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Review Article

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Controversy over Mild Stroke

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Abstract

Mild stroke patients are a special and controversial population. Mild stroke patients usually have a naturally good prognosis, and thrombolysis, can alleviate the symptoms of mild stroke effectively, but thrombolysis increase the risk of bleeding. For the administration of IV rtPA in the setting of acute stroke, Mild deficit is a relative contraindication. However, recently the terminology of "mild stroke" has not been well specified. Advance studies have shown that patients with mild ischemic stroke have substantial disability rates at hospital discharge.

Keywords: Mild stroke • Intravenous thrombolytic therapy • Controversy • Prognosis

Introduction

If all mild stroke patients are treated with thrombolytic therapy, these patients with good prognosis may bear additional thrombolytic costs and bleeding risk. In fact, 29% of patients did not receive thrombolytic therapy because of slight or rapid improvement of symptoms, resulting in a poor prognosis at 90 days [1]. In the early stage of the disease, the potential severity of mild stroke may be underestimated due to mild symptoms, so as to miss the opportunity of thrombolysis and lead to poor prognosis.

Literature Review

Controversy over the concept of mild stroke

After slogan "small stroke, big trouble" was put forward on World Stroke Day in 2008, the research on mild stroke has becoming a hot research topic. However, the definition of mild stroke is difficult, and there is still no unified definition standard. In the currently published guidelines, the definitions of mild symptoms, rapid improvement of symptoms and other common thrombolytic criteria are vague and easy to cause major misunderstandings.

In clinical practice, NIHSS score is one of the common stroke evaluation methods. It is found that there are still some limitations in using NIHSS score to define mild stroke: (1) Insufficient evaluation of posterior circulation ischemia; (2) Hemispheric bias (the NIHSS score of right hemisphere infarction will be less than that of left hemisphere with the same infarct volume). (3) The total score of NIHSS can be the sum of several sub items with mild neurological deficit, or only a single sub item with severe neurological deficit, which may cause severe disability. (4) Unable to evaluate neurological deficits such as cognition and depression. (5) Based on clinical neurological deficit symptoms, it does not include imaging information, and cannot reflect whether there is stenosis of extracranial and extracranial vessels, the degree of collateral compensation and cerebral perfusion.

Different studies have different definitions of mild stroke. The inconsistency of the definition of mild stroke may directly lead to the inconsistency and uncertainty of relevant research results.

Controversy over intravenous thrombolytic therapy for mild stroke

Whether thrombolysis can be used in mild stroke is controversial. Scholars who agree with thrombolytic therapy believe that thrombolytic therapy can improve vascular recanalization rate, reduce early disability rate, and is safe and feasible. Scholars who do not agree with thrombolytic therapy believe that there is no significant difference in the outcome of patients with mild stroke, and even thrombolysis will bring a higher risk of bleeding.

At present, the American Heart Association (AHA)/American Stroke Association (ASA) guidelines for the treatment of acute ischemic stroke [2], point out that it is reasonable to consider intravenous thrombolytic therapy in patients with non-disabling mild stroke, and it is recommended to conduct more studies to determine the risk ratio in this population. The Chinese guidelines for the diagnosis and treatment of acute ischemic stroke 2018 [3], lists mild stroke as the Relative Contraindication of Tissue Plasminogen Activator (rt PA) intravenous thrombolysis. The risks and benefits of thrombolysis need to be carefully considered and weighed. Intravenous thrombolysis can be considered on the premise of full evaluation and communication.

The US "get with the guidelines" registration study retrospectively analyzed mild stroke patients (NIHSS ≤ 5) who came to the hospital within 4.5 hours of onset and received rt PA treatment, found that even with thrombolytic therapy, 30% of patients still had a poor prognosis at discharge (unable to walk independently or go home directly) [4]. Meta-analysis results showed that mild stroke patients who received intravenous rt PA, the proportion of patients with poor prognosis was 23.9%. There was no significant difference in 3-month prognosis between mild stroke patients who received intravenous rt PA thrombolytic therapy and mild stroke patients who did not receive rt PA thrombolytic therapy [5]. Another Meta-analysis found that alteplase thrombolysis could improve the prognosis of mild stroke, but significantly increased the probability of symptomatic intracranial hemorrhage [6]. And another article demonstrated that the benefit of intravenous thrombolysis in mild stroke patients (NIHSS ≤ 5) was not obvious, but it did not increase the incidence of symptomatic intracranial hemorrhage [7], subgroup analysis of IST-3 trial also showed that rt PA had no significant effect on patients with mild stroke [8]. The preliminary results of prisms showed that there was no significant difference in the outcome of thrombolysis or not, but the thrombolytic treatment group had a higher rate of symptomatic intracranial hemorrhage [9].

An analysis based on TIMS-China and China Stroke Registration Study (CNSR) showed that patients with mild stroke who received rt PA had a better prognosis trend than those who do not receive thrombolytic

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therapy (the proportion of patients with Mrs 0 to 1 at 3 months was 77.6% vs. 69.5%), but the overall difference was not statistically significant. The study also found that intravenous thrombolysis had different effects on the prognosis of different subtypes of mild stroke, and the LAA subgroup benefited more from rt PA than other subgroups [10].

These data suggested that the benefits of intravenous thrombolysis for disabled stroke patients may not be extended to mild stroke patients without obvious disability, and thrombolysis for non-disabled mild stroke patients may be unreasonable.

There are three potential causes for final disability in patients with mild stroke: (1) initial event: because the definition of mild stroke is inaccurate, it is not accurately identified or the disability is not fully recognized. The disability is the direct result of stroke. Or the early stage of stroke is non-disable light stroke, then progress to disabling stroke. (2) Stroke recurrence. (3) Medical events caused by related comorbidities leading to mild stroke.

Solution 1: Starting from the definition of mild stroke, explore more appropriate evaluation criteria and treatment options.

The biggest defect of NIHSS score is that it cannot reflect the degree of perfusion of extracranial and extracranial blood vessels and brain tissue, but it is the key to reperfusion treatment in acute stage. In 2008, Torres mozqueda, et al. proposed to define mild stroke by imaging method (BASIS): there is no large extracranial and extracranial vascular occlusion on CTA or MRA, and there is no obvious infarct on CT or MA Compared with NIHSS and ASPECTS, this classification can better predict the prognosis of mild stroke. It is not only suitable for posterior circulation infarction, but also directly reflect the situation of responsible vessels, and provide a more reasonable basis for ultra-early treatment of mild stroke [11].

In 2010, Fischer, et al. compared six definition methods for mild stroke and pointed out that two of them are most suitable for the diagnosis of mild stroke: (1) each NIHSS score must be 0 or 1, and each consciousness score must be zero. (2) The total baseline NIHSS score is less than 3. The patients with mild stroke with these two definition methods have the best short-term and medium-term prognosis [12]. Spokoyny, et al. applied the new definition of mild stroke (TREAT derived mild stroke criteria) to evaluate the effect of intravenous thrombolysis. The results suggested that intravenous thrombolysis did not increase the risk of symptomatic intracranial hemorrhage, and patients with mild stroke did not benefit from thrombolysis [13].

In 2016, China's guidelines for the diagnosis and treatment of high-risk non-disabling ischemic cerebrovascular events [14], defined mild stroke as any of the following: NIHSS score ≤ 3, NIHSS score ≤ 5 and Modified Rankin Scale (MRS) score ≤ 3.

The existing definition of mild stroke is gradually improved and closer to the clinic, with the combination of specific NIHSS score, non-disabling clinical symptoms and multimode imaging evaluation. However, these definitions do not consider the length of onset and the dynamic evolution of the disease. Evaluating the severity by the state of the patient at the time of treatment cannot reflect the overall picture of the patient's condition, and still cannot perfectly define the patients with mild stroke.

The ideal concept of mild stroke should have the following clinical characteristics [15]: (1) mild symptoms without aggravation and good prognosis; (2) It is suitable for stroke patients with different etiological subtypes; (3) It is simple and practical in clinical practice. (4) It does not overlap with transient ischemic attack. Developing an international consensus definition of mild stroke will contribute to the improvement of clinical diagnosis, medical intervention management, appropriate referral and prognosis evaluation of such patients.

Solution 2: Improve thrombolytic risk and benefit decision-making of mild stroke through multimodal imaging evaluation.

Patients with low NIHSS score often do not show obvious disability or show the real face of the disease. Clinicians often underestimate the severity of the disease or mistake similar stroke as stroke when deciding whether to thrombolytic treatment for mild stroke based on clinical symptoms. Imaging examination can more intuitively display the degree, nature, vascular status, collateral compensation, pathophysiological changes and so on, so as to make up for the deficiency of clinical standards.

1. Excluded stroke and TIA: Negative results of DWI may occur in up to 25% to 30% of patients with ischemic stroke [16]. 28% of mild stroke patients with NIHSS 0 to 5 were DWI negative (NIHSS 0: 46%, NIHSS 1: 32%, NIHSS 2: 23%, NIHSS 3: 12%, NIHSS 4: 10%, NIHSS 5: 14%). The lower the NIHSS score, the higher the DWI negative probability. The DWI negative proportion of acute stroke patients with NIHSS 0 to 2 score is higher than NIHSS 3 to 5 score. The DWI positive probability of mild stroke patients with ataxia, dysarthria, facial and motor defects is higher. All patients with neglect and visual defects are DWI positive, while patients with sensory disorders are unlikely to have DWI positive performance. Mild stroke patients with motor dysfunction, ataxia and high NIHSS scores, especially those with visual or neglect scores, have a high probability of DWI positive, while patients with simple sensory impairment may be stroke like rather than acute stroke [17]. However, the study did not dynamically track the evolution of DWI and the relationship between the length of onset and the positive rate of DWI. Some patients may have negative DWI due to too short onset time, or TIA rather than acute cerebral infarction.

2. Screening silent type stroke and active type stroke and determining the population benefiting from thrombolysis

Adequate assessment using multimode imaging techniques may help to distinguish patients at risk of deterioration and disability from patients with a benign natural history and identify markers of reperfusion benefits.

Infarct location and prognosis: subcortical infarction and brainstem infarction are more likely to affect patients' ability of daily living after 3 months [18].

Infarct volume and prognosis: Khatri, et al. showed a similar correlation in patients with mild stroke (mild stroke defined as NIHSS score less than 5) [1]. Subjects with poor prognosis of mild stroke had larger infarct focus at baseline DWI, and increased infarct focus often occurred, and early neurological deterioration often occurred within 5 days. Early deterioration of nervous system and enlargement of infarct size are associated with poor prognosis. However, there was no significant difference in the incidence of early neurological deterioration (NIHSS score increased by ≥ 2 points 0 to 5 days after admission) between patients with NIHSS score of 0 to 3 and patients with NIHSS score of 4 to 5 [19].

Final Infarct Volume (FIV) is a recognized prognostic factor for moderate and severe stroke, and there is a significant correlation between infarct volume and clinical prognosis [20,21]. Recent pilot studies on mild stroke (NIHSS 0 to 7) have shown that thrombolytic therapy in patients with large infarct size on Diffusion Weighted Imaging (DWI) may reduce the expansion of infarct size [22]. Vagal, et al. found that setting the final infarct volume threshold of MRI to 20 mL can distinguish the prognosis of patients with mild stroke. Whether intravenous thrombolytic therapy may improve clinical outcomes by reducing FIV is unclear [23].

Proximal vascular occlusion and prognosis: another factor that may lead to nervous system deterioration and poor prognosis in patients with mild stroke is Proximal Vascular Occlusion (i.e. PAO) [24,25]. PAO patients are more likely to have larger infarct volume. In mild stroke (when DWI lesion is relatively small compared with moderate/severe stroke), the growth of infarct is less frequent and smaller [22,26]. Mair, et al. found that 51% of patients without vascular occlusion by MRA/CTA had no obvious thrombolytic effect [27]. Patients with early deterioration of neurological function are often complicated with vascular occlusion [28]. These factors may lead to the negative results of the prisms study, which does not require imaging other than plain CT scan of the head [29].

Collateral circulation and prognosis: the relationship between collateral compensation and functional prognosis in patients with moderate and severe stroke has been fully documented [30], but the role of collateral circulation in mild stroke has not been fully studied. Olivot, et al. applied multimode imaging cohort study to show that low perfusion intensity ratio is related to slow infarct growth and small final infarct volume. These imaging features

can evaluate the quality of collateral circulation and predict the growth of infarct volume [31]. Brown, et al. directly compared the mild stroke group (NIHSS ≤ 4 points) with the moderate and severe stroke group (NIHSS>4 points) and evaluated it with multimode images. The results showed that the clinical symptoms of stroke patients without atrial fibrillation were mild in men, small PWI lesion volume, small DWI lesion volume, small mismatch volume (PWI-DWI). In patients with similar occlusive sites, patients with mild symptoms tend to have smaller DWI volume and slower growth rate of early infarction. In addition, no other clinical or baseline imaging features change with symptom severity. It is conceivable that in mild stroke, patients with good collateral compensation may have better tissue perfusion protection and better embolic clearance. Therefore, the infarct volume is small, the risk of nervous system deterioration is low, the natural prognosis is good, and the benefit of intravenous thrombolysis may not be significant [32].

Majidi, et al. studied the safety and efficacy of thrombolytic therapy in patients with acute stroke with low NIHSS score screened by MRI. All patients underwent MRI scans before and 24 hours after thrombolytic therapy, including Diffusion-Weighted Imaging (DWI), Hemosiderin Weighted Imaging (SWI), Fluid Attenuated Inversion Recovery (FLAIR), Time-of-flight Magnetic Resonance Angiography (MRA), and Perfusion Weighted Imaging (PWI) to identify stroke, macrovascular lesions, the number of microbleeds Compared with thrombolysis after routine CT screening, thrombolysis after MRI multimode image screening has higher good prognosis and lower bleeding rate [33].

It is very important to link the clinical results with the imaging findings. Before making a treatment decision, it may be more helpful to identify the group of mild stroke patients who may have early neurological deterioration and may benefit from ultra-early reperfusion treatment by confirming the infarct volume, whether there is perfusion injury or vascular occlusion, and the advantages and disadvantages of collateral circulation.

Solution 3: Prevent stroke recurrence.

The poor prognosis of patients with mild stroke is not necessarily caused by the stroke itself or bleeding transformation. The poor prognosis of 90 days may be due to the disability caused by non-neurological causes during this period (such as falls caused by improper nursing), and more importantly, recurrent stroke.

10% to 20% of patients with mild stroke relapse within 3 months [34]. The 2013 CHANCE study showed that aspirin combined with clopidogrel in the acute phase can reduce the recurrence risk and the incidence of disabling recurrence events within 90 days in patients with TIA and mild stroke, do not increase the bleeding risk of patients, and may benefit patients with large atherosclerosis [35]. The 2018 point study once again confirmed the research results of the chase scheme. Compared with the Chinese population included in the chase study, the point study is mainly aimed at the European and American population, and the race is more diverse. The heavy publication of the results of the two studies is of great significance to improve the prognosis of patients with mild stroke, so the guidelines for the treatment of non-disabling stroke have been rewritten [36].

Conclusion

At present, the controversy about thrombolysis in the treatment of mild stroke is based on different definitions and different views on the risk/benefit ratio of treatment. If we can ideally identify patients at risk of poor prognosis and give thrombolytic therapy, there may be ideal benefits. These patients include: 1. Extracranial and extracranial large vessel occlusion. 2. Diffusion weighted MR imaging in acute phase showed relatively large infarct. 3. Perfusion imaging showed a large low perfusion area.

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