Q, informed persons have certain subjectivity in the assessment and evaluation of AD patients' conditions,[45] which may have an impact on the results. Third, in the early stage of AD, the CDR scores usually fluctuate between 0 and 0.5.[46] In conclusion, our study found that T2DM had a significant effect on the occurrence of NPS in the early stage of AD patients, and preventing the occurrence of T2DM might reduce the incidence of NPS, providing a theoretical basis for clinical treatment of AD patients with T2DM.

Ethics and Consent Statement

The study was approved by the Ethics Committee of Daping Hospital of the Third Military Medical University. The subjects received oral and written information regarding the study and provided informed consent prior to their inclusion in this study.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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