DOI:10.4274/tnd.2020.04864
Turk J Neurol 2020;26:346-348

Case Report / Olgu Sunumu

Orolingual Angioedema After Intravenous Tissue Plasminogen Activator in a Patient with Insular Cortex Ischemia: A Case Report

İnsular Korteks İskemisi Olan Hastada İntravenöz Doku Plazminojen Aktivatörü Sonrası Gelişen Orolingual Anjiyoödem: Olgu Sunumu

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Abstract

Intravenous tissue plasminogen activator (tPA) increases survival rates without sequelae in acute ischemic stroke. Complications and management of this treatment have become more important with the increasing use of tPA. An 80-year-old male patient was admitted with a sudden-onset speech disorder and loss of strength in his right arm, which started 3 hours ago. Magnetic resonance imaging revealed acute ischemia localized in the left insular cortex. Lip and tongue swelling, difficulty in speaking, and deepening in voice were observed in the 30th minute of infusion. There was mild respiratory distress. Orolingual angioedema was diagnosed. He completely recovered after treatment. Angioedema is a rare but potentially life-threatening complication of tPA. When this clinical symptom occurs, it should be recognized and treated quickly. This report aims to reveal the relationship of this rare complication with the localization of the ischemia.

Keywords: Intravenous thrombolysis, stroke, insula, angioedema

Öz

Akut iskemik inmede intravenöz doku plazminojen aktivatörü (tPA) sekelsiz sağkalım oranını artırmaktadır. Artan tPA kullanımı ile bu tedavinin komplikasyonları ve yönetimi daha önemli hale gelmiştir. Seksen yaşında erkek hasta 3 saat önce ani başlayan konuşma bozukluğu ve sağ kolda güç kaybı nedeniyle başvurdu. Manyetik rezonans görüntülemede sol insular kortekse uyan lokalizasyonda akut iskemi saptandı. İnfüzyonun 30. dakikasında dilde ve dudakta şişkinlik, konuşurken zorlanma ve seste kabalaşma gözlendi. Hafif solunum sıkıntısı saptandı. Orolingual anjiyoödem tanısı konuldu. Tedavi sonrası hasta tamamen düzeldi. Anjiyoödem tPA'nın nadir ancak potansiyel olarak yaşamı tehdit edici bir komplikasyonudur. Bu klinik semptomun hızlı bir şekilde tanınması ve tedavi edilmesi gerekir. Bu nadir komplikasyonun özellikle iskemik alanın lokalizasyonu ile ilişkisinin ortaya konulması amaçlanmıştır.

Anahtar Kelimeler: İntravenöz tromboliz, inme, insula, anjiyoödem

Introduction

Intravenous (IV) tissue plasminogen activator (tPA) is an important treatment option in appropriate patients with acute ischemic stroke within the first 4.5 hours of symptom onset. It is necessary to give patients treatment as early as possible because the benefit of IV tPA is time dependent (1). IV tPA in acute cerebral ischemia has become one of the main treatments in recent years because it increases the rate of survival without sequela (2). With the increased use of tPA in ischemic stroke, its complications and their management have become more understandable (3). The most feared complication of treatment is intracranial bleeding. A lesser known, but also potentially life-threatening complication, is angioedema (4).

In this case report, we present a patient who developed orolingual angioedema after administration of tPA due to acute ischemic stroke. Showing the relation between this rare complication and the localization of the ischemic area was specifically aimed.

Case Report

In November 2019, an 80-year-old male patient was admitted with sudden-onset slurred speech and a loss of strength in the right arm, which started 3 hours before. He had coronary artery disease in his medical history. For this reason, he was using acetylsalicylic acid 100 mg/day and clopidogrel 75 mg/day. He had been smoking 20 cigarettes a day for 60 years. He was conscious in his neurologic examination. His speech was dysarthric. No cranial nerve deficits

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Received/Geliş Tarihi: 05.12.2019 **Accepted/Kabul Tarihi:** 31.03.2020

were detected. Cerebellar tests were normal. The muscle strength was 4/5 in the upper right extremity and there were no motor deficits in the other extremities. There was no Babinski sign. Deep tendon reflexes were bilateral hypoactive.

The laboratory test results were as follows: leukocyte: 7.51 $10^3/mm^3$ (3.91-10.9), hemoglobin (hg): 9.9 g/dl (13.5-16.9), platelet: 362 $10^3/mm^3$ (150-450), international normalized ratio: 0.9 (0.8-1.2), glucose: 99 mg/dl (74-106), urea: 48 mg/dl (17-43), creatinine: 1.08 mg/dl (0.81-1.44), aspartate transaminase: 18 U/l (0-50), and alanine transaminase: 11 IU/ (0-50). Intracerebral hemorrhage was not detected in the brain computed tomography performed in an external center 2.5 hours after the onset of symptoms, and there was a hypodense field in the left insular cortex (Figure 1). In diffusion-weighted magnetic resonance imaging, there was a hyperintensity in the left insular cortex, and in apparent diffusion coefficient imaging, there was a hypointensity in the same location (Figure 2A, 2B).

Acute ischemic stroke was considered in the patient with the present findings. The patient's blood pressure was 170/100 mmHg and blood sugar was 123 mmol/l. The patient and his relatives were informed and written and oral consents were obtained. All contraindications for IV tPA were evaluated. IV tPA (alteplase) was started 3.5 hours after the onset of stroke symptoms. Seven point two milligrams of Alteplase was administered as IV bolus to the patient who weighed 80 kg. The remaining 64.8 mg was given as IV infusion. At the 30th minute of infusion, swelling of the tongue and lips, difficulty in speaking, and vulgarity in the voice were observed. Mild respiratory distress was present. IV tPA treatment was terminated. The patient was diagnosed as having orolingual angioedema. Antihistaminics, corticosteroids, and epinephrine were administered. Thirty minutes later, the symptoms completely resolved.

Discussion

In patients with ischemic stroke, IV tPA is an effective treatment but it should also be considered in terms of its complications. Treatment complications can be classified into five major categories: intracranial hemorrhage, systemic hemorrhage, immunologic complications, hypotension, and myocardial rupture (5). Angioedema, an immunologic complication, occurs in 1.3-5.1% of patients (4). Angioedema is caused by the movement of intracellular fluid into interstitial tissues as a result of increased vascular permeability due to inflammatory mediators. Angioedema has three main causes: mast cell-mediated due to allergic reactions or non-steroidal antiinflammatory drug use; bradykinin-mediated due to angiotensin-converting enzyme (ACE) inhibitor use or C1 inhibitor deficiency; and unknown mechanisms such as idiopathic angioedema or fibrinolytic agent use (6,7,8,9). In our patient,

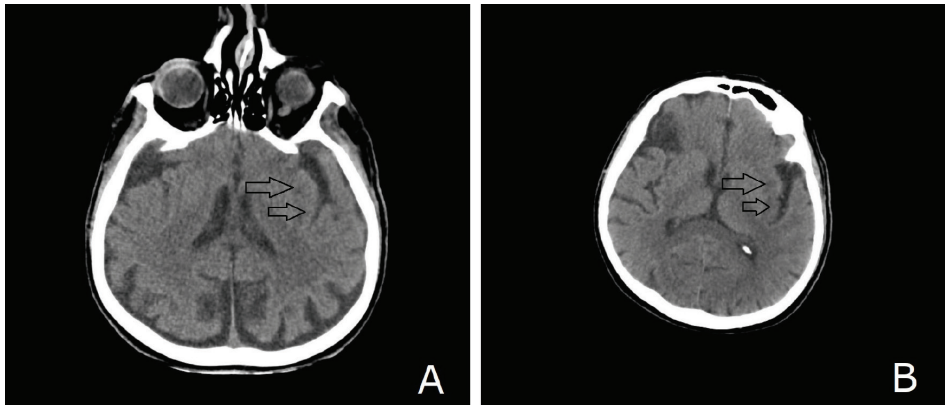

Figure 1A, B. Brain computed tomography: No area of hyperdensity suggesting hemorrhage. Mild edema and asymmetry present in the insular area consistent with early ischemia

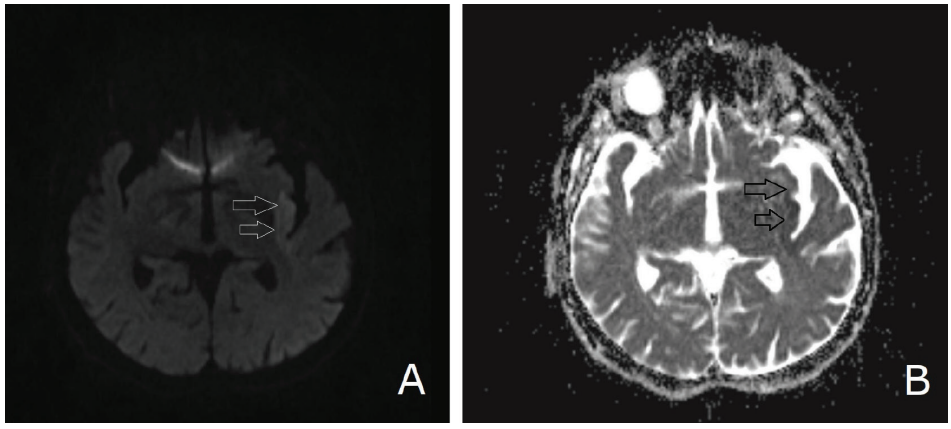

Figure 2. A) Brain diffusion-weighted magnetic resonance imaging: Hyperintensity in the localization of left insular cortex, **B)** brain apparent diffusion coefficient magnetic resonance imaging: hypointensity in the same location

orolingual angioedema developed due to IV tPA, which is a fibrinolytic agent.

Angioedema has been reported to develop 25-120 minutes after the onset of thrombolytic therapy as a complication (10). In our case, angioedema developed 30 minutes after starting the treatment. It has been suggested that angioedema that develops following IV tPA infusion is mediated by bradykinin. TPA is involved in the formation of plasmin, which allows the separation of bradykinin from kininogen. Bradykinin, a vasodilator, increases vessel permeability, allowing fluid to pass into interstitial tissues. Bradykinin-mediated angioedema is also seen in the use of ACE inhibitors and C1-esterase deficiency. Patients using ACE inhibitors are more susceptible to angioedema caused by tPA due to higher levels of bradykinin in circulation (4). Patients using ACE inhibitors were reported to have a 13.6% risk of developing angioedema when tPA was administered. There was no history of ACE inhibitor use in our patient.

It is thought that tPA-mediated angioedema may be associated with acute ischemia of certain regions in the brain (11,12). In particular, when tPA is administered in cases of frontal and insular cortex ischemia, the risk of development of angioedema has been reported as 9.1%. It has been suggested that ischemia in the insular cortex region affects the angioedema cascade by leading to autonomic dysregulation and vasomotor changes (11). Some studies in the literature have shown that the development of angioedema after thrombolytic therapy is associated with insular cortex involvement (12). However, others have not seen such a relationship (13). In our case, a lesion consistent with acute ischemia was present in the insular region and clinical findings consistent with orolingual angioedema were observed after IV tPA was administered. Although most patients with tPA-associated angioedema have mild clinical symptoms that limit themselves, they may also progress fast enough to lead to asphyxia (14). Patients with symptoms limited to the lip and anterior tongue generally do not require endotracheal intubation. However, endotracheal intubation may be required in patients in whom angioedema progresses towards the base of the mouth, affecting the palate, hypopharynx or larynx. Most patients who do not need intubation respond well to antihistaminics, steroids, and epinephrine (4). In angioedema induced by ACE inhibitors, ACE inhibitors should be discontinued. Use of corticosteroids, antihistaminics, and epinephrine may be ineffective in some severe patients. Treatments such as fresh frozen plasma, icatibant (bradykinin B2 receptor antagonist) and ecallantide (a recombinant protein that inhibits kallikrein) are useful (15). In our patient, the symptoms were limited to the lip and anterior tongue. He was treated with antihistaminics, steroids, and epinephrine. Endotracheal intubation was not required in the patient whose symptoms improved with treatment.

As a result, tPA in the treatment of acute cerebral ischemia became a landmark due to increased survival without sequela and its use gradually increased. The fact that physicians are aware of the complications that may occur due to tPA allows them to manage the complications correctly. Angioedema is a rare but severe complication of tPA therapy that can be life-threatening. When this clinical symptom occurs, it needs to be quickly recognized and treated. In particular, it should be considered that the use of ACE inhibitors increases the risk of development of angioedema after thrombolytic therapy. Although there are different results regarding whether insular ischemia increases this risk, care should be taken in terms of the risk of development of angioedema after thrombolytic therapy with involvement of this region.

Ethics

Informed Consent: The patient and his relatives were informed and written and oral consents were obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.T.Y., F.E., Ş.Ö., Concept: A.T.Y., F.E., Ş.Ö., Design: A.T.Y., F.E., Ş.Ö., Data Collection or Processing: A.T.Y., F.E., Ş.Ö., Analysis or Interpretation: A.T.Y., F.E., Ş.Ö., Literature Search: A.T.Y., F.E., Ş.Ö., Writing: A.T.Y., F.E., Ş.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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