Orolingual Angiodema Associated with Alteplase Treatment of Acute Stroke: A Reappraisal

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Background: Orolingual angioedema has been increasingly recognized as a potentially life-threatening complication associated with alteplase treatment of stroke. Concomitant treatment with an angiotension converting enzyme inhibitor (ACEi) and localization of infarction in the territory of middle cerebral artery seem to be associated with a higher risk of this complication. *Methods:* We report the cases of orolingual angioedema among the patients undergoing alteplase treatment in our Stroke Unit. Additionally, we reviewed the literature to evaluate the pathophysiology, clinical characteristics, and treatment options. *Results:* In our Stroke Unit, among 236 patients given alteplase for acute stroke, 8 patients (3.4%) developed angioedema. The clinical picture varied from localized labial edema to extensive lingual edema with respiratory distress but in all cases it gradually resolved with symptomatic treatment. Seven patients had a hemispheric stroke (4 with lateralized angioedema, contralateral to the ischemic lesion), whereas the other 1 patient had a right superior cerebellar artery stroke (with lateralized angioedema, ipsilateral to the ischemic lesion). The National Institutes of Health Stroke Scale score at admission ranged from 6 to 24 (median 12.5). Five patients were taking an ACEi. Our results are similar to previously published data. In the literature, it appears that orolingual angioedema occurs in .2-5.1% of all stroke patients receiving Alteplase treatment. *Conclusions:* Orolingual angioedema is a potential complication of which treating physicians in stroke units need to be aware, even in those cases without history of ACEi treatment and without infarction in the territory of the middle cerebral artery. All patients who receive alteplase treatment should be monitored carefully. **Key Words:** Alteplase—rt-PA—thrombolysis—angioedema—anaphylactoid.

Introduction

Angioedema is a nonpitting edema of the skin and mucous membranes that has many etiologies, including hereditary and acquired forms. Among the acquired cases medications are important causes and orolingual angioedema has been increasingly recognized as a potentially life-threatening complication associated with alteplase treatment of acute ischemic stroke.[1] It has been attributed

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to an anaphylactoid reaction resulting from plasmin activation of bradykinin and complement pathways.[2] An increased risk was reported in patients concomitantly being treated with angiotensin converting enzyme inhibitors (ACEi) and in those with ischemia involving the insular cortex.[3]

The clinical characteristics of the patients who develop this complication and the features of orolingual angioedema associated with alteplase are still being defined. Furthermore, as the underlying pathophysiology is not yet clear and no guidelines are available, the best way to manage this reaction remains to be described. Further experience is needed to determine the appropriate symptomatic treatment, to define if alteplase infusion should be stopped when the angioedema occurs before the end of the thrombolysis and to conclude whether aggressive measures to achieve airway patency are required. We hope to shed some light on this topic and contribute to find answers to these questions.

The objectives of our study are to describe all cases of orolingual angioedema associated with recombinant tissue plasminogen activator (rt-PA) therapy in our Stroke Unit from a tertiary care center in Portugal and to perform a review of previous cases reported in the medical literature.

Methods

Patients undergoing thrombolysis for acute ischemic stroke were consecutively included in a database since 2008. We reviewed the medical records of all cases of orolingual angioedema among the patients treated with rt-PA therapy until January 2014. Demographic characteristics and clinical data (including medical history and medication, stroke presentation, onset-to-treatment time, imaging data, characteristics of orolingual angioedema—time between rt-PA initiation and development of angioedema, lateralization of angioedema, associated symptoms and clinical signs, symptomatic treatment, and evolution—and in-hospital outcome) of patients were collected, as well as all available photographs illustrating orolingual angioedema.

Thrombolysis and monitoring were performed in the Stroke Unit for all patients. The severity of stroke was assessed with the National Institutes of Health Stroke Scale (NIHSS) scoring system.[4] All patients performed a baseline computed tomography scan and another scan within 24-48 hours after thrombolytic therapy.

Orolingual angioedema was defined as unprovoked swelling of the tongue, lips, or oropharynx. It was systematically searched before initiation of treatment, by careful inspection of the tongue and orolabial mucosa. Development of angioedema was attributed to rt-PA because of the temporal relationship with thrombolysis. As no patient had prior oral trauma, we believe that a misdiagnosis with hematoma is unlikely. Whenever possible, photographs of orolingual angioedema were taken with patient consent.

In addition, to perform a review of previous cases reported in the medical literature, we identified relevant articles through searches of PubMed with the following terms: (1) “Alteplase” and “angioedema,” (2) “Alteplase” and “orolingual,” (3) “Alteplase” and “anaphylactoid,” (4) “rt-PA” and “angioedema,” (5) “rt-PA” and “orolingual,” (6) “rt-PA” and “anaphylactoid,” (7) “thrombolysis” and “angioedema,” (8) “thrombolysis” and “orolingual,” and (9) “thrombolysis” and “anaphylactoid,” in the title and/or abstract, published until March 2014. Further cases were identified from the references cited in those articles and also from citations of those reports. Eligible papers fulfilled the following selection criteria: (1) diagnosis of orolingual angioedema associated with alteplase, probably in the context of an anaphylactoid reaction and (2) manuscript written in English, French, Spanish, or Portuguese. Moreover, we considered the following exclusion criteria: (1) recent orolingual trauma or intubation and (2) orolingual angioedema attributed to other causes, namely hematoma or anaphylaxis. When available, we collected demographic and clinical data of the patients described in those articles, including gender, age, vascular risk factors, previous ACEi or angiotensin II receptor blocker medication, stroke presentation, blood pressure and NIHSS score at admission, onset-to-treatment time, characteristics of orolingual angioedema—time between rt-PA initiation and development of angioedema, lateralization of angioedema, associated symptoms and clinical signs, symptomatic treatment, and evolution—imaging data, occurrence of hemorrhagic transformation, and NIHSS score at discharge.

Results

Among 236 patients given rt-PA (alteplase) for acute stroke, 8 developed orolingual angioedema (3.4%; Tables 1–3). The clinical picture varied from localized labial edema to extensive lingual edema with respiratory distress (Fig 1), but in all cases it gradually resolved with symptomatic treatment. Seven patients had a hemispheric stroke (4 with lateralized angioedema, contralateral to the ischemic lesion), whereas the other 1 patient had a right superior cerebellar artery stroke (with lateralized angioedema, ipsilateral to the ischemic lesion). The NIHSS score at admission ranged from 6 to 24 (median, 12.5). Five patients were taking an ACEi, and 3 of our patients took captopril just before rt-PA treatment (patients IV, VI, and VII). None of our patients had a known history of previous allergies.

The clinical description of each individual case is presented as Appendix.