Review of Symptomatic Intracranial Artery Stenosis

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Abstract: Symptomatic Intracranial arterial stenosis (sICAS) refers to intracranial arterial stenosis caused by atherosclerosis and presents ischemic stroke or transient ischemic attack in the blood supplied area. sICAS is a major risk factor in recurrent stroke. This review summarizes research datas of sICAS in recent years respectively from epidemiology, etiology and mechanism, risk factors, diagnosis, clinical manifestation, treatment and prognosis, aiming to raise awareness of this disease and provide basis for the further study.
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Symptomatic intracranial atherosclerotic stenosis (sICAS) refers to intracranial arterial stenosis caused by atherosclerosis and presents ischemic stroke or transient ischemic attack in the blood supplied area. Stroke is the second death cause only following cardiovascular disease and is the first disease cause of adult disability, and is also the common pathogeny for dementia, depression and elderly epilepsy. The information published by the statistical center of health ministry show that there are about 2 million cases of new stoke patients and 1.5 million death cases due to cerebrovascular disease every year. About 75% patients surviving after stroke are disabled to different extents. Among them, 40% patients are of severe disability. In china, the annual aggregate expenditure for treatment of cerebrovascular disease reaches 20 billion Yuan, which causes a great economic burden to both society and family. sICAS is a major risk factor in recurrent stroke. However, the efficacy of current treatments is still limited and controversial. Therefore, it is important to clarify the predictors of recurrent ischemic stroke and establish more efficacious secondary prevention strategies. This review summarizes research datas of sICAS in recent years respectively from epidemiology, etiology and pathology, diagnosis, clinical manifestation and mechanism, treatment and prognosis, aiming to raise awareness of this disease and provide basis for the further study.

1. Epidemiology

Worldwide, stroke is the second death cause only following cardiovascular disease and is the first disease cause of adult disability, and is also the common pathogeny for dementia, depression and elderly epilepsy. In China, both morbidity and mortality of cerebrovascular disease have been increased year by year with the development of economics, changes of people's lifestyle and the rapid accelerated population aging process. According to China Guideline for Cerebrovascular Disease Prevention and Treatment (2010), stroke has become the first death cause in urban residents and the second death cause in rural residents in china.

In North America, 8%-10% ischemic strokes are induced by sICAS (Turan et al., 2009), whereas in China, 33% ~ 56% cerebral arterial thrombosis are related to sICAS (Wong, 2006). Angiography of 1500 cases of patients with cerebral arterial thrombosis in Xuanwu Hospital of Capital Medical University showed that there were 850 cases (56.67%) of intracranial arterial stenosis. Among them, there were 250 cases of cerebral artery stenosis accounting for 29.41% of all intracranial arterial stenosis. Arterial stenosis extent is directly related to the development of stroke (Kasner et al., 2006). Some studies suggested that in case of increased intracranial arterial stenosis extent by 10%, onset risk of cerebral arterial thrombosis rose by 26%. Multivariate analysis for 569 cases of patients with symptomatic intracranial arterial disease receiving WASID (the Warfarin vs Aspirin for symptomatic Intracranial Disease) test indicated that severity of intracranial arterial stenosis was obviously related to the development of stroke in the corresponding supply area, and the incidence of stroke was linearly associated with stenosis rate (Kasner et al., 2006). sICAS is taken as an important risk factor of stroke recurrence and death (Sacco et al., 1995; The EC / IC Bypass Study Group, 1985;Wityk et al., 1996), and its incidence has an significant ethnic difference

(Wong et al., 1998; Huang et al. 1997): sICAS is commoner in Asian, Spanish and black races ,and atherosclerotic stenosis is usually more serious in Asian and African races.

There is a significant difference in the incidence of both sICAS and sICAS-related stroke between races (Wong et al., 1998; Huang et al. 1997). sICAS is commoner in Asian, Spanish and Black races. Artery stenosis severity is usually more serious in Asian and African races and is also the most important pathogeny for ischemic stroke in Asian, African and Black, especially in Chinese (Suri and Johnston, 2009). For the incidence of sICAS-related stroke, it is 3/100,000, 15/100,000 and 15/100,000 respectively in Caucasian, Spanish 13/10 and African American (White, 2005). In China, 33%-56% cerebral arterial thrombosis are related to sICAS (Wong, 2006). A study in London showed that 17.9% Black patients with cerebral arterial thrombosis presented intracranial arterial stenosis, while only 2.1% Caucasian patients with cerebral arterial thrombosis presented intracranial arterial stenosis (Markus et al., 2007). Among 13587 patients with acute cerebral arterial thrombosis reported in Germany, only 2.2% patients were attributed to symptomatic intracranial artery stenosis (Weber, 2010). Among 1167 cases of stroke patients included in a study in South Korea, the ratio symptomatic intracranial artery stenosis cases to symptomatic extracranial artery stenosis cases was 7:3 (Kim et al., 2006). In a word, intracranial arterial stenosis-related stroke is the main stroke type in Asian, Spanish and Black races, whereas the population is the main part of world's population. In other words, sICAS-related stroke has become the most common type of cerebral apoplexy around the world (Gore lick et al., 2008; Qureshi et al., 2009).

2.Etiology and Mechanism

sICAS is a result of interaction by multiple factors such as genes and environment and is a chronic degenerative inflammatory disease process formed chronically in the aortic endothecium. Vascular endothelial injury is the initiating agent for the process of plaque rupturing to thrombogenesis, while hypertension, hyperglycemia, hyperlipidemia, smoking, infection, etc. are risk factors of stimulating occurrence of oxidative stress and inflammatory reaction.

For pathogenesis of sICAS-related strokes, there are many hypotheses currently: ① Low perfusion status caused by artery stenosis: in case of more serious intracranial arterial stenosis, if collateral circulation may be compensatory, blood supply of terminal brain tissue can be still adequate; However, when collateral circulation cannot be compensatory, which causes decreased distal blood flow, it is also feasible to maintain cerebral nutrient supply by cerebrovascular self-reflective expansion and active oxygen uptake of brain tissue; once this compensation cannot maintain normal cerebral metabolic requirements, ischemic stroke will occur. ② Platelet-activated thrombosis following unstable plaque rupture: after original plaques on vessels rupture, both exposed rough plaque surface and exposed lipid core are factors of promoting thrombosis. ③ Distal embolization caused by deciduous embolus at plaque site: after plaque ruptures, both blood clots on its surface and in its inside can fall off to become embolus and thus embolize distal vessels to cause stroke occurrence. ④ Small perforating vessel occlusion at plaque site: perforating vessels of basilar artery supply to brain stem, Willis ring also sends many perforating vessels to supply to deep brain tissues, such as basal nuclei and cerebral ganglion. Lesions at initiation site of perforating artery easily involve the opening to cause occlusion of small vessels. Interventional therapy can be considered for stroke caused by artery stenosis, and strokes due to plaques can be prevented routinely by anti - thrombosis, regulating blood lipid, stabilizing plaques and controlling other risk factors for cerebrovascular disease. In case of acute period, thrombolytic therapy is considerable. As small perforating vessel occlusion is uneasily determined, it must be cautious to avoid blocking the opening of perforating branch in case of interventional surgery.

3. Risk factors

The primary point for prevention and treatment of sICAS is to control its risk factors. Known risk factors with relevant evidences include the uncontrollable risk factor such as age and the controllable risk factors such as hypertension, hyperglycemia, hyperlipidemia, hyperhomocysteinemia (Hcy), fibrinogen (FIB) and coronary artery lesions.

Hypertension: hypertension can make small artery hyalinize and can also damage endothelial cells of large vessels by mechanical stimulus to destroy the intimal structure and to result in stenosis. The study on WASID showed that in the follow-up period of average 1.8 years, the most important risk factor of adverse event occurrence lay in poor control of blood pressure and elevation of blood lipid (Kasner et al., 2006). Among patients with mean systolic blood pressure ≥140mmHg, 30.7% patients were suffered from stroke, cerebrovascular death and myocardial infarction events; total incidence of the three events was 18.3% ($P<0.05$) in case of mean systolic blood pressure <140mmHg ($P<0.05$). Another study suggested that blood pressure decrease of 9/4mmHg could reduce stroke risk by 28% (2006).

Dyslipidemia: Similarly, during the follow-up period of WASID study, 25.0% patients with low density lipoprotein cholesterol (LDL-C) ≥2.99mmol/L were suffered from stroke, cerebrovascular death and myocardial infarction events, while among patients with mean LDL-C <2.99mmol/L, total incidence of the three events was 18.6% (P=0.03). In case of LDL-C target value <1.82mmol/L, 22.5% patients with mean LDL-C value more than this target value were suffered from adverse events of stroke, cerebrovascular death and myocardial infarction, while only 7.4% patients with mean LDL-C less than this target value were suffered from the above adverse events. Therefore, it is feasible to reduce recurrent risk of ischemic stroke by actively treating high LDL-C and hypertension (Amarenco et al., 2006).

Diabetes: diabetes is also the important risk factor of sICAS (Wong, 2003). Hyperglycemia promotes oxidation and generates oxygen free radicals of damaging blood vessel wall, and patients with diabetes can be accompanied with a variety of hemodynamic changes, such as increased aggregation and decreased deformability of red blood cells and change of plasma components. These changes cause elevated blood viscosity and vascular endothelial cell damage and accelerate the occurrence and development of atherosclerosis and simultaneously make capillary basement membrane thicken and transparent material deposit to cause microvascular injury (Maj, 2004). The stroke risk of diabetes patients is 3~5 times more than that of non-diabetes patients. In case of fasting glucose level >5.15 mmol/L, the incidence of cerebral arterial thrombosis in patients with arteriosclerosis is significantly increased. If glycosylated hemoglobin level is elevated by 1%, stroke risk will be increased by 17% (Wong et al., 1998).

Hyperhomocysteinemia (Hcy): Hcy level influences the thickness of middle endangium and has a certain predictive value for extent of intracranial atherosclerosis and stenosis. A large number of studies at home and abroad suggest that high Hcy can cause or accelerate the process of atherosclerosis to result in arterial stenosis (Makris, 2000), and can increase the recurrent risk of stroke in patients with sICAS.

Fibrinogen (FIB): FIB level is positively associated with sICAS severity and is the important predictor of sICAS. FIB can promote adhesion of leucocyte with vascular endothelial cell, mediate migration and aggregation of leucocyte and release inflammatory media and thus damages vascular endothelial cells. It can still stimulate vascular smooth muscle cell proliferation, activate tissue plasminogen complex and influence endothelial function and thus promotes formation and progress of atheromatous plaques.

Coronary artery lesions: studies suggest that more than half patients with symptomatic coronary artery stenosis can be accompanied with different extents of intracranial and extracranial artery stenosis.

Statistical data from Xuanwu Hospital of Capital Medical University showed that among patients with intracranial arterial stenosis, 21% patients were accompanied with hyperlipemia, 27% patients were accompanied with diabetes, 39% patients were accompanied with both diabetes and hypertension, and 47% patients presented unknown aetiologies. Among patients with unknown aetiology, patients aged below 45 years accounted for 78%. A study on a group of patients with intracranial arterial stenosis accompanied with hypertension suggested that lipid metabolism abnormities were high risk factors of cerebrovascular atherosclerosis. Among them, levels of high triglycerides, high cholesterol, high- and low-density lipoproteins, high apolipoprotein A (ApoA) and high apolipoprotein B (ApoB) and low Apo A/ApoB ratio were promoting factors of cerebral atherosclerosis. Therefore, the prevention and control of the above risk factors is critical for establishing an effective secondary stroke prevention system.

4. Diagnosis

In recent years, the development of imaging technology provides convenience for evaluating the characteristics of cerebral infarction and vascular condition. Digital subtraction angiography (DSA) is the gold standard for cerebral arterial stenosis diagnosis. Although it is of higher spatial resolution and reliable accuracy, its invasiveness and expensive examination fee make patients give up DSA examination. CT angiography (CTA) is also of higher spatial resolution and is of moderate cost, and can partially replace DSA examination, but it is not suitable for the population allergic to contrast. Both Trans Cranial Doppler ultrasound (TCD) and Magnetic Resonance Angiography (MRA) developing in recent 30 years have gradually become the main screening means of cerebral artery stenosis due to its non- invasiveness. It is a development trend of vascular imaging diagnosis to replace the invasive angiography with one or more non-invasive imaging methods. These examination methods have their advantages and shortcomings can be selected according to the individual demand in the actual clinical application.

At present, DSA is still the gold standard of examining intracranial arterial stenosis and can clearly display the stenosis extent of cerebrovascular branches at all levels and the establishment status of collateral circulation to provide reliable anatomical information for vascular interventional treatment. However, as an

invasive examination method, DSA will cause risks of serious complications in the operation process and is forbidden to be used for patients with serious heart, liver and renal insufficiency and bleeding tendency. Also, long operation time and expensive examination fee limit its application in clinic.

In recent years, TCD is highlighted increasingly in the diagnosis of cerebrovascular diseases. It can be used for arterial stenosis or occlusion extent and hemodynamic change caused by arterial stenosis by detecting blood flow velocity and direction and has high specificity and sensitivity for intracranial arterial stenosis diagnosis. Color Doppler Power imaging has advantages of high direction resolution, less influences of sound velocity and blood flow velocity and direction and high accuracy of blood vessel boundary. Some studies showed that TCD had better accuracy for intracranial severe arterial stenosis, while for mild stenosis (stenosis extent <50%), Doggler Power Imaging (PDI) was more than Color Doppler Power imaging (CDFI). Although TCD operation is simple, it depends on operator's skill and level largely. Therefore, inaccurate positioning, misdiagnosis and missed diagnosis are easily caused. Experienced physicians receiving formal training are required to make a comprehensive analysis by combining their clinical experiences.

MRA is used to diagnose vascular morphology by use of characteristics such as phase change and entry enhancement of endovascular blood flow in magnetic resonance imaging, and it is more visualized than TCD. Also, it is convenient for bilateral comparison and observation of whole vascular situation. Domestic studies showed that DSA and MRA had a diagnostic accordance rate of 83.5% for intracranial arterial stenosis. In the Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis intracranial (SONIA) study (Feldmann et al., 2007), comparison of outcome of MRA with DSA showed that for patients with stenosis extent of 50%~90% examined by DSA, the positive predictive value of MRA was 59%, and the negative predictive value was 91%. MRA is a reliable measure for intracranial arterial stenosis diagnosis. Sadsikin et al. suggested that sensitivity and specificity of MRA in the diagnosis of intracranial arterial stenosis extent >29% were respectively 94% and 96%, while sensitivity and specificity of MRA in the diagnosis of intracranial arterial stenosis extent > 49% were respectively 95% and 96%, and both sensitivity and specificity of MRA in the diagnosis of intracranial vascular occlusion reached 100%. However, MRA have still some shortcomings. Firstly, MRA conducts real time imaging and does not provide continuous blood flow signals of intracranial vessels. Therefore, Hemodynamic changes in different clinical periods cannot be observed dynamically. Moreover, MRA is dependent on Blood flow velocity and direction, and its spatial resolution is poor. For small vessels, developing efficacy is poor, and estimation of stenosis extent is too high (Sadikin et al., 2007). In addition, MRA is forbidden to be used for patients in a critical condition, patients with metal in body and patients with claustrofobia.

CTA can present 3-level branches and vascular lesions of intracranial arterial system more stereoscopically, and is a safe, accurate and rapid method. Multi spiral CT angiography (MSCTA) can show both situations in the arterial lumen and situations of vascular wall and can accurately present size and surface condition of soft plaque. Compared with MRA, CTA has higher sensitivity of showing anterior, middle and posterior cerebral arteries and anterior communicating artery. Compared with DSA, CTA is more suitable for evaluation of artery stenosis of posterior circulation under the condition of slow blood flow velocity (Bash et al., 2005). Nguyen-Huynh et al. (Kim et al., 2006; Gore lick et al., 2008; Qureshi et al., 2009; Chimowitz et al., 2005) selected 41 cases of patients with ischemic stroke from 2000 to 2006 and conducted DSA and CTA examinations respectively. With DSA as the reference, both sensitivity and specificity of CTA in the diagnosis of arterial occlusion reached 100%, and sensitivity and specificity of CTA in the diagnosis of stenosis extent ≥50% were respectively 97.1% and 99.5%. However, it is necessary to inject contrast in case of CTA examination. Therefore, there is a radiation risk, and accuracy will be reduced for judgment of extensive compactly-calcified arterial stenosis.

5. Treatment

For patients with sICAS, it is very critical to control relevant risk factors, for example antiplatelet therapy, lowering lipid to stabilize plaques and regulating blood glucose and blood pressure. Animal experiment results showed that the combination therapy of three drugs probucol, antiplatelet drug and statins had significant inhibition to both atherosclerotic plaque formation and expression of inflammatory factor and was better than monotherapy. In WASID test, the incidence of stroke or vascular death in Aspirin group and Warfarin group was respectively 22.1% and 21.8%, while the incidence of cerebral hemorrhage in Warfarin group was significantly higher than that in Aspirin group (8.3% vs. 3.2%) (Chimowitz et al., 2005). At present, there is no strong evidence for supporting sICAS patients to receive anticoagulant therapy, and antiplatelet therapy is still recommended. CLAIR (Clopidogrel plus Aspirin for infarct reduction) test was compare efficacy of dual

antiplatelet therapy (Clopidogrel plus Aspirin) with efficacy of single Aspirin therapy. Results suggested that there was no significant difference in the event incidence between the two groups (Wong et al., 2010). The current more widely-used drugs in clinic include antiplatelet drug and statins.

The ever-expected extracranial -intracranial bypass surgery was denied by a large multicenter clinical study ago. In recent years, the endovascular stent angioplasty has become a new hope for treating sICAS with the progress of intravascular treatment technology and the emergence of new scaffold materials. Pure balloon dilatation was firstly and successfully used to treat intracranial basilar artery stenosis by Sundt et al. in 1980. As a result, there were risks of immediate elastic recoil, higher intimal injury, interlayer and restenosis. Mark et al. pointed out that the incidence of stroke or death within 30 days following pure balloon dilatation changed greatly (4%~40%), and restenosis incidence was higher (24%~50%)(Marks et al., 2006). Balloon dilatation-assisted stent implantation partially avoids the above risks. For prevention of restenosis, drug stents coated with immunosuppressant and cytotoxic drugs so on appear later, but there are different statistical results about postoperative restenosis (from 0%-14% to 10%-50%). In addition, feasibility and safety of drug stents shall be still further proved because of difference of morphology of both coronary artery and intracranial vascular tissues and adverse reaction such as possible vascular toxicity. Wingspan self-expanding stent system is the first apparatus that is approved by U.S. Food and Drug Administration to be suitable for sICAS patients with stenosis rate of 50%-99% subject to failed drug treatment failure. It has better flexibility and easily reaches vessels of stenosis. The stent placed in the delivery catheter coated with hydrophilic layer reduces vascular endothelial damage and has a better metal memory. However, a multicenter study in the United States after Wingspan appearing on the market confirmed that postoperative restenosis extent for Wingspan stent still reached 25%~ 28%, similar to that of common bare-metal balloon dilatation stents (Zaidat et al., 2008). Stent therapy has unique advantages that drugs lack for severe arterial stenosis, but in-stent restenosis is a big problem urgently to be solved in the interventional therapy field.

A randomized controlled study on stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis (SAMMPRIS) (Chimowitz et al., 2011) indicated that pure active drug treatment was better than Wingspan stent plus active drug treatment. The early stroke incidence after angioplasty is high, while the recurrent risk of stroke after pure drug treatment is low. But a study in China drew a opposite conclusion: the incidence of 1-year end point events of sICAS patients with stenosis rate ≥70% in the group of Wingspan stent plus drug treatment was significantly lower than that in the pure drug group in WASID test (Jiang et al., 2011). Therefore, it shall be further and deeply researched how to select the best therapy for intracranial arterial stenosis for long-term benefit.

6. Epilogue

sICAS is one of main reasons for ischemic stroke. After drug treatment, its recurrence rate remains high. Although the endovascular stent implantation has a certain therapeutic effect, its long-term benefit is still unclear. So, it is of important significance to actively seek its pathogeny and risk factors and conduct first and secondary preventions for reducing the incidence of ischemic stroke and improving the prognosis of patients. Moreover, it is very critical for long-term benefit of stroke patients to further investigate the efficacy and safety of drugs and therapies such as endovascular interventional treatment.

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