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Case Report

Bradykinin-Mediated Angioedema Related to Alteplase Successfully Treated by Frozen Fresh Plasma: First Case Report with Literature Review

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Abstract

Angioedema can be a life-threatening complication after thrombolytic therapy Alteplase. The incidence is 1-5%, the risk of developing bradykinin-mediated angioedema is multiplied by 6 in patient on angiotensin converting enzyme inhibitor. Most therapeutic options are ineffective or expensive and not available. FFP is known as effective treatment for bradykinin- mediate angioedema since 1969 but never reported in case of angioedema rtPA induced. We report a case of 60 year old patient with history of hypertension treated with angiotensin converting enzyme inhibitor, who developing severe bradykinin-mediates angioedema 10 min after the end of thrombolytic therapy. The patient was treated successfully with FFP. We are reporting this case to increase the awareness of physicians and to widen their therapeutic options when encountering this clinically significant condition.

Keywords: *Angioedema; Frozen Fresh Plasma; Thrombolysis Therapy; Stroke*

Introduction

Following our literature research, this is the first case of bradykinin angioedema related to alteplase reported in the literature that has been successfully treated with frozen fresh plasma.

Recombinant tissue Plasminogen Activator (rtPA) is used for the treatment of acute ischemic strokes. The use of this medication is not without complication. One complication of this therapy is bradykinin angioedema which is a rare form of a non-pruritic, non-inflammatory allergic reaction. This complication can be severe in some cases requiring advanced management measures. Fresh frozen plasma has been used off-labeled in some case reports to improve and to prevent worsening of the angioedema in a few cases of bradykinetic angioedema.

Case Report

A 60-year-old man with history of hypertension managed with angiotensin-converting enzyme inhibitor (ACE-I), presented with sudden onset of weakness in the left side with dysarthria and facial drop from less than one hour. His vital sign on presentation on emergency department (ED) were blood pressure was 156/76 mmHg, Blood sugar was 98, respiratory rate 13 per minute, and oxygen saturation 100% on room air. The neurological examination consisted on left brachio-facial hemiparesis with dysarthria, with National Institute of Health Stroke Scale (NIHSS was 19). All lab investigations were unremarkable; especially platelets account, INR and blood sugar.

Code stroke was activated and non contrast Computed tomography (CT) scan of the brain was done immediately which ruled out any acute intracranial hemorrhage, mass effect or midline shift (Figure 1).

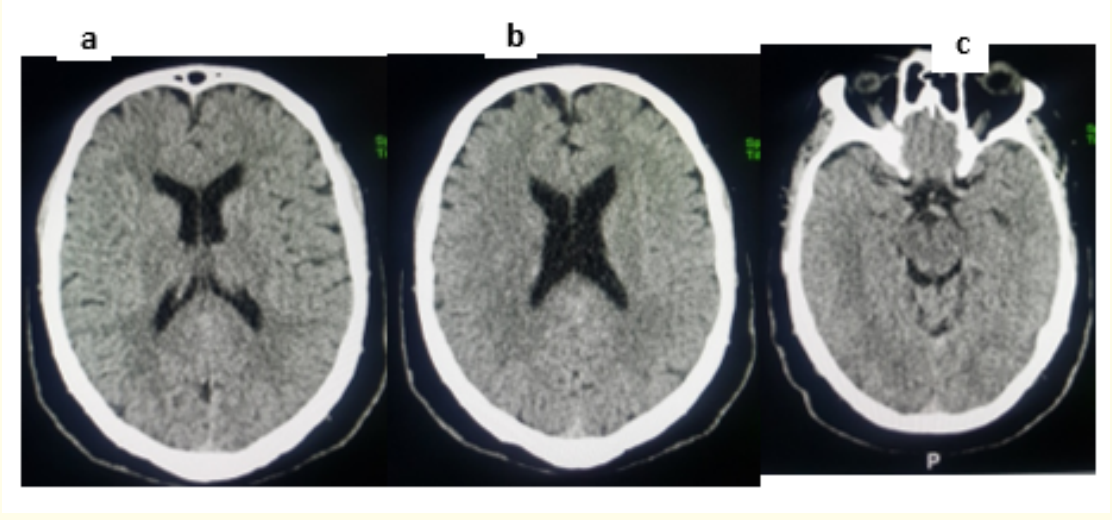

Figure 1a-1c: *CT brain (axial) show no indirect sign of ischemia, no hemorrhge and no midline shift.*

As there was no contraindication for thrombolytic therapy, the patient started the treatment and shifted to Intensive Care Unit (ICU). 10 min after the end of intravenous treatment the patient start developing stridor with difficulty to breath and a swelling was noted on the left side of the neck and lower part of face. The decision to give the patient intravenous diphenhydramine (50 mg) and methyl prednisolone (125 mg) after an urgent evaluation by the neurologist and resuscitator did not improve the symptoms but instead the patient subsequently developed rapidly progressing severe angioedema with laryngeal edema leading to airway compromise. The patient was intubated with some difficulty. The angioedema was resistant to antihistaminic and corticosteroid tried three times. Bradykinin- mediated angioedema was suspected but no C1 esterase inhibitor was available in our hospital**.** Based on the data in the literature concerning the efficacy of FFP in the treatment of bradykinin angioedema, it was decided to give patient two units of intravenous FFP. Three days after the patient improved and he was extubated.

Discussion

Intravenous tissue plasminogen activator (rtPA) was approved by FDA since 1996 as effective therapy for ischemic stroke [1]. However, this treatment is not exempt from adverse effects such as intracranial hemorrhage, allergic reaction and Orolingual angioedema. The incidence of the latter is low (1% to 5%) in patients receiving rtPA but clinicians must remember it [2].

This disorder can have an immunological and non-immunological mechanism. The literature is rich with proposed classifications for angioedema.

In practice, there are two categories of angioedema, either histamine-mediated or bradykinin-mediated angioedema. This has had a relevant impact on guiding the therapeutic approach of patients in emergency rooms.

Angioedema has been reported to develop 25 - 120 minutes after the onset of thrombolytic therapy as a complication. In our case, the symptoms started 10 minutes after the end of rtPA [3].

The underlying mechanism of histamine-mediated angioedema mediators is based on the localized or systemic release of mastocysts and basophils which induce vascular leakage [4].

While, the mechanism of bradykinin mediated angioedema is related to increased bradykinin levels which results in vasodilation and hence increased tissue permeability and edema [3,4]. It has been believed that rtPA is involved in the formation of plasmin and hence the release of bradykinin from the kininogen this induces an increase in the concentration of bradykinin in the body. This same phenomenon is observed with the use of angiotensin converting enzyme inhibitor or in the case of C1-esterase deficiency. That is why the risk of developing bradykinin-mediated Angioedema is more frequent on patient using angiotensin converting enzyme inhibitor [6].

The common symptoms of bradykinin-mediated angioedema is swelling of deep dermis, subcutaneous, or submucosal tissue of lip (49%), cheeks (8%), tongue (64%) and pharynx (6%); however, angioedema may affect other parts of body, including respiratory mucosa and laryngeal swelling which can be life-threatening [4].

According to a recent study published in 2019, the incidence of bradykinin-mediated angioedema is more common in female patients (62%), with a history of previous ischemic stroke (23%), hypertension (87%) and mostly treated with an angiotensin converting enzyme inhibitor (70%) [6].

Our patient has the history of hypertension treated by angiotensin converting enzyme inhibitor (ACE-I), and this for itself increases the risk of developing bradykinin-mediated angioedema by a factor of six in ischemic patient receiving thrombolytic therapy [6].

No additional examination is necessary for a positive diagnosis of acquired angioedema. When evaluating a patient with angioedema it is important to rely on the history and physical examination of the patient. In case of resistance of angioedema to antihistamines, epinephrine and steroids we must suspect bradykinin- mediated angioedema.

When angioedema is caused by bradykinin, treatment with antihistamines, corticosteroids and epinephrine is generally ineffective [7]. However, initial and maintenance doses of these medications are often administered. Icatibant, Ecallantide or a C1-esterase inhibitor remains the treatment of choice for bradykinin mediated angioedema. In 1969 Fresh frozen Plasma (FFP) was used for the first time successfully to treat hereditary angioedema and since that several therapeutic trials have shown the effectiveness of this therapeutic option on hereditary angioedema and non- hereditary angioedema (given within 45 minutes to 12 hours) [5,10].

However, no randomized clinical trials have investigated the use of FFP for patients who develop severe bradykinin-mediated angioedema secondary to thrombolysis.

Our management is based on several studies which speak of the effectiveness of FFP in the treatment of bradykinin-mediated angioedema, especially since we were faced with a situation where the prognosis was vital and the etiology was difficult to determine [5].

FFP helps to decrease the amount of accumulated bradykinin by supplying the body with a kininase II enzyme which participates in catalyzing the degradation of the excess amount of bradykinin. Thus rendering it ineffective [5,8].

Our patient received 2 units of FFP. According to a study published in 2016 the FFP dosing for angioedema has not been studied. An infusion of 2 units of 200 ml as in the case of coagulation disorders was adopted [9]. This dose can be reduced to 10- 15 ml per kg body weigh if there is high risk of overload [8,9].

Conclusion

Bradykinin- mediate angioedema is a rare but it is a serious complication in patients receiving rtPA, especially those with a history of taking ACE-I [4]. The treatment with antihistamines, corticosteroids and epinephrine is not very effective in this type of complication [5]. Our case study shows the effectiveness of FFP which is an inexpensive treatment for a complication that can be life-threatening.

Disclosure

I declare that I have no financial interest or any conflict of interest.

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