Hemorrhagic transformation after cerebral infarction: current concepts and challenges

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Abstract: Hemorrhagic transformation (HT) is a frequent complication of acute ischemic stroke that is especially common after thrombolytic therapy. The risk of HT limits the applicability of tissue plasminogen activator (tPA). Here, we sought to review the rate, classification, predictors, possible mechanism, and clinical outcomes of HT, as well as existing therapeutic approaches, in order to call attention to the current challenges in the treatment of this complication.

Keywords: Acute ischemic stroke; hemorrhagic transformation (HT)

Hemorrhagic transformation (HT), which refers to a spectrum of ischemia-related brain hemorrhage, is a frequent spontaneous complication of ischemic stroke, especially after thrombolytic therapy (1). Therefore, HT limits the use of tissue plasminogen activator (tPA) treatment, the only method of clinical management of acute ischemic stroke. To search for new treatments as well as intervention measures for HT, it is important to understand its underlying mechanism and identify its predictors. In this review, we summarize the published results on the incidence, predictors, possible mechanism, and clinical outcomes of HT.

Classification and incidence

With regard to the type of hemorrhage, HT can be divided into hemorrhagic infarction (HI) and parenchymal hematoma (PH) (2). HI is a heterogeneous hyperdensity occupying a portion of an ischemic infarct zone on computed tomography (CT) images, whereas PH refers to a more homogeneous, dense hematoma with mass effect. Each of them has two subtypes: HI type 1 (HI1) and HI type 2 (HI2) for HI and PH type 1 (PH1) and PH type 2 (PH2) for PH. On radiographic images, HI1 is characterized by small hyperdense petechiae, whereas HI2 refers to more

confluent hyperdensity throughout the infarct zone. Both of the two types are without mass effect. PH1 refers to the homogeneous hyperdensity occupying less than 30% of the infarct zone, with some mass effect, and PH2 refers to the homogeneous hyperdensity occupying over 30% of the infarct zone, with significant mass effect.

The incidence of spontaneous HT ranges from 38% to 71% in autopsy studies and from 13% to 43% in CT studies, whereas the incidence of symptomatic HT is from 0.6% to 20% (3,4). The incidence depends on many factors, such as age, blood glucose level, thrombolytic agent used, route of administration, and time window allowed for the initiation of the therapy (3,5,6). The rate of HI is higher than that of PH. In particular, in a large cohort of consecutive patients with acute ischemic stroke, the incidence of HI from the refereed paper was found to be about 9%, whereas that of PH was about 3% (7).

Predictors

Massive cerebral infarction

Massive cerebral infarction is one of the most dangerous factors of HT development (8). Given that there is a positive correlation between the infarction area and the incidence of HT (9,10), the risk of HT increases remarkably when

massive cerebral infarction is present (11,12). Furthermore, massive cerebral infarction is often accompanied by substantial brain edema, which results in compression of the peripheral vasculature. The enhanced permeability of the vascular wall because of prolonged ischemia and hypoxia caused by vascular compression greatly increases the chances of HT after the release of the edema. Therefore, in patients with massive cerebral infarction, it is very important to perform cranial CT or magnetic resonance imaging (MRI) regularly, regardless of whether the clinical symptoms worsen or improve. Moreover, it is necessary to choose the treatment plan carefully, especially with respect to thrombolytic therapy.

Area of infarction

HT often occurs in the gray matter, especially in the cerebral cortex, because of its abundant collateral circulation, which tends to worsen the reperfusion injury. Gray matter infarction, which is often due to a large artery occlusion, can lead to massive edema, causing ischemic injury by compressing the surrounding blood vessels. In contrast, most instances of white matter infarction are of lacunar type, and caused by the terminal vascular occlusion.

Atrial fibrillation and cerebral embolism

Atrial fibrillation and cerebral embolism are associated with an increased risk of HT (9,13,14). The blockage of intracranial vessels as a result of atrial fibrillation is one of the major causes of cardioembolic cerebral infarction. The embolus can then be dislodged with thrombolytic therapy or on its own, leading to recanalization of the previously occluded vessels. Ischemia-impaired occlusion vessels and undeveloped neovascularization increase the probability of HT. Atrial fibrillation is associated with higher volumes of more severe baseline hypoperfusion, leading to greater infarct growth, more frequent severe HT, and worse stroke outcomes (15). In previous studies, the factor independently linked to the risk of HT of cardioembolic infarcts was the volume of infarction edema on the initial CT scan. In particular, the probability of bleeding was about 95% if the volume of infarction edema exceeded 10 cm^3 (16).

Higher National Institute of Health Stroke Scale (NIHSS) score

The NIHSS score measures the severity of cerebral infarction. It is likely that a high NIHSS score is a predictor of larger infarcts. In previous studies, the NIHSS score emerged as a powerful predictor of HT in both univariate and multivariate analyses (5).

Hyperglycemia

Hyperglycemia has a major role in post-ischemic HT. In experimental transient middle cerebral artery occlusion (tMCAO) models, acute hyperglycemia reliably and consistently resulted in HT (17). Furthermore, human clinical trials also revealed a close association between HT and high blood glucose (7). Hyperglycemia during acute ischemic stroke predisposes to PH, which in turn determines a non-favorable outcome at 3 months, and this relationship seems to be linear (18). Furthermore, several studies have shown that in diabetic patients with acute ischemic stroke, prior and continued use of sulfonylureas drugs is associated with reduced symptomatic HT compared to those whose treatment regimen does not include sulfonylureas drugs (19). The mechanism of the hyperglycemia effect on HT is complex, and some studies suggest that hyperglycemia can aggravate the hypoxia and malnutrition of the artery wall, which makes the artery wall prone to degeneration and necrosis, promoting the incidence of HT.

Lower total cholesterol (TC) and low-density lipoprotein cholesterol (LDLC) levels

Various reports suggest that lower LDLC and TC levels are associated with all the types of HT and symptomatic HT, respectively (20-22), whereas HDL cholesterol and triglycerides are not linked to the HT risk (20). For example, Kim *et al*. found that low levels of LDLC, and possibly TC, are associated with a greater risk of HT after acute ischemic stroke attributable to large artery atherothrombosis but not cardioembolism (23). These results are particularly important because LDLC can be influenced by statins. Therefore, the question of whether recombinant tPA (rt-PA) is safe in patients with low LDLC levels or on statin treatment deserves more attention. As of now, a consensus has not been reached. On one hand, although patients treated with statins have less severe cerebral infarcts (24), a large European multicenter study showed that this effect is lost in individuals concomitantly treated with rt-PA (25). On the other hand, according to the opinion of some experts, the use of statins does not increase HT rates and severity when it is combined with tPA administration (26). The mechanism underlying

the link between the increased susceptibility to HT and low levels of TC or LDLC is not yet established. It may be speculated that cholesterol may be important for the integrity of small cerebral vessels (27) and the neurovascular unit.

Lower platelet count

Lower platelet count is associated with the presence of early HT in patients with non-lacunar ischemic stroke (28). It is likely that the decreased overall number of platelets available for activation and aggregation directly increases the risk of HT.

Poor collateral vessels

Collateral vessels sustain the ischemic penumbra, which limits the growth of the infarct core before recanalization. The angiographic grade of collateral flow strongly influences the rate of HT after therapeutic recanalization for acute ischemic stroke. Poor baseline collaterals may limit effective reperfusion, and recanalization upstream from the regions of severe hypoperfusion may enhance hemorrhagic conversion. Consequently, poor baseline collaterals may result in a high frequency of HT with worsened clinical neurological status (4).

Treatment plan

Intravenous rt-PA is the most effective treatment of acute ischemic stroke. However, the most significant concern about the use of rt-PA is an increased risk of hemorrhage. Many studies have showed that thrombolysis is independently associated with HT (7). The use of fibrinolytic agents may increase potent fibrinolytic activity, so the risk of systemic and intracranial hemorrhage increases. Alternatively, endovascular treatment may result in mechanical damage to the blood vessel endothelium, therefore increasing hemorrhage risk. Several controlled clinical trials in acute ischemic stroke reported the rates of total HT over the first 5 days from 3.2% to 37% in the placebo group and from 10.6% to 44% in the group receiving thrombolytic treatment, meanwhile, symptomatic HT ranged from 0.6% to 7% in the placebo group and from 6.4% to 20% in the thrombolyzed group (3). Therefore, thrombolytic therapy can increase the risk of HT, and its incidence depends on the thrombolytic agent used, route of administration, and time window allowed for the initiation of the therapy.

In the mouse model of ischemic stroke during anticoagulant therapy, warfarin pretreatment dramatically increases the risk of HT in 24 hours after middle cerebral artery occlusion (29). Reperfusion injury seems to be a critical component in this condition. Several trials suggested that patients with various anticoagulants (0.6% to 6.1% risk) have a higher risk of bleeding complications than the control groups (0.2% to 1% risk) (30). These results suggest that most patients with acute stroke should not be treated with unfractionated heparin or other rapidly acting anticoagulants after stroke.

Meanwhile, a prospective pilot study suggests that NIHSS scores at 7 and 14 days and the modified rank in scale (mRS) at 90 days post-rt-PA were significantly lower in non-antiplatelets group than in antiplatelets group, duration of hospitalization was significantly shorter, and the favorable outcome rate was higher at 90 days (31). A retrospective study of consecutive prospectively registered 235 patients after acute ischemic stoke. A total of 72 patients were pre-treated with antiplatelet agents, and 33 occurred PH, and 16 occurred symptomatic intracerebral haemorrhage. The adjusted odds ratios of PH for patients pre-treated with AP therapy was 3.5 (1.5-7.8, P=0.002) and for symptomatic intracerebral hemorrhage (SICH) 1.9 (0.6-5.9, P=0.2). It shows that pre-treatment with antiplatelet agents is associated with an increased risk of PH after intravenous thrombolysis in patients with acute ischaemic stroke (32).

Globulin level

Previous studies showed that the elevated globulin level is an independent risk factor of HT in patients receiving intra-arterial thrombolytic therapy. Possible mechanisms may involve inflammatory cytokines (IL-1, IL-6, TNFα), matrix metallopeptidase 9 (MMP-9), and positive acute-phase reactants synthesized by the liver (33).

Early CT signs

Some early CT findings are strong predictors of both HT and symptomatic HT, including the loss of the density contrast of the lentiform nucleus, loss of the density contrast of the insular ribbon, and hemispheric sulcus effacement, either alone or with a hyperdense middle cerebral artery sign (HMCAS). Patients exhibiting these signs are at high risk of bleeding (3).

Hyperdense middle cerebral artery sign (HMCAS)

The HMCAS is a possible radiological predictor of HT.

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Several studies have shown that patients with HMCAS had higher baseline NIHSS scores and more frequent early ischemic changes on the baseline CT scan than those without HMCAS. Thus, HMCAS is common in anterior circulation infarction and is independently predictive of HT after thrombolytic therapy (34).

Micro- and macro-albuminuria

Albuminuria has been found to be a marker of chronic endothelial damage. Therefore, the presence of micro- and macro-albuminuria may be an independent predictor of HT in patients with acute ischemic stroke, particularly in cases with the most severe bleeding (35,36).

Several other factors have been suggested as predictors of HT after acute ischemic stroke in the published studies, such as age, serum S100B levels (37), plasma cellular-fibronectin concentration (38), low glomerular filtration rate (39), serum ferritin level (40), serum cytokines (41), blood-brain barrier (BBB) permeability (42), and MMP-9 variations (43). Further research is needed to confirm the relationship between these factors and HT.

Recently, various risk score models have been developed to predict SICH after intravenous thrombolysis for acute ischemic stroke, such as Cucchiara score, the hemorrhage after thrombolysis (HAT) score, the safe implementation of thrombolysis in Stroke-SICH risk score, the glucose race age sex pressure stroke severity score, and the stroke prognostication using age and national institutes of health stroke scale-100 index. Sung *et al.* found that the Cucchiara score, the HAT score, and safe implementation of thrombolysis in Stroke-SICH risk score could reasonably predict SICH regardless of the definitions of SICH. Of them, the HAT score had the best ability to discriminate between patients with and without SICH (44). These score could aid clinicians to identify patients at high as well as low risk of SICH after intravenous thrombolysis.

Pathophysiology

HT is a dynamic and complex phenomenon, and its pathophysiology is still not clear. The potential mechanism is summarized below. Within seconds to minutes after the onset of cerebral ischemia, the level of ATP decreases substantially, compromising the activity of the Na^+-K^+ ATPase (45). This creates a series of cellular and metabolic imbalances that cumulatively lead to a disruption of the BBB (46). Furthermore, ischemia results in a strong inflammatory response (47), further distorting normal cerebrovascular anatomy and physiology. The resulting disruption of the BBB and the impairment of the autoregulatory capacity of the cerebral vasculature predispose to blood extravasation when the ischemic tissue is eventually reperfused (48). Importantly, the degree of anatomical and physiological disruption appears highly dependent on the duration of ischemia (45,48).

Thrombolytic treatment with tPA can successfully reperfuse the ischemic brain, but it increases the rate of HT, which limits its use. Recent data suggest that the signaling activities of tPA in the neurovascular unit are responsible for some potentially neurotoxic side effects. Besides its intended role in clot lysis, tPA is also an extracellular protease and signaling molecule in the brain. In particular, tPA mediates matrix remodeling during brain development and plasticity. By interacting with the NMDA-type glutamate receptor, tPA may amplify potentially excitotoxic calcium currents. Furthermore, at certain concentrations, tPA may be vasoactive. Finally, by augmenting matrix metalloproteinase (MMP) dysregulation after stroke, tPA may degrade the extracellular matrix integrity and increase the risks of neurovascular cell death, BBB leakage, edema, and hemorrhage (49).

Clinical outcome

Previous studies suggest that HT does not have a serious negative effect on the clinical outcome in most cases. On the contrary, mild to moderate HT represent a sign of successful treatment and vascular recanalization (50). However, the prognosis of HT is dependent on its type. Thus, only PH2 is found to be a significant predictor of neurological deterioration and higher mortality (1,51). Several reviews showed that risk of early neurological deterioration and of 3-month death was severely increased after PH2, indicating that large hematoma is the only type of HT that may alter the clinical course of ischemic stroke (52).

Intervention

At present, effective intervention measures for HT after thrombolytic therapy are limited. Some studies suggest that inhibition of MMP-2 or MMP-9 can protect against HT during the early stage of cerebral ischemia and reperfusion. In particular, it was found that both MMP-2 and MMP-9 are significantly upregulated and activated in the early stage of ischemic reperfusion injury, suggesting that these

enzymes are associated with early ischemic brain damage. Therefore, reduction of activity of MMP-2 or MMP-9 can decrease the incidence of HT (53).

Research has shown that early administration of deferoxamine (DFX) has a neuroprotective effect in cerebral ischemia, cerebral hemorrhage, and subarachnoid hemorrhage. In this regard, we are currently investigating whether DFX administration can affect the rate of HT. Our previous studies suggest that DFX reduces the death rate, HT, infarct volume, and brain swelling in a rat model of transient focal ischemia with hyperglycemia (54). Therefore, DFX can potentially be used to reduce HT after stroke.

Estrogen is known to have a neuroprotective effect in experimental ischemic stroke and to preserve the BBB integrity with consequent reduction of brain edema. In agreement with this, studies show that acute administration of 17β-estradiol (E2) at the onset of ischemia diminishes the adverse effects of tPA, including the increase of MMA-9 activity, BBB permeability, and HT (55). These findings suggest that estrogen may be a potential therapy for HT after thrombolytic treatment of ischemic stroke.

Cilostazol, a phosphodiesterase-III inhibitor used for the treatment of intermittent claudication, has been reported to offer neuroprotection and endothelial protection in animals with ischemic brain injury. In particular, Ishiguro *et al.* found that cilostazol reduces the rate of HT induced by focal cerebral ischemia in mice treated with tPA or subjected to MCA occlusion and reperfusion (56).

Further studies are required to confirm the effects and investigate the mechanisms of these potential treatments, as well as to develop new therapies for HT.

Now, we have recognized very little about HT. There are several obstacles to look into HT. Firstly, HT is a series of very complex pathological changes, so it's a very difficult task to thoroughly understand its etiology and pathophysiology. We need a lot of efforts to overcome them. Secondly, as its pathogenesis and treatment are still not clear, we need to establish ideal animal model to research it. So, the building and selection of animal model is very important. Its feasibility, stability and similarity with HT in human directly influence the value of the related experimental study of HT. We have established some animal models recent years, for example, acute hyperglycemia reduced rat model, tPA reduced rat model, but each animal model has its advantages and disadvantages, so they can not explain HT absolutely. Therefore, we should look for a more ideal animal model to research it deeply, and then step into the clinical trial as soon as possible. Moreover, the

interventions of HT are difficult. How to treat and prevent HT specifically is still unclear. We found that DFX can reduce brain injury after transient focal cerebral ischemia in rats with hyperglycemia, but the different function of DFX on blood brain barrier depends on the time of application of DFX (53). Therefore, the intervention of HT is very complex. There are still many obstacles in the research of HT, so we should try our best to conquer it.

To summarize, HT is a complex and multifactorial phenomenon. More attention should be paid to patients with acute cerebral infarction, particularly massive infarction, cortical infarction, atrial fibrillation and cerebral embolism, hyperglycemia, low TC and LDLC levels, low platelet count, poor collateral vessels, thrombolytic treatment, increased globulin, early CT signs, HMCAS, and other predictors. The treatment of patients with the above predictors should be conducted more carefully. To discover HT as soon as possible, CT and MRI need to be performed timely and regularly. Furthermore, the PH2 type of HT is often associated with higher mortality. Close monitoring is needed in such cases.

Acknowledgements

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