Cardiovascular Instability Preceded by Orolingual Angioedema after Alteplase Treatment

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Abstract

An 87-year-old man taking antihypertensive medications, including 10 mg enalapril, daily visited our hospital complaining of motor aphasia, dysarthria, and right hemiparesis. Magnetic resonance imaging revealed an ischemic lesion in the left frontal lobe including the insular cortex and severe stenosis of the left middle cerebral artery. After he received intravenous alteplase infusion, he developed orolingual angioedema followed by transient bradycardia with subsequent hypotension, resulting in the deterioration of his neurological signs and expansion of the ischemic lesion. Orolingual angioedema after intravenous alteplase infusion may follow cardiovascular instability and disease progression in stroke patients.

Key words: cerebral infarction, orolingual angioedema, rt-PA, alteplase, bradykinin

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Introduction

Orolingual angioedema is observed in 1.7-5.1% of stroke patients treated with intravenous alteplase (recombinant tissue plasminogen activator; rt-PA) (1, 2). While it is potentially life-threatening because of its obstructive nature in the upper airway, orolingual angioedema may spontaneously disappear and does not necessarily require endotracheal intubation or cricothyroidotomy. However, careful attention to possible development of orolingual angioedema remains critical because it may accompany cardiovascular instability and affect the severity of stroke, as observed in the following case.

Case Report

An 87-year-old man presented to our hospital complaining of motor aphasia, dysarthria, and right hemiparesis. He had a history of hypertension and chronic kidney disease and was taking 10 mg enalapril, 40 mg olmesartan, and 16 mg azelnidipine daily. He had no history of angioedema (Quincke’s edema), either prior to or since commencing enalapril. His initial score on the National Institutes of Health Stroke Scale (NIHSS) was 16. Magnetic resonance imaging (MRI) revealed an ischemic lesion in the left frontal lobe including the insular cortex (Fig. 1a), and magnetic resonance angiography (MRA) showed severe stenosis of the left middle cerebral artery (MCA; Fig. 1b). Ultrasound also demonstrated stenosis of the bilateral internal carotid arteries (ICAs). Area stenosis of the left and right ICAs was 79% and 82%, respectively. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) method indicated 64% stenosis in the left ICA, whereas the right ICA could not be evaluated because its stenosis extended beyond the distal end of the observed area.

Alteplase infusion was started 140 minutes after the onset of symptoms. Although the patient’s hemiparesis significantly ameliorated during the treatment and his NIHSS score decreased to 8, by the end of alteplase infusion, he had developed swelling on the right side of his tongue with a hemorrhage on its surface (Fig. 2). Although there was no evidence of airway compromise or a skin rash, his heart rate suddenly started to decrease from 72 beats/minute to less than 50 beats/minute at 2 hours from the end of the rt-PA treatment, followed by the fall of his blood pressure from 140/60 mmHg to 54/26 mmHg. Neither electrocardiography nor ultrasound cardiography detected any abnormality in the...
Hydrocortisone was commenced and the edema disappeared confirming right-sided orolingual angioedema (Fig. 3c, d). rt-PA treatment followed by transient cardiovascular instability. The NIHSS score increased to 23. Brain MRI revealed expansion of the ischemic lesion to include the entire territory of the left MCA and left MCA occlusion was identified using MRA (Fig. 3a, b). It also showed the asymmetrical swollen tongue without parenchymal hematoma, confirming right-sided orolingual angioedema (Fig. 3c, d). Hydrocortisone was commenced and the edema disappeared within 2 days.

**Discussion**

We herein present a case of orolingual angioedema after rt-PA treatment followed by transient cardiovascular instability. This hemodynamic change, in combination with a significant stenosis in the ipsilateral ICA as indicated by the NASCET method, resulted in the progression of ischemic stroke.

At least two distinct factors appear to be involved in the emergence of orolingual angioedema after the rt-PA treatment: 1) enhanced bradykinin activity and 2) autonomic dysfunction caused by lesions in the insular and frontal cortices (1). It should be noted that both of these factors may also potentially affect the cardiovascular function.

Bradykinin belongs to a family of vasodilator peptides, the kinins, which are generated as a result of the hydrolysis of high molecular weight kininogen. rt-PA converts plasminogen to plasmin, which processes prekallikrein to kallikrein (3). Kallikrein hydrolyzes high molecular weight kininogen in the plasma to cleave out bradykinin (4). Bradykinin is then metabolized by three kinds of enzymes: angiotensin-converting enzyme (ACE), aminopeptidase P (APP), and kininase I enzymes. Although kininase I enzymes are basically a minor pathway in bradykinin metabolism, they degrade bradykinin to des-Arg9-bradykinin, which acts as a vasodilator and contributes to angioedema (5). Because des-Arg9-bradykinin is also degraded by ACE and APP, bradykinin degradation ultimately depends on the activity of APP in the presence of ACE inhibitors. In the plasma of patients with ACE inhibitor-associated angioedema, the degradation of bradykinin is slower and the accumulation of des-Arg9-bradykinin is higher than in healthy controls (6). This suggests the importance of a link between the generation of ACE inhibitor-associated angioedema and the genetic background in terms of APP activity. It has recently been shown that the polymorphism of the APP gene is related to the occurrence of ACE inhibitor-associated angioedema (7, 8). It should be noted that the same polymorphism has been also demonstrated to correlate with the occurrence of acute hypotensive transfusion reaction (9).

Several clinical observations have previously indicated that the risk of rt-PA-associated orolingual angioedema also increases with the concomitant use of ACE inhibitors (1). This suggests that similar genetic factors to those of ACE inhibitor-associated angioedema may be involved in this
phenomenon. Therefore, increased production and decreased breakdown of bradykinin would be expected in patients showing orolingual angioedema after the treatment with both rt-PA and ACE inhibitors. Bradykinin and des-Arg9-bradykinin increase vascular permeability and cause vasodilatation by binding to the kinin B2 and B1 receptors, respectively, in vascular endothelial cells. Bradykinin can also affect the heart rate through B2 receptors; however, des-Arg9-bradykinin does not significantly alter the heart rate (10). It remains controversial as to precisely how bradykinin affects the chronotropic state. However, Cloutier et al. showed that intracerebroventricular injection of bradykinin induces bradycardia in Wistar-Kyoto rats (10). Ribuot et al. also demonstrated that bradykinin reduces the heart rate when injected into the sinus node artery in dogs, in which the baroreceptor-mediated reflex has been inhibited (11). These findings support the possibility that the enhancement of bradykinin activity may induce both hypotension and bradycardia.

Another epidemiological factor that increases the risk of rt-PA-associated orolingual angioedema is the presence of ischemic lesions in the insular and frontal cortices (1), as was the case in the present patient. According to the observations in cases of epilepsy, the insular cortex is known to be associated with the autonomic function, including the cardiovascular state (12). Although there is controversy regarding whether the insular cortex exerts a positive or negative chronotropic effect, Jing et al. demonstrated that left insular infarct is related to sinus bradycardia in humans (13). Therefore, the initial ischemic lesion in the left insular cortex may also have contributed to the evolution of bradycardia and hypotension in the present case.

It is not clear why the changes in the cardiovascular state were transient and self-limited in the present case. One explanation is the relatively short period of bradykinin action. During rt-PA treatment, the duration of bradykinin activity would depend on the rate of its generation by rt-PA because the half-life of bradykinin is as short as 17 seconds (14). Therefore, a decrease in the plasma rt-PA concentration may be associated with the resolution of cardiovascular instability. Another possible explanation is that metabolic dysfunction and excitotoxic neurotransmitter production, rather than the functional loss of cortical neurons in the ischemic lesion, may change the hemodynamic state, as is assumed to be the case in early seizures experienced by stroke patients (15).

In cases of orolingual angioedema, rt-PA infusion should be immediately discontinued. Although several kinds of antiallergy agents, such as antihistamines, corticosteroids, and

Figure 3. Brain MRI after rt-PA treatment. An axial view of a diffusion-weighted image after rt-PA treatment shows expansion of the high-intensity lesion (a). A frontal view of brain MRA after rt-PA treatment shows left middle cerebral artery occlusion without any signal of the distal branches (b). A sagittal view of a T1-weighted image demonstrates swelling of the tongue without intraparenchymal hemorrhage (c). A coronal view of a fluid-attenuated inversion recovery image of MRI depicts deviation of the median lingual sulcus (arrow) to the left by right-sided tongue swelling (d).
epinephrine, have been proven effective in previous cases, the pharmacological mechanism underlying their efficacy for angioedema has not been fully evaluated (16). Recently, specific inhibitors of the kinin-kallikrein system have been developed to treat acute attacks of hereditary angioedema (17). These treatments could be beneficial in cases of orolingual angioedema associated with rt-PA and ACE inhibitors.

In conclusion, the development of orolingual angioedema after rt-PA treatment in stroke patients taking ACE inhibitors suggests latent bradykinin hyperactivity and central autonomic dysfunction. These phenomena are also highly likely to affect the cardiac function. Accordingly, we suggest that the presence of orolingual angioedema should alert the clinician to the possibility of upcoming cardiovascular instability that may result in reduced blood supply to the penumbra, even in the absence of airway complications.

The authors state that they have no Conflict of Interest (COI).

References