The pathogenesis and clinical features of cerebrovascular disease in diabetes mellitus

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Abstract

Cerebrovascular disease is a kind of complications in diabetes mellitus which is induced by sugar, fat and protein metabolic disorder. These series of nutrient metabolic disorder can lead to intracranial large blood vessels and microvascular lesions. About 20-40 percent of type 2 diabetes patients will suffer from cerebrovascular diseases which become the main causes of death in diabetic patients [¹]. Recently many kinds of pathogenesis have been found by researchers about cerebrovascular diseases in diabetes mellitus such as hyperglycemia, insulin resistance [²], endothelial cell dysfunction [³], abnormal lipids metabolism and so on. The major clinical manifestations of diabetic cerebrovascular diseases are asymptomatic cerebral atherosclerosis, stroke, cerebral small vessel diseases and acute cerebral vascular diseases. This article will introduce the...
pathogenesis and clinical features of diabetic cerebrovascular diseases in detail. We will also focus on its latest research progress.

**Key words:** cerebrovascular disease; diabetes mellitus; pathogenesis; clinical features.

1 Introduction

As the rapid development of economic and people's living standard, the incidence of diabetes mellitus and cerebrovascular diseases is also higher and higher. Diabetes mellitus is a type of chronic metabolic disease, of which the level of the blood glucose is above the average. The present research has found that diabetes mellitus has serious effects on a prognosis of acute cerebrovascular diseases [4]. Acute cerebrovascular diseases are a kind of common complications in diabetes mellitus. In addition, the chronic complications in patients are very complicated, mainly including the microvascular diseases. The cerebrovascular diseases in patients with diabetes mellitus are the most severe complications, especially in patients with type 2 diabetes mellitus. The hyperglycemia in patients with type 2 diabetes mellitus, caused by the insulin resistance or the reduction of the insulin secretion, can induce many risk factors to damage the blood vessel, such as the various cytokines in inflammatory reaction [5], the metabolic disorders of sugar or lipid, and the changes of hemodynamics.

2 The pathogenesis of diabetic cerebrovascular disease

Diabetic cerebrovascular diseases include intracranial large blood vessels
and microvascular lesions. The main pathological changes of intracranial large blood vessels lesions are the atherosclerosis. The typical pathological changes of microvascular lesions are vascular basement membrane thickening and microcirculation disturbance.

2.1 The pathogenesis of intracranial large blood vessels lesions

2.1.1 Hyperglycemia

The toxic effect of hyperglycemia is an important cause of cerebrovascular disease in diabetes mellitus. Diabetes is a disease of glucose intolerance, and so much of the research on complications has focused on the role of hyperglycemia. Clinical trials have clearly demonstrated the role of hyperglycemia in cerebrovascular complications of diabetes.

Hyperglycemia can increase the activity of glucose transporter 1 in the nerve cells which can product all kinds of traumatic medium. It can also increase lactate production and exacerbates brain tissue acidosis by increasing the available glucose for anaerobic glucose metabolism and inhibiting mitochondrial respiration. It also causes vasogenic edema, which impairs collateral blood flow, increases the hyperthrombotic state, decreases cerebral blood flow and possibly impairs cerebral autoregulation.

Hyperglycemia mainly damages brain tissue through four ways: advanced glycosylation end products; the activation polyol pathway; the activation of DAG-PKC pathway; the activation of Hexosamine pathway.

2.2.2 Insulin resistance
Insulin resistance has a close relationship to diabetes mellitus which is a fundamental aspect of the aetiology of type 2 diabetes. Insulin resistance has been shown to be associated with atherosclerosis, glucose intolerance, hyperuricaemia, hypertension, Ischemic stroke and so on\textsuperscript{[9]}. It may play a key role at the beginning of these complications.

The insulin can stimulate the insulin-like growth factors which have the function of promoting the synthesis of lipid in vascular smooth muscle cells and fibroblasts. The synthesis of very low density lipoprotein will also increase in the liver. In addition, the insulin can make the content of original plasma fibrinolytic enzyme activators inhibitors rise. Thus the insulin finally results in the formation of blood clots.

2.2.3 Endothelial cell dysfunction

The Diabetes mellitus is often accompanied with endothelial dysfunction and endothelial-dependent vasodilatation dysfunction which can result in the damage of endothelial cells. The damage of endothelial cells is a series of inflammatory responses in essence. In the process of the endothelium damage, many cytokines and adhesion molecules are secreted in a high level, then the inflammatory cells adhere to the endarterium and move into the vascular wall. The blood platelets get together and adhere to the vascular wall in the inflammatory reaction process. At the same time, the serum inflammatory factors, such as C-reactive protein (CRP), interleukin-6 and interleukin-17, is released into the blood. They play a great role in the process of the vascular
Vascular endothelial dysfunction can also make vascular tension and hemodynamics change and increase the capillary permeability. The blood coagulation system and platelet will be activate\textsuperscript{[10]}. Because of inflammation, the vascular wall is damaged and the endothelial cells become necrotic. Thus the thrombus forms in the brain and a series of intracranial large blood vessels lesions occur such as hemorrhagic stroke\textsuperscript{[11]}.

2.2.4 Abnormal lipids metabolism

Diabetes mellitus is associated with abnormal postprandial lipoprotein metabolism, with a significant delay in the clearance of many lipid parameters\textsuperscript{[12]}. It has been reported that the levels of diabetes patients triacylglycerol, low density lipoprotein cholesterol and total cholesterol are categorized as higher than normal people; the levels of diabetes patients high density lipoprotein cholesterol are categorized as lower than normal people\textsuperscript{[13]}.

It has been found that the sedimentary of low density lipoprotein cholesterol is related to the migration of mononuclear leucocytes. The mononuclear leucocytes can adhere to the vascular wall, then go across the endothelium layer toward the vascular wall and become macrophagocytes. The macrophagocytes phagocytize the low density lipoprotein cholesterol which is increased in diabetes mellitus patients. Then these cells become the xanthoma cells. When the xanthoma cells degenerate and become necrotic cells, the lipid within the cells will be released.
into the vascular wall, and the extracellular lipid nuclear is formed. Then the blood platelets are activated and the thrombus is formed. Afterwards, the vessels become narrow or completely occlusive in the very severe cases\textsuperscript{[14]}. In addition, the abnormal lipids metabolism can increases the blood viscosity and changes the haemodynamics, both of which maybe accelerate the development of atherosclerosis\textsuperscript{[15]}.

2.2 The pathogenesis of microvascular lesions

The intracranial microvascular lesions of diabetes mellitus are often initiated by hemodynamic abnormalities of brain capillaries. Then it will lead to the microvascular thrombosis. In recent years, a series of vascular factors, growth factors\textsuperscript{[16]} and cytokines have been found that they are closely related to the occurrence of microvascular lesion development such as Angiotensin II, endothelin, nitric oxide, tumor necrosis factor \(\alpha\). They play a key role in the formation of microthrombus through a variety of different mechanisms.

3 clinical features of diabetic cerebrovascular diseases

The cerebrovascular diseases complicated in diabetes mellitus patients include the ischemic cerebrovascular disease and the hemorrhagic cerebrovascular disease. Through the pathogenesis mentioned above, it is known that the DM can induce the ischemic cerebrovascular disease by multiple factors, such as cerebral infarction and transient ischemic attack.
The hemorrhagic cerebrovascular disease is mainly caused by the rupture of the brain blood vessels. The rate of hemorrhagic cerebrovascular disease in DM patients with the hypertension is higher than those without hypertension. Both hyperglycemia and hypertension can induce the risk factors to act on the brain vessels and to make them easy to be ruptured. It provided an evidence that the risk of ischemic stroke increased continuously with the duration of diabetes mellitus [17].

3.1 Transient ischemic attack

Transient ischemic attack is considered to be a major risk factor of cerebral infarction. The manifestations of transient ischemic attacks are varied and include events that involve the anterior and posterior cerebral circulations. It is uncommon that syndromes such as syncope, isolated dizziness, drop attacks, or global amnesia are caused by transient ischemic attack. Hemiparesis, hemisensory loss, hemifacial weakness of upper motor neuron distribution, amaurosis fugax, and aphasia are some of the typical presenting symptoms of transient ischemic attack [18]. A differential diagnosis of transient ischemic attack includes a wide variety of neurologic disorders. Space-occupying lesions, such as seizures, hypoglycemia, migraine headaches and syncope are all part of the differential diagnosis.

3.2 Cerebral infarction

Cerebral infarction is a kind of major complications in diabetes mellitus patients. It has been studied that patients with diabetes presented more
frequently with ischemic stroke, especially lacunar infarction, compared with non-diabetes\textsuperscript{[19]}. In the aspect of clinical symptoms, it is easier for patients with diabetic cerebral infarction to have movement dysfunctions. Although the clinical symptoms of movement dysfunctions are not very severe, it is difficult to recover. The morbidity of pseudobulbar palsy and vascular dementia are higher than non-diabetic patients. Tuttolomondo\textsuperscript{[20]} has studied that the clinical symptoms of Ischemic stroke patients accompanied with hyperglycemia are more severe than normal blood glucose patients, especially in disturbance of consciousness and spirit symptoms.

3.3 Cerebral hemorrhage

It provides an evidence that diabetes mellitus induce the risk factors to act on the brain vessels and to make them easy to be ruptured. A study showed that among those with diabetes, risk of ischemic stroke is 3 times higher than those without diabetes, and it also provided an evidence that the risk of ischemic stroke increased continuously with the duration of diabetes mellitus.

The role of diabetes mellitus in the etiopathogenesis of spontaneous intracerebral hemorrhage is controversial. In recent years Herzig\textsuperscript{[21]} has reported that the morbidity of Cerebral hemorrhage in diabetic patients is higher than those of non-diabetes. Its clinical symptoms is severe and its mortality is high. The cure rate is low.

4 Summary

Diabetic cerebrovascular diseases are
a kind of severe complications following diabetes mellitus. It is not an easy thing to cure them. We conclude that the prevention of DM complications is the best approach at the moment. The preventive measures include good living habits, such as smoking cessation, limiting alcohol and avoiding high-glucose and high-fat diet, is an effective way to prevent the stroke. It helps decrease the morbidity and mortality in stroke patients with DM and improve the patients' life quality. It is notable that these treatments can only prevent the development of the complications in the brain vessels in DM patients but cannot thoroughly rescue the brain damage. More effective treatments are needed to prevent the occurrence and development of the cerebrovascular disease in DM patients.

Reference


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