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Orolingual angioedema after thrombolysis is not associated with insular cortex ischemia on pre-thrombolysis CT

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ABSTRACT

Objective: Orolingual angioedema (OA) is a well known early complication of treatment with alteplase in ischemic stroke patients. Our aim was to study risk factors for OA in these patients, namely insular cortex ischemia.
Methods: Retrospective case-cohort study using the prospective registry of all consecutive ischemic stroke patients submitted to intravenous thrombolysis with alteplase. Clinical data was retrieved from the registry and medical records. Two independent observers evaluated early signs of insular cortex ischemia on pre-thrombolysis computed tomography (CT) and of insular cortex infarct on early follow-up imaging. Univariate and multivariate analysis were performed to identify predictors of OA.
Results: Of the 659 patients with acute ischemic stroke treated with alteplase, 32 developed OA (4.9%, 95%CI = 3.3–6.6). Frequency of early signs of insular cortex ischemia on pre-thrombolysis CT and of insular cortex infarct on follow-up imaging was similar in patients with and without OA ($p = 0.241$ and $p = 0.145$, respectively). The only independent predictors of OA occurrence were female sex (OR = 5.47, 95%CI = 1.98–15.10) and angiotensin-converting enzyme inhibitor (ACE-I) use (OR = 3.87, 95%CI = 1.71–8.75).
Conclusions: Female sex and ACE-I use are independent risk factors for OA occurrence in ischemic stroke patients treated with alteplase. Early signs of insular cortex ischemia on pre-thrombolysis CT were not significantly associated with OA.

1. Introduction

Orolingual angioedema (OA) is a well known early complication of alteplase when used for treatment of acute ischemic stroke, occurring in up to 7.9% of patients [1–3]. It consists of painless swelling of lips, tongue, face and occasionally oropharynx, occurring shortly after intravenous alteplase administration, which usually resolves during the first 24 h. Most case-control studies recognize use of angiotensin-converting enzyme inhibitors (ACE-I) as the main risk factor for occurrence of this potentially serious adverse event [1–4], and other authors found a higher frequency of insular ischemia in patients who developed angioedema [2,5]. In addition to contribute to several high order complex cerebral functions, insular cortex is known to mediate autonomic responses and it is involved in cardiac and vascular autonomic tone regulation and visceromotor control. The imbalance of sympathetic and parasympathetic control induced by insular ischemic lesions was proposed by several authors to contribute to the pathophysiology of OA [2–5]. Our aim was to study risk factors for OA occurrence in ischemic stroke patients treated with alteplase, in particular association with insular ischemia.

2. Materials and methods

We performed a retrospective case-cohort study using the prospective registry of consecutive ischemic stroke patients submitted to intravenous thrombolysis with alteplase, in the first author's hospital, between February 2007 and January 2016. Demographic and clinical data, namely occurrence and characteristics of OA, was collected from the registry and confirmed by analysis of individual medical records. OA is routinely searched by the treating physician, as determined by our Stroke Unit protocol, every 15 min during the first hour after thrombolysis and every 30 min after the first hour up to 6 h. Insular cortex ischemia in baseline pre-thrombolysis computed tomography (CT) was

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independently evaluated by authors JMA and MR, and was defined as partial or total insular cortex hypoattenuation or focal swelling [6]. Insular cortex infarct on follow-up imaging during the first 7 days was also independently evaluated by authors JMA and MR, and was defined as new hypodense lesion involving part or the whole insular cortex in CT or insular cortex restricted diffusion lesion on magnetic resonance imaging (MRI) when available. Both observers were blinded for the occurrence of angioedema, interobserver agreement was determined using Cohen's kappa coefficient, and interobserver disagreements were subsequently settled by consensus. Groups of patients with and without angioedema were compared using χ^2 and Mann-Whitney *U* tests as appropriate. Binary logistic regression was calculated using angioedema as the dependent variable and variables with $p < 0.05$ in univariate analysis as the independent variables. Early signs of insular cortex ischemia on pre-thrombolysis CT scan was also entered in the model as an independent variable. Statistical threshold for significance was $p < 0.05$. The study complies with the Helsinki Declaration and the Hospital de Braga ethics committee requirements for clinical research.

3. Results

Of the 659 patients with acute ischemic stroke submitted to intravenous thrombolysis with alteplase, 32 developed OA (4.9%, 95% confidence interval [95%CI] = 3.3–6.6), at a median time of 60 min after the alteplase bolus (range = 15–720). OA was strictly unilateral in 15 patients (contralateral to ischemia in 10, ipsilateral to ischemia in 5) and bilateral in 17 patients. Accompanying manifestations included bronchospasm and peripheral desaturation (n = 9), truncal or facial urticaria (n = 2) and hemodynamic instability (n = 2). The majority of patients were treated with steroids or antihistaminic drugs (n = 29) and subcutaneous adrenalin was used in 10 patients. No patient required emergent airway management and in 3 patients OA resolved spontaneously. In univariate analysis (Table 1), patients who developed OA were more frequently women, more frequently had arterial hypertension and were medicated with ACE-I. Despite no differences in pre-treatment blood pressure values in the two groups, urgent labetalol was used more frequently in the OA group. Vomiting and use of intravenous metoclopramide before or during thrombolysis were also more frequent in the OA group. Frequency of early signs of insular cortex ischemia on pre-thrombolysis CT and frequency of insular cortex infarct on follow-up neuroimaging were similar in patients with and without OA ($p = 0.241$ and $p = 0.145$, respectively).

Interobserver agreement was good for both pre-thrombolysis insular ischemia on CT (kappa = 0.69, $p < 0.001$) and insular infarct in follow-up imaging (kappa = 0.78, $p < 0.001$). In the logistic regression model (Table 2), the only independent predictors for OA were female sex (odds ratio [OR] = 5.47, 95%CI = 1.98–15.10) and current ACE-I use (OR = 3.87, 95%CI = 1.71–8.75).

Forced entry of insular cortex infarct on follow-up neuroimaging and exclusion of early signs of insular ischemia as variables in the regression model did not change the results (Supplementary Table 1).

4. Discussion

This study is one of the largest studies analyzing clinical predictors of the occurrence of OA and the largest study which performed a systematic, independent and blinded evaluation of occurrence of insular ischemic lesions on neuroimaging. Prevalence of OA in patients with acute ischemic stroke treated with alteplase was 4.9%, which is in accordance to previous studies [1–4,7]. We found no significant differences in the frequency of insular cortex ischemic lesions on pre-thrombolysis CT, and early signs of insular cortex ischemia were not independent predictors of OA occurrence in multivariate analysis. The clinical significance of this finding is that early signs of insular cortex ischemia on pre-thrombolysis CT should not be regarded as a marker of risk for OA. Despite the well known limitation of CT for diagnosis of very early cerebral ischemic changes, early signs of insular ischemia on CT had the higher interobserver agreement among all cerebral regions evaluated in the Alberta Stroke Program Early CT Score in a relevant study by Gupta et al. [8], which supports the clinical value of our findings. A recent study compared the frequency of insular infarcts in MRI in 19 patients who developed OA after thrombolysis and 77 selected patients who did not develop OA and there was no difference [4]. Despite this, these authors reported a similar frequency of small insular infarcts but a significantly higher frequency of total insular infarcts in patients with OA, which should be interpreted with caution because of the scarce number of patients with total insular infarcts. Higher frequency of insular involvement in OA patients was found by Hill et al. [2], however, a non-blinded assessment of imaging was performed by the treating physician, which could have introduced a potential imaging assessment bias. The high frequency of insular cortex ischemia in OA patients (80%) found by Werner et al., was evaluated by MRI in 15 patients with OA, however, patients without OA were not analyzed [5]. Although

Table 1
Characteristics of the study population according to occurrence of orolingual angioedema.

	Patients without orolingual angioedema (n = 627)	Patients with orolingual angioedema (n = 32)	*P* value
Female sex	343 (54.7)	27 (84.4)	0.001*
Age (years)	74 (65–79)	78 (71–81)	0.054
Arterial hypertension	409 (65.2)	28 (87.5)	0.011*
Diabetes	128 (20.4)	7 (21.9)	0.842
Dyslipidemia	274 (43.7)	71 (53.1)	0.295
Ischemic heart disease	45 (7.2)	3 (9.4)	0.641*
Autoimmune co-morbidity	5 (0.8)	0	0.612*
Current ACE-I use	139 (22.2)	16 (50.0)	<0.001
Current ARB use	176 (28.2)	9 (28.1)	0.992
Current steroid or imunossupressor use	14 (2.2)	2 (6.3)	0.180*
Vertebrobasilar circulation stroke	57 (9.1%)	3 (9.4)	1.000*
Admission NIHSS	14 (10–19)	17 (10−21)	0.157
Systolic BP (mmHg)	145 (130–162)	155 (132–168)	0.334
Diastolic BP (mmHg)	81 (72–91)	79 (72–93)	0.996
Admission BP >185/105 mmHg	77 (12.5)	4 (12.5)	1.000*
Urgent captopril use before/during thrombolysis	35 (5.6)	2 (6.3)	0.700*
Urgent labetalol use before/during thrombolysis	57 (9.1)	7 (21.9)	0.018
Admission glucose	125 (108–158)	135.5 (113–161)	0.196
Vomiting before/during thrombolysis	72 (11.5)	9 (28.1)	0.005
Urgent metoclopramide use before/during thrombolysis	39 (6.2)	8 (25.0)	<0.001
ASPECTS/pcASPECTS	9 (8–10)	8.5 (7–10)	0.494
Symptoms-needle time (minutes)	155 (115–200)	154.5 (110.5–195)	0.861
Intravenous contrast (angio-computed tomography or angiography)	67 (10.7)	3 (9.4)	1.000*
Hyperacute endovascular revascularization	49 (7.8)	1 (3.1)	0.502*
Early signs of insular cortex ischemia on pre-thrombolysis CT†	202 (33.7)	14 (43.8)	0.241
Insular cortex infarct on follow-up neuroimaging	309 (49.3)	20 (62.5)	0.145
MRI as follow-up imaging	80 (12.7)	3 (9.4)	0.786*

Results are represented as n (%) or median (interquartile range). Pearson's chi square used for categorical variables except where noted (* Fisher's exact test). Mann-Whitney U test used for continuous variables. ACE-I: angiotensin-converting enzyme inhibitor. ARB: angiotensin II receptor blocker. NIHSS: National Institute of Health Stroke Scale. BP: blood pressure. ASPECTS: Alberta Stroke Program Early Computed Tomography Score. pcASPECTS: posterior circulation ASPECTS. CT: computed tomography. MRI: magnetic resonance imaging.

† Data available for 632 patients (27 patients with no available pre-thrombolysis CT for analysis).

Table 2
Multivariate analysis for orolingual angioedema predictors using binary logistic regression model.

Independent variables	Odds ratio (95% confidence interval)	*P* value
Female sex	5.47 (1.98–15.10)	0.001
Arterial hypertension	1.90 (0.60–6.02)	0.275
Current ACE-I use	3.87 (1.71–8.75)	0.001
Urgent labetalol use before/during thrombolysis	2.51 (0.92–6.87)	0.072
Vomiting before/during thrombolysis	1.49 (0.44–5.06)	0.523
Urgent metoclopramide use before/during thrombolysis	3.74 (0.99–14.13)	0.051
Early signs of insular cortex ischemia on pre-thrombolysis computed tomography	1.73 (0.79–3.75)	0.168

ACE-I: angiotensin-converting enzyme inhibitor.

we are not able to definitely exclude a possible contribution of insular ischemia for development of alteplase-related OA, our study does not support the suggestion that insular ischemia plays a key role in its pathophysiology.

Other case control-studies found a higher frequency of OA in women [3,5] and, in our study, female sex was an independent risk factor for OA, which is in accordance to a large cohort study of medication-related angioedema incidence [9]. The reason for this sex difference is not clear, but may include the influence of sex hormones on the regulation of inflammation and an increased T_h2 immune response in women [10], which is further supported by the female predominance of chronic urticaria, a condition with a pathophysiology closely linked to acquired angioedema [11].

Current use of ACE-I was independently associated with a 4-fold risk increase in the development of OA. This association is well known in the literature and is explained by inhibition of bradykinin metabolization by ACE-I and concomitant alteplase-mediated bradykinin generation [12] (Supplementary Fig. 1). The possibility of increased risk of OA in patients treated with angiotensin receptor blockers [13] was not confirmed in our study.

The fact that this is a single center study weakens the statistical power needed to demonstrate the association of insular ischemia and OA development, and these results need confirmation in other larger case-control multicentre studies. Another important limitation of our study is absence of pre-thrombolysis MRI or perfusion imaging techniques, which could provide more accurate information on insular ischemia or insular hypoperfusion, and absence of follow-up MRI in the majority of patients, which is more sensitive than CT for the diagnosis of recent small insular infarcts.

5. Conclusions

Orolingual angioedema occurred in 4.9% of acute ischemic stroke patients treated with alteplase and the only independent risk factors found were female sex and ACE-I use. Early signs of insular cortex ischemia in pre-thrombolysis CT were not significantly associated with orolingual angioedema occurrence.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jns.2016.07.043.

Conflicts of interest

None.

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