

Advances in the study of the pathogenesis of ischemic stroke

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Abstract: Ischemic stroke is a common neurological disease with the characteristics of high morbidity, high mortality and high recurrence, and its pathogenesis has been one of the hot spots of research. In recent years, with the continuous development of neuroscience and biomedical research methods, a lot of progress has been made in the study of the pathogenesis of ischemic stroke. This paper reviews the literature on the pathogenesis of ischemic stroke at home and abroad in recent years, and summarizes the pathophysiological changes involved in the development of ischemic stroke and the risk factors that may lead to its occurrence and progression, to better understand the pathogenesis of ischemic stroke and provide more effective means for its prevention and treatment.

Keywords: ischemic stroke; pathogenesis; genetic susceptibility

1. Introduction

Cerebral infarction, also known as ischemic stroke (IS), is a limited ischemic necrosis or softening of brain tissue due to impaired blood circulation to the brain [1]. As one of the most common neurological disorders in adults, the annual global incidence varies from approximately 80-130 cases per 100,000 population, in addition to being the second leading cause of disability and death worldwide and the most burdensome disease in low- and middle-income countries [2]. IS has different staging, the most common being the TOAST staging. The TOAST staging treats IS as a syndrome, based on imaging IS is classified into 5 types based on imaging features and other positive findings of ancillary tests: large artery atherosclerosis (LAA), cardiogenic embolism (CE), small artery occlusion (SAO), other etiologies, and unknown causes. Of these, the LAA type is the most common type of TOAST staging, accounting for approximately 20% of IS patients [3]. Clinically, the diagnosis of ischemic stroke relies on the typical clinical presentation combined with relevant imaging examinations (cranial CT, diffusion-weighted MRI, MRA, CTA and DSA, etc.). However, in some cases, there are diagnostic challenges, such as unknown time of onset, atypical symptoms, and delayed imaging examinations, leading to misdiagnosis or missed diagnosis. Therefore, it is important to predict the occurrence of ischemic stroke early and intervene in a timely manner to stop the onset and progression of the disease. Clarifying the pathogenesis of ischemic stroke can help to determine prognosis, guide treatment and select individualized secondary prevention measures, and also help to conduct relevant clinical studies on unknown areas to better address patient-specific problems. In this article, we review the pathogenesis of ischemic stroke to prevent and guide the treatment of ischemic stroke.

2. Genetic mechanism

Ischemic stroke is a multifactorial disease that includes traditional modifiable risk factors such as hypertension, smoking, diabetes mellitus and hyperlipidemia [4, 5]. However, with the development of modern medicine, personalized prevention and treatment strategies based on patients' genetic information have gradually become routine [6]. In Asian populations, several studies have shown that certain genes are associated with ischemic stroke, such as CELSR1, PRKCH, PTCSC3, C10RF156, and XYLB [7-10]. Among them, the 1425G/A polymorphism in the PRKCH gene has the strongest association with lacunar stroke [11]. A recent study by Pulit et al [12] also found that the HDAC9 gene variant within chromosome 7p21 was associated with a 39% increased risk of LAA. In addition, Steffensen et al. found [13] that the small vessel disease-associated genes associated with ischemic stroke are COL4A1 and COL4A2, which are located at the 13q34 locus and encode the $\alpha 1$ and $\alpha 2$ chains of type IV collagen.

Although these genetic variants are mainly inherited in an autosomal dominant manner, the rate of de novo mutations is also high (approximately 40%). Recent studies have also found [14] that ACSL4 is inhibited early in ischemic stroke and that this inhibition is induced by HIF-1 α . Lower ACSL4 protected mice from cerebral ischemia, however, forced overexpression of ACSL4 exacerbated ischemic brain injury. ACSL4 promotes neuronal death by enhancing lipid peroxidation. These findings suggest that the etiology of ischemic stroke is complex and includes environmental and genetic factors, as well as their interactions. For people with stroke, early screening may help to identify genetic risk factors, which will help to develop individualized prevention and treatment strategies.

3. Immunological mechanisms

Immune cells play an important role in the pathogenesis of ischemic stroke. Among them, migration and activation of immune cells such as neutrophils, monocytes and T cells are the main causes of inflammatory response and neuronal damage. In a study by Vidal et al [15], it was noted that neutrophils induce the formation of neutrophil outer networks (NETs) by releasing IL-8, an inflammatory mediator, and release harmful substances such as DNA, proteases and oxygen free radicals from NETs, further exacerbating ischemia-reperfusion injury. This finding demonstrates the role of neutrophils in ischemic stroke injury, and also provides new therapeutic ideas to alleviate neutrophil-mediated neuronal injury. In contrast, monocytes and T cells can disrupt the blood-brain barrier (BBB) by releasing cytokines and chemokines, inducing more immune cells into the ischemic areas of the brain and exacerbating the inflammatory response [16,17]. In addition, immune cells can cause a more complex immune response by activating the complement system, producing antibodies and other mechanisms that disrupt the immunity of the brain and expose neuronal antigens to the periphery, further stimulating the inflammatory response [18]

4. Mechanisms of inflammatory response

Inflammation exerts an important and complex influence throughout the ischemic stroke process [19]. Although the mechanisms of inflammation in stroke have not been fully elucidated, studies have shown that the blood inflammation-related factors homocysteine (Hcy), C-reactive protein (CRP), and alkaline phosphatase (ALP) are significantly associated with stroke etiology, risk factors, severity, and clinical outcome. Proliferation, endoplasmic reticulum stress, and other pathological changes that play an important role in the pathogenesis of diseases such as atherosclerosis and ischemic stroke [20, 21]. In a 2017 study [22], Hcy has been shown to promote neuroinflammation and microglia activation by activating signal transduction and transcriptional activator-3 in a middle cerebral artery occlusion-reperfusion model in rats. A study by A. Zhang et al. in China [23] showed that hyperhomocysteinemia has become one of the recognized independent risk factors for cerebrovascular disease, and the mechanism of its occurrence involves cystathionine beta synthase (CBS), methionine synthase (MS) and betaine-homocysteine methyltransferase (BHMT), which are key enzymes in the metabolic process of Hcy, and mutations in the corresponding genes cause alterations in enzyme activity, which in turn affect the metabolic process of Hcy. A study by Seo et al [24] found that C-reactive protein (CRP) levels were independently correlated with early neurological deterioration after ischemic stroke, suggesting a role for inflammatory responses in late stroke recovery. A study by Cai et al [25] also confirmed that circulating levels of high-sensitivity C-reactive protein (hs-CRP) were associated with adverse clinical outcomes. In addition, a study by Wu et al [26] found that high hs-CRP circulating levels were an independent risk factor for mortality at different follow-up times in a study of elderly patients with ischemic stroke with small cerebral artery lesions over 60 years of age, suggesting a predictive and preventive role of hs-CRP in elderly patients with ischemic stroke with small cerebral artery lesions. In contrast, a study by Tan et al [27] revealed that elevated circulating levels of alkaline phosphatase (ALP) in the blood of stroke patients may be associated with an increased risk of stroke, suggesting a potential role of ALP in the pathophysiological mechanisms of stroke, although the underlying molecular mechanisms are not known, an observation supported by other studies suggesting that ALP may be an important inflammatory biomarker of stroke. In addition, a study by Uehara et al [28] also showed that in patients with transient ischemic attack, the higher the serum ALP level at admission, the higher their risk of subsequent stroke. Taken together, these findings provide new insights and evidence for the role of inflammatory response in stroke pathogenesis, prediction, and prevention.

5. Lipid metabolism and accumulation

Liu Ning et al [29] studied 63 patients with large atherosclerotic cerebral infarction and 38 healthy individuals. They use flow cytometry direct immunofluorescence staining for peripheral blood NK cell levels and fully automated biochemical analyzer for serum cholesterol values, comparing the differences between the two groups. Shen Xueyang [30] used univariate analysis and multifactor logistic regression combining carotid plaque, and the results showed that high levels of cholesterol were closely associated with carotid plaque in ischemic stroke patients and were an independent risk factor for the occurrence of carotid plaque events, which identified high levels of cholesterol as an independent risk factor for the occurrence of carotid plaque events, which can help to strengthen the monitoring and intervention for people with high cholesterol. Monitoring and intervention for people with high cholesterol. Zhai Qijin [31] demonstrated an association between trimethylamine oxide (TMAO), a metabolite of intestinal flora, and cardiovascular disease, with plasma TMAO levels correlating with internal carotid artery plaque stability. Shuai et al [32] showed that LDL, cholesterol and triglycerides are etiologically underlying ischemic stroke, particularly large artery and small vessel ischemic stroke, and Yang et al [33] found that lower LDL-C and higher glucose were independent risk factors for LAA. The in-depth study of these literature explored the pathogenesis and risk factors of ischemic stroke provides new ideas for ischemic stroke prevention, which can help early screening and intervention in high-risk groups. However, the shortcomings of the study are that the number of study subjects is small, and the application of the findings needs to be verified in more clinical practice. Meanwhile, the depth of the study also needs to strengthen the exploration and analysis of lipid molecules separately in order to understand the pathogenesis of ischemic stroke more comprehensively.

6. Other non-genetic risk factor mechanisms

Alcohol consumption is a global social habit and cultural phenomenon, but the relationship between alcohol consumption and ischemic stroke is highly controversial. Some studies suggest that alcohol consumption may promote the development and progression of atherosclerosis. This is because alcohol is a pro-oxidant [34] and can cause changes in certain substances, such as elevated prostaglandin levels and altered lipid peroxidation. These changes may lead to cerebrovascular endothelial dysfunction and play a role in the early stages of atherosclerosis. Some related studies have shown that alcohol consumption may also cause impairment of endothelial function by activating the cyclooxygenase and phosphatase systems and generating oxygen radicals [35]. In addition, alcohol consumption enhances and prolongs the inflammatory effects of pro-inflammatory factors [36] and microglia [37], such as interleukin-1, interleukin-6, and tumor necrosis factor TNF- α , leading to extensive damage to brain tissue and cerebrovascular vessels. In addition, alcohol consumption may enhance the oxidative toxicity of LDL [37]. Arenillas et al [38] showed that in diabetic patients, alcohol consumption may cause more severe effects on the neurological and cardiovascular systems. Patients with type II diabetes are more likely to develop intracranial atherosclerosis and have a significantly higher number of diseased vessels compared to non-diabetic patients. Intracranial atherosclerosis is strongly associated with the development of large-artery atherosclerotic stroke, which confirms that diabetes increases the risk of large-artery atherosclerotic stroke. Similarly, Zafar [39] study also confirmed diabetes as a risk factor for ischemic stroke. Therefore, in people with chronic diseases such as diabetes, alcohol consumption should be limited, especially in terms of frequency and intake of alcohol. It should be noted that the effects of alcohol consumption vary from person to person and depend on a variety of factors such as the type, amount, frequency, individual characteristics and environment of alcohol consumption. To prevent the occurrence and progression of ischemic stroke disease, comprehensive measures should be taken, including improving lifestyle, controlling diet, quitting smoking and limiting alcohol consumption, and enhancing physical exercise. These measures can effectively reduce the risk of ischemic stroke and improve the quality of life.

7. Problems and future trends

Ischemic stroke is a complex disease whose pathogenesis involves a combination of factors, including genetic susceptibility, immune imbalance, inflammatory response, lipid metabolism and accumulation, alcohol, and diabetes mellitus. Together, these factors lead to ischemic brain injury and neuronal death, resulting in the development of ischemic stroke. In addition, the pathogenesis of ischemic stroke is closely related to individual genetic background, environment, and lifestyle factors, making it a multifactorial and comprehensive disease. Although some research progress has been made in the

pathogenesis of ischemic stroke, there are still opinions and disagreements in some respects. For example, some studies suggest that the pathogenesis of ischemic stroke is due to inadequate cerebral perfusion [40], whereas others suggest that it is due to thrombosis and vascular stenosis [41]. In addition, there is still controversy and confusion regarding the prognosis and treatment of some ischemic stroke patients. Also, we are faced with several challenges and problems. The lack of targeted therapeutic approaches, the lack of effective prognostic assessment methods, and the lack of efficient early diagnosis methods are the main factors that limit our ability to investigate and address the pathogenesis of ischemic stroke in depth. However, the development in the fields of bioinformatics, genomics and translational medicine will provide more new ideas and methods for early diagnosis, treatment, and prognosis assessment of ischemic stroke. We can develop more targeted and effective prevention and treatment methods through further in-depth research and exploration of the pathogenesis of ischemic stroke. These methods will hopefully provide better prognosis and treatment outcomes for ischemic stroke patients, thus better addressing the serious social problems caused by ischemic stroke.

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