Review

The effect of cerebral microbleeds in trearment of cerebral infarction and its related research progress

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Abstract:

Cerebral microbleeds(CMBs) is a manifestation of cerebrovascular disease, and the correlation between CMBs and ischemic stroke and its treatment (antithrombotic, anticoagulant, improving collateral circulation, thrombolysis, statin, etc) is a hot research topic at present. This paper mainly discussed the relationship between CMBs focus and the risk of bleeding in patients with cerebral infarction, and judged whether it could be a predictor of bleeding, This paper mainly summarized the literatures in recent years to understand the influence of CMBs in the treatment of cerebral infarction and related research progress. At the same time, through the discussion and analysis of the literature, the clinical significance of CMBs was obtained, and the clinical application of CMBs was prospected.

Keywords:

Cerebral microbleeds, thrombolysis, anticoagulation, antithrombotic, improved collateral circulation, statins

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Cerebral microbleeds (CMBs) refers to the subclinical damage caused by small(micro) blood vessel wall injury, and blood seeps from the blood vessel wall to form hemosiderin deposit, generally without corresponding clinical symptoms and signs. However, in recent years, there are also some reports that CMBs can cause neurological deficit symptoms[1-2]. CMBs, lacunar infarction, leukoaraiosis and enlargement of perivascular space all belong to the category of cerebral small vessel disease (CSVD). CMBs is usually detected by imaging method, excluding the structures such as vascular void effect, calcium and iron deposition, bone and other similar signals. CMBs is shown as a round or oval with a diameter of about 2-5mm, with clear boundary, no peripheral edema and homogeneous high signal shadow on T2 gradient echo sequence or magnetic sensitivity weighted imaging sequence (SWI) of MRI. At present, SWI is considered to be more sensitive than the traditional T2 weighted gradient echo imaging (GRE) [3], which was confirmed by jeroen d.c. goose, MD [4] through a retrospective

study of 156 people who conducted GRE and SWI simultaneously. At the same time, studies have shown that the incidence of CMBs in ischemic stroke patients is 35% ~ 71%, while that in healthy people is 5%, and there are great differences among different races. The incidence of CMBs in Asian population is 66.4%, that in African population is 56.2%, the detection rate of single or multiple microbleeds in blacks is 74%, while that in whites is 42%. Therefore, it can be speculated that there may be a certain relationship between CMBs and ischemic stroke [5-6].

CMBs and the treatment of cerebral infarction

1. anticoagulant therapy

Atrial fibrillation is one of the most common causes of cerebral infarction. For patients with atrial fibrillation, anticoagulant therapy is an effective means to prevent and reduce stroke caused by atrial fibrillation. At present, the main anticoagulants for nonvalvular atrial fibrillation are traditional anticoagulants warfarin and non-vitamin K antagonist anticoagulants (NOACS), including dabigatran and rivaroxaban, etc. While using anticoagulants, we should also pay attention to the changes of intracerebral microbleeds before and after use. Song [7] conducted a prospective study on 550 patients with cerebral infarction who took oral anticoagulants. During the follow-up period of 3.1±1.6 years, it was found that the number of CMBs was positively correlated with the occurrence of intracranial hemorrhage related to oral anticoagulants. Meanwhile, the study found that with the increase of CHADS2 or CHADS2-VASc score, the occurrence of intracranial hemorrhage related to oral anticoagulation became more frequent. Andreas Charidimou,MD,PhD and others [8] not only have the same results in a prospective study of 1500 patients, but also find that the risk of intracranial hemorrhage is particularly high when the number of CMBs ≥5. Some studies have also shown that the new anticoagulant has greater advantages than the traditional anticoagulant in clinical application. Paolo[9] found that the risk of NOACS in intracranial hemorrhage is significantly less than warfarin, which is about 52%. In addition, some NOACS are better than warfarin in reducing the risk of thromboembolic complications. At the same time, the former also shows less drug-drug and drug-food interactions. For patients, except for some patients with renal insufficiency who regularly monitor serum creatinine, other NOACS users do not need to take blood frequently to detect INR. However, the high cost is still the main reason why most people choose warfarin. Takizawa[10] conducted a one-year follow-up study on 23 patients with atrial fibrillation who took different types of anticoagulants and suppositories, and found that those who took NOACS continuously showed no CMBs on MRI, while those who took warfarin or used antiplatelet aggregation drugs at the same time showed CMBs on MRI. Through multiple regression analysis, warfarin has an independent relationship with newly-issued CMBs. However, the sample size is small, and the follow-up

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time is short. This conclusion should be confirmed by large sample study, so as to guide the clinical application of drugs. Since the most dangerous risk of anticoagulant therapy is bleeding, the number of CMBs displayed on SWI sequence may be used as an index to judge the risk of bleeding after using anticoagulants.

2.antithrombotic therapy

Anti-platelet aggregation drugs are the main treatment drugs for patients with noncardiac cerebral infarction. Aspirin and clopidogrel are the most commonly used drugs at present, which can effectively reduce the risk of stroke recurrence. Meanwhile, attention should be paid to the occurrence of CMBs caused by damage to platelet function and cerebral hemorrhage caused by CMBs. Wobith [11] recorded the number of CMBs at baseline and at the time of follow-up by following up 40 cerebral infarction patients who took anti-platelet aggregation drugs for 6 months, and analyzed the risk factors that might cause CMBs, and found that the number of CMBs was not only related to the number of baseline CMBs, but also significantly affected by age and atherosclerotic cerebral infarction. In recent years, some studies have confirmed that the use of antiplatelet drugs will increase the occurrence of CMBs, which is closely related to the CMBs in the cerebral lobe [12]. Further research shows that if the number of CMBs in the cerebral lobe is more than 10, the probability of rebleeding risk of patients is significantly higher than that of others [13]. Therefore, the incidence of CMBs can be minimized by closely monitoring related risk factors in clinic. Non-familial cerebral amyloid angiopathy (CAA) is a amyloid β-protein deposited in cerebral cortex and arterioles at the junction of gray matter and white matter, which leads to atrophy and oxidative stress of vascular smooth muscle cells, and further leads to the formation of CMBs [14]. Some scholars have found that CMBs in cerebral lobes is a powerful predictor of recurrent cerebral hemorrhage in CAA patients [15]. According to the above literature summary, the number of CMBs foci can be used as a predictor of intracranial hemorrhage. For cerebral infarction patients who are using antithrombotic drugs, we should also pay close attention to the number of CMBs , pay close attention to the risk of hemorrhage and adjust the use of antithrombotic drugs in time.

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3. improve collateral circulation

The formation of neovascularization after cerebral infarction can increase the compensatory ability of collateral circulation, improve the cerebral perfusion of patients with ischemic stroke and improve local symptoms. At present, there is relatively little research on this aspect. Gregoire [16] found that about 25% of patients had new CMBs after 5 years MRI follow-up of cerebral infarction patients with CMBs. Dassan [17] found that vascular endothelial cell factor in CMBs group was significantly higher than that in CMBs group. Meanwhile, Ferrara[18] thinks that VEGF is an effective inducer of vascular leakage, and its concentration will be up-regulated after ischemic stroke,

which may trigger or increase the occurrence of CMBs [19]. According to the above research, CMBs may appear in angiogenesis, which may lead to the risk of intracerebral hemorrhage. Therefore, we can assess the benefits and risks of angiogenesis to patients with cerebral infarction by detecting the concentrations of nitric oxide synthase (NOS), vascular endothelial growth factor (VEGF), matrix metalloproteinase (MMPs) and other factors in blood at an early stage, and guide the adjustment of treatment plan.

4. thrombolytic therapy

Intravenous thrombolysis can quickly restore the blood perfusion of ischemic brain tissue and improve the long-term prognosis, which is the most effective method at present. However, intravenous thrombolytic therapy will also have some complications, such as cerebral hemorrhage, reperfusion injury, neurogenic edema and so on. Among them, the most dangerous and clinically concerned complication is symptomatic intracranial hemorrhage (sICH), and avoiding hemorrhage is an important way to evaluate the curative effect of thrombolytic therapy. Therefore, before thrombolysis, it is necessary to evaluate the risk factors of easy bleeding (such as platelet count, coagulation function, recent post-traumatic hemorrhage, cerebral infarction, etc). Kakar P [20]through a retrospective study, evaluated the relationship between the number of CMBs and the risk of bleeding before thrombolysis, and concluded that there was no significant difference in the bleeding rate between the two groups before thrombolysis, whether there were CMBs foci or not. A study by Dannenberg [21] on the number of micro-hemorrhage foci and the risk of hemorrhage after intravenous thrombolysis in 326 participants showed that the risk of hemorrhage after intravenous thrombolysis was still significantly related to CMBs foci, and was positively correlated with the classification of baseline CMBs number. Ramin[22] reached the same conclusion by following up 672 patients. The research of Kwok C[23] further found that the risk of bleeding was more significant when there were more than 10 CMBs foci. Therefore, it can be concluded that it is very important to assess the risk of bleeding before thrombolytic therapy, and monitoring the number of CMBs in brain is also helpful to guide the use of antithrombotic or anticoagulant drugs in the later period.

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5. statins

Statins, as the main anti-plaque and lipid-regulating drugs at present, can reduce LDL-C and increase HDL-C by selectively inhibiting HMG-CoA reductase and increasing the uptake and catabolism of LDL-C in liver. Therefore, some scholars began to study the relationship between CMBs and the use of statins. Some scholars [24] have suggested that the decrease of serum cholesterol (TC) level after the use of statins is related to the existence of CMBs in the deep/infratentorial region of the brain. It is also believed that lipid-lowering treatment will change the internal model structure of blood vessel wall and change the balance of oxidative stress, thus increasing the risk of bleeding [25]. In 2009, Noda H[26] studied the theory of cerebral

microcirculation, stating that too low TC level also has the risk of bleeding. La Rosa [27] researched on lipid-lowering treatment with different doses of atorvastatin in 1001 patients with stable coronary heart disease suggested that the incidence of midbrain stroke and cerebral hemorrhage in intensive lipid-lowering group was significantly higher than that in other control groups, indicating that intensive lipid-lowering has the risk of secondary cerebrovascular rupture. In recent years, some studies have concluded that atorvastatin will not increase the risk, but will reduce the bleeding focus of stroke complicated with CMBs [28]. At present, there are few related studies, the sample size is small and the time is long, and whether the chain effect caused by age and poor vascular condition has been ruled out, so it is still uncertain whether the use of statins will lead to CMBs.

Summary and prospect

For patients with cerebral infarction, the use of anticoagulants, antiplatelet aggregation drugs, thrombolysis and improvement of collateral circulation may increase the risk of bleeding. However, it is still uncertain whether statins will lead to CMBs, and more well-designed large samples, multicenter and longitudinal studies are needed in the later stage to clarify its risk factors and clinical significance. At the same time, more attention should be paid to CMBs and its harm in clinic, that is, routine SWI examination should be performed to determine the number and location of CMBs, and CMBs can also be used as a predictor of whether it is easy to bleed.

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