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Progress in the application of HRMR-VWI in ischemic stroke

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Abstract: *China is facing the biggest stroke challenge in the world. At the same time, due to the improvement of production technology and the change of survival mode, stroke diseases appear younger trend, of which ischemic stroke accounted for the main proportion, mainly due to intracranial artery disease caused by artery stenosis, the main cause is atherosclerosis disease. At the same time, it also includes aneurysm, vasculitis, artery dissection, moyamoya disease and other reasons. High resolution vascular wall imaging is a non-invasive and advanced examination technology, which can directly visualize intracranial vascular wall and its pathological changes, and has been widely studied and applied in various intracranial artery diseases in recent years. In this paper, the advantages, imaging evaluation, risk factors and application progress of this technique in intracranial atherosclerosis were reviewed.*

Keywords: *Vascular wall imaging; Ischemic stroke; Risk factors*

1. Introduction

Stroke is a cerebrovascular disease. Ischemic stroke is the most common type of stroke, and hemorrhagic stroke is also included. It is characterized by sudden onset of symptoms and clinical signs, and high rates of mortality, morbidity, recurrence, and disability. The "China Stroke Report 2020" shows that China is facing the biggest stroke challenge in the world, with stroke mortality, morbidity and prevalence still increasing. According to the Global Burden of Disease (GBD) study, the leading cause of disability adjusted life years (DALYs) in China is stroke[1].In addition, due to the improvement of production technology and the change of survival mode, the incidence of stroke in young people is increasing year by year, and the incidence of stroke tends to be younger[2]. In clinical practice, ischemic stroke can be caused by a variety of reasons. On the one hand, extracranial atherosclerotic disease (ECAD), which is dominated by carotid artery stenosis, accounts for about 18%25% of ischemic stroke[3].Another common cause of ischemic stroke is intracranial artery stenosis(ICAS)[4],that is, the artery stenosis caused by intracranial artery lesions, including atherosclerosis, aneurysm, arteritis, artery dissection, moyamoya disease and so on. Therefore, the diagnosis of intracranial artery disease is very important.

2. Advantages of HRMR-VWI technology

Compared with traditional imaging techniques such as CT angiography (CTA), digital subtraction angiography (DSA) and magnetic resonance angiography (MRA), CTA examination technology has certain risk of radiation exposure, requires intravenous contrast agent, and only reflects the degree of lumen stenosis, which is simple and non-specific. Nowadays, the "gold standard" for the diagnosis of intracranial vascular diseases is DSA examination, but it is not used as a routine method due to its invasive nature and high operational difficulty[5]. MRA addresses the limitations of DSA and CTA, eliminates the need for ionizing radiation or intravenous contrast agents, but is prone to blood flow artifacts, may overestimate stenosis measurements, and may be limited in the detection of vascular lesions in the absence of stenosis[6], High resolution vascular wall imaging (HRMR-VWI) is currently the only examination technique that can evaluate specific vascular wall pathology in vivo. With its absolute advantages of high tissue resolution and noninvasive, it can visualize the vascular wall and thus evaluate the degree of vascular stenosis, plaque composition and distribution, and plaque stability. The main techniques used by MR to evaluate ICAS include:(1) The 3D-TOF sequence, the so-called "bright

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blood" technique, is superior in evaluating the overall degree of cerebrovascular stenosis, acting as a locator to evaluate the site of vascular narrowing, but it cannot reveal the blood vessel wall;(2) T1-weighted contrast enhancement sequence, vascular images obtained after intravenous gadolinium contrast medium, can be used to better characterize a single lesion, can well represent the site of lesion inflammation, and evaluate plaque stability characteristics;(3) HRMR-VWI, commonly known as "black blood" technology, through the inhibition of blood signals in blood vessels, only small lesions in the blood vessel wall are retained, which can clearly display plaque details, analyze spot components and accurately locate them to identify inflammatory components, micro thrombosis and neovascularization [7]. 3D TOF-MRA acts as a locator to evaluate the location of blood vessel narrowing, and HRMR-VWI can better display the blood vessel wall and supplement the deficiency of MRA, so as to find the plaque that is difficult to find on MRA, and then analyze its stability, composition, distribution and other characteristics.

3. Imaging evaluation of plaque by HRMR-VWI

3.1. Assessment of vascular stenosis

For the evaluation of intracranial vascular stenosis, 3D TOF-MRA has the limitation of over evaluating the degree of stenosis, while HRMR-VWI technology improves the quantification of the severity of stenosis, has good consistency with DSA, has high sensitivity and specificity, and has the advantage of non-invasive imaging, so it is a better choice at present. However, it may overestimate the rate of luminal stenosis, such as incomplete suppression of blood or cerebrospinal fluid, resulting in false thickening of the tube wall. Therefore, DSA is still the “gold standard” [8, 9].

3.2. Assessment of plaque stability

3.2.1. Bleeding within the plaque

Internal plaque bleeding (IPH) occurs when red blood cell exosmosis or iron builds up in a plaque that ruptures [7] , resulting in internal plaque bleeding. It has been widely established that IPH is a strong independent predictor of ischemic stroke[10, 11]. One of the main features of intracranial artery vulnerable plaque is enhanced T1WI with high signaling[12]. Some relevant studies have suggested that extravascular blood/thrombosis suggestive of rupture or erosion may lead to recurrence of thrombosis. IPH can be used as a new imaging predictor of stroke recurrence and as a marker for individualized evaluation of anticoagulation therapy[13].Chronic kidney disease may be associated with IPH, and other factors may be involved. The predictors of IPH in vulnerable plaques need to be further investigated.

3.2.2. Plaque enhancement

Plaque enhancement is considered an indicator of persistent plaque inflammation, neovascularization, and instability,[14] and may also be one of the markers of plaque progression. Plaque enhancement was graded using the previous grading scale[15], and by comparison with the signal strength of the pituitary stalk, plaque enhancement can be divided into grades 0,1 and 2;Grade 0 indicates that the degree of reinforcement is similar to that of intracranial artery wall without plaque, and grade 1 and 2 indicate that the degree of reinforcement is less than or greater than the pituitary stalk[16],respectively. Grade 2 was shown to be independently associated with pathogenic plaque and showed an association with recent ischemic events (within 4 weeks), which were independent of thickness[17].In a prospective longitudinal study, intracranial plaque enhancement was associated with a four-fold higher rate of recurrent stroke at 1 year compared with non-enhanced plaque[18]. A meta-analysis study[14] showed that intracranial plaque enhancement was strongly associated with ipsilateral acute ischemic stroke. Plaque enhancement may be a relatively simple way to detect high-risk vascular wall features that may be complementary to lumen stenosis measurements in diagnosing the cause of stroke.

3.2.3. Vascular remodeling

HRMR-VWI can be used for qualitative and quantitative assessment of arterial remodeling by observation of the state of vascular remodeling and calculation of lumen remodeling index, including positive and negative remodeling index. Remodeling index > 1.05 indicates positive remodeling, which is considered to be compensatory for the outward expansion of the artery wall to maintain the patency of lumen in the case of plaque formation. However, positive remodeling increases the vulnerability of plaques and is a feature of unstable plaques. The mechanism of positive remodeling may be that compensatory dilation preserves the actual lumen area, thereby preventing lumen stenosis. However, the

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greater burden eventually increases the risk of plaque rupture, this compensatory process is clearly limited[19]，and lumen damage is mainly due to plaque expansion beyond the limit of compensatory remodeling[20, 21]. A remodeling index < 0.95 indicates negative remodeling, which is defined as the adaptive contraction of blood vessels, and its principle may be related to smooth muscle contraction and intimal hyperplasia. This compensatory change may exacerbate lumen stenosis. In contrast, negative remodeling seems to accelerate lumen stenosis, but the plaque tends to stabilize, which may be associated with clinical complications[22],in addition, studies have shown that when the plaque itself is small, the risk of plaque rupture is small[23] .

3.3. Assessment of plaque distribution

Plaque distribution is also closely related to the occurrence of ischemic stroke. One study classified plaques in cross section as upper, lower, dorsal, and ventral[24]. In a MCA study of 40 patients with symptomatic stenosis and 52 patients with asymptomatic stenosis, plaque was found to be located significantly more in the anterior and inferior walls than in the upper and posterior walls that penetrate arterial origin, and plaque was more often located in the upper walls in patients with symptomatic stenosis compared to patients in the asymptomatic stenosis group[24]. Therefore, HRMRVWI technology can be used to further study the plaque distribution in more patients, so as to discover more possibilities and correlations.

4. Application of HRMR-VWI in intracranial atherosclerosis

Intracranial atherosclerotic disease (ICAD) refers to the abnormal deposition of fibrous tissue on the blood vessel wall, accompanied by different amounts of lipids, cell fragments and bleeding[25],due to the continuous and gradual growth of plaque, it may evolve into severe lumen stenosis, resulting in high morbidity, mortality and disability. In China, about 33% ~ 50% of ischemic stroke patients have intracranial atherosclerosis[26],in which the middle cerebral artery and basilar artery account for a high proportion. Therefore, accurate assessment of atherosclerotic plaque features has become an important means of stroke prevention. HRMR-VWI is a non-invasive examination technique, which has the advantages of high spatial resolution, multi-parameter MRI sequence and high signal-to-noise ratio, and can clearly display the signals of vascular intima, fiber cap, lipid core and adjacent tissues, and then analyze plaque stability, vascular remodeling and plaque load, which has a unique advantage in determining the cause of ischemic stroke[27], Until now, the possibility of diagnosing the disease was limited to demonstrating intracranial arterial stenosis[28]. The typical manifestations of ICAD on HRMR-VWI are eccentric, heterogeneous mild to moderate enhancement, outward remodeling lesions with heterogeneous T2 signal and juxta luminal T2 hyperintensity, usually involving intracranial proximal branches or bifurcation points[29]. It has been found that HRMR-VWI technology can accurately classify ischemic stroke subtypes (CISS) in China, and then provide a basis for ICAD treatment[30]. In the clinic, the treatment process of ICAD is based on the degree of stenosis. In a Warfarin-aspirin symptomatic Intracranial disease (WASID) trial[31], 70% stenosis was found to be the tipping point for intravascular treatment of refractory ICAD lesions. However, current HRMR-VWI techniques suggest that significant ICAD may not be associated with lumen stenosis. Initial vascular wall remodeling can maintain the lumen, while the wall itself thickens dramatically, and these findings are associated with a higher incidence of atherosclerotic plaque rupture [32-35]。 HRMR-VWI may provide a better imaging marker for the selection of ICAD lesions in future trials[29]。In addition, HRMR-VWI technology has certain value in the differential diagnosis of atherosclerosis, aneurysm, arteritis, arterial dissection, moyamoya disease and other diseases.

5. Clinical risk factors

Many studies have shown that vascular risk factors, including high blood pressure, diabetes, hyperlipidemia, family history of stroke and heart disease, smoking, alcoholism, hyperhomocysteinemia, and being overweight, are associated with ICAS[4]. High blood pressure is one of the important risk factors for intracranial small vessel disease. Most researchers believe that hypertension increases the risk of ischemic stroke because it causes vascular damage[36]. Studies have shown that if hypertension is not effectively controlled, the structure and function of the basal ganglionic artery may be affected, leading to stroke[37]. Lin Weilong et[38] al used HRMR-VWI to analyze the characteristics of lenticulostriate artery in patients with hypertension. Through the study of a part of patients with grade II and III

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hypertension, they found that the diameter, shape and depth of single/bilateral lenticulostriate artery in this group of people would change, thus confirming that hypertension would affect the shape of lenticulostriate artery in patients. HRMR-VWI technology can be used in clinical application to further analyze the characteristics of the vessel of the bean stripe artery. In addition, HRMR-VWI technology can explore more possibilities and correlations in more vascular risk factors.

6. Conclusions

Ischemic stroke accounts for the main proportion of stroke in China, and intracranial atherosclerosis is the main cause of ischemic stroke. The current guidelines only rely on the rate of lumen stenosis to stratify stroke risk, decide treatment plan and judge the severity, which has certain limitations. In recent years, the application of HRMR-VWI technology can overcome the limitations of previous imaging techniques, upgrade the assessment of intracranial atherosclerosis from the traditional lumen stenosis to the assessment of plaque stability, contribute to the stratification of stroke risk, and make differential diagnosis by plaque characteristics and vascular wall abnormalities, which are radiation-free and have high soft tissue resolution. With the advantages of multi-sequence and multi-dimensional flexible observation of cerebral vessels, HRMR-VWI can be used to further explore the clinical risk factors of vulnerable plaques, so as to improve the prevention and treatment of ischemic stroke. However, the limitations of this technology are also very obvious, such as more contraindications, long examination time, some patients cannot adhere to it, and high requirements for equipment and technology. Currently, the sample size of the study is relatively small, and it is expected that future studies can overcome them.

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