Concealment of Allergic Reactions to Alteplase by Face Masks in Non-Communicating Acute Stroke Patients: A Warning Call to Improve Our Physical Examination Practices during the COVID-19 Pandemic

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Concealment of allergic reactions to alteplase by face masks in non-communicating acute stroke patients: A warning call to improve our physical examination practices during the COVID-19 pandemic

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Abstract:

Neurological emergencies, such as acute stroke, are especially challenging during the current Coronavirus disease (COVID-19) pandemic. Symptoms as aphasia or dysarthria are severely impacting cooperation and communication with patients. During physical examination, both the patient and the medical team are fitted routinely with surgical masks to minimize potential exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, such a practice can lead to concealment of particularly relevant physical signs. We report a case series of four acute stroke patients who were transferred for endovascular mechanical thrombectomy to our Institute after intravenous thrombolysis was initiated at primary stroke centres. Upon arrival, after removing their masks, we observed oral angioedema, as a reaction to thrombolytic agent alteplase. Symptoms remained obscured by face masks through patient care at the referring stroke unit and during transportation, nevertheless they resolved after treatment. Most probably, there are a number of similar cases encountered at emergency departments and acute stroke units. To improve patient safety, a compromise between ensuring protection against the novel coronavirus and facilitating detection of potentially life-threatening physical signs must be found.

Keywords: acute stroke, alteplase, COVID-19, personal protective equipment, physical examination.
Introduction

Over the last two years more than 440 million Coronavirus disease (COVID-19) cases have been documented globally, which has claimed the lives of 6 million people (World Health Organization, 2021; Zhu et al., 2021). Alongside respiratory symptoms a wide spectrum of neurological manifestations have been described in SARS-CoV-2 infected patients (Guan et al., 2020; Huang et al., 2020). Anosmia and dysgeusia are considered as a hallmark of the disease, but more serious neurological conditions are also prevalent, such as cryptogenic ischaemic stroke, seizures, Guillain–Barré syndrome or acute disseminated encephalomyelitis (Abdi et al., 2020; Helms et al., 2020; Khosravani et al., 2020; Koralnik and Tyler, 2020; Mao et al., 2020; Shahjouei et al., 2021).

Acute stroke patients are of particular interest, as one must balance between delivering timely care and also minimizing the risk of infection exposure (Khosravani et al., 2020). In spite of an increase in cryptogenic strokes associated with COVID-19 endothelial inflammation and thrombotic diathesis (Bakola and Giannopoulos, 2022), a decline in the number of patients receiving reperfusion therapies was reported globally (Nogueira et al., 2021). Acute stroke patients pose a higher infection risk due to increased aerosol emission as a result of the lack of cooperation, drooling and coughing. Risk assessment and personal protective procedures inevitably increase the door to needle time for patients eligible for intravenous thrombolysis. Thus, the use of face masks is considered as an important preventive measure. However, the mask can hide important symptoms that can potentially impair the prognostic outcome (Nimmo et al., 2020).

We report four cases of oral angioedema, related to administration of the thrombolytic agent alteplase, that have not been recognized due to face masks. The cases serve as a warning call to improve our physical examination practices in acute stroke care during the COVID-19 pandemic.

Case presentation

All patients or their legal representative/next of kin agreed with the publication of their case and image, and have signed a Patient Consent Form.
Case 1-4

We report a case series of four patients whom developed alteplase related angioedema before arriving to our Institute. Due to patient’s mask wearing, the symptoms of three of the patients remained concealed both at the referring stroke unit and during transfer. Clinical data is summarized in Table 1. Figure 1 illustrates the angioedema of different severity. To grade the severity of angioedema we used the following objective criteria: mild: involvement of lips, but not the tongue; moderate: involvement of both lips and tongue; severe angioedema: involvement of uvula, oropharynx - airway involvement. For indisputable ethical and therapeutic considerations, we pursued photographic documentation only after patients were stable. In the case where photographing was omitted, a CT image is shown.

All four patients arrived primarily at different regional stroke centres. Since they were eligible for reperfusion therapy, intravenous thrombolysis with alteplase was administered. All four patients presented large vessel occlusion and were therefore referred and transferred to our national mechanical thrombectomy centre for endovascular recanalization therapy (mechanical thrombectomy). 50 % of the patients claimed a history of mild allergies, while 50 % denied any allergic history.

Three out of the four patients were treated during a low infection risk period (low number of active COVID-19 cases), whereas Patient 2 was treated at the beginning of the third wave (778 new cases/9.6 million population). At the time of care of the first two patients, no vaccines were authorised yet neither for healthcare professionals, nor for the general population. The two later patients were vaccinated (Sinopharm and Comirnaty). Symptoms relevant for COVID-19 risk assessment and increased aerosol emission were as follows: Patient 1: confusion, dysarthria, central facial paresis related drooling. Patient 2: global aphasia, central facial paresis with some drooling. Patient 3: severe dysarthria and central facial paresis with drooling. Patient 4: mild central facial paresis without drooling and with no relevance. The confused and global aphasic patients were unable to cooperate
to risk assessment questionaries, however they did not present any of the main COVID-19 symptoms (coughing, fever).

Patients were transferred to our hospital by ambulance from varying distances (from 3.5 km to 70 km) with their face covered by surgical masks. Alteplase treatment was finished before transfer for Patients 1, 2 and 4; whereas Patient 3 was on syringe pump during transfer, but finished treatment before arrival. The time between start of alteplase treatment and angioedema onset was minimum 30 minutes - 1 hour for Patients 1 and 3, and minimum 1 - 1.5 hours for Patients 2 and 4. None of the patients was able to alert the medical team about their developing symptoms: Patient 1 due to confusion, Patient 2 due to global aphasia, Patient 3 due to severe dysarthria, Patient 4 for unknown reasons. Vital parameters for all patients were monitored during transfer; however, except for Patient 4 all other patients were receiving oxygen therapy due to slight desaturation (94-97% SpO₂) associated with drooling, dysphagia, confusion. None of the patients developed systemic allergic symptoms (e.g. hypotension) or skin rashes. In the absence of warning signs, the swelling of the lower lip was observed only for Patient 2 by the transporting paramedics. Treatment with parenteral chloropyramine was started, and the admission team was alerted upon arrival. For the other cases, the angioedema was only noticed during neurological examination, when we removed the face mask for a short period of time to assess facial paresis or dysphagia.

Interestingly the patient with the most severe angioedema (Patient 1) had no allergic history. Arterial blood gas values were within normal range before transport. Upon arrival severely swollen lower lips and tongue were observed and signs of airway compromise started to develop. Therefore, parenteral steroid therapy (methylprednisolone 125 mg i.v.) was initiated immediately. The patient’s condition worsened despite the steroid therapy. Furthermore, signs of congestive heart failure (lower limb oedema) and pneumonia (pulmonary X-ray performed later) were also revealed. Even though diagnostic criteria of anaphylaxis were not fulfilled (no hypotension), the accelerating clinical situation prompted the intervention of the critical team and administration of norepinephrine (0.5 mg i.m.) and oxygen therapy (5 l/min, face mask). After stabilization acute stroke care was resumed. The
circumferential mucosal thickening and airway narrowing, corresponding to an oedematous oropharynx of Patient 1 is illustrated on a CT image (Fig. 1A) which was performed after stabilization of the patient, and before mechanical thrombectomy. The oral angioedema resolved within ours.

The two other patients with known allergies (Patient 2 and 3) developed moderate angioedema, with moderate lip and tongue swelling, without airway compromise (Fig. 1B, C). Both received intravenous chloropyramine and methylprednisolone after which stroke care was resumed. Patient 4 with no known allergies developed the mildest symptoms with only upper lip swelling (Fig. 1D). In her case, due to the very mild angioedema we proceeded with the pre-operative CT and we administered prednisolone (100mg i.v.) prior to endovascular mechanical thrombectomy. The oral angioedema resolved within hours in all four patients.

Discussion

Personal protective equipment, used by health care workers, patients and members of the public is of utmost importance alongside vaccination to bring an end to the COVID-19 pandemic. Although use of face masks during physical examination of patients reduces infection exposure, it inevitably undermines the likelihood of detecting physical signs of complications, such as allergic reactions. We report four cases of oral angioedema related to alteplase treatment in acute stroke, that remained undetected due to face masks. To our knowledge, these are the first documented cases of concealment of potentially severe physical signs by face masks during the past two-years of pandemic.

The incidence of oral angioedema in acute stroke patients receiving intravenous thrombolysis with alteplase is relatively high (0.9% to 5.1%; Fröhlich et al., 2019). The exact mechanism of how the tissue plasminogen activator (t-PA) alteplase induces such adverse reactions is still under debate. Female sex, hypertension, diabetes, previous angiotensin-converting-enzyme inhibitor (ACE-I) treatment were identified as risk factors in a metaanalysis by Mas-Serrano et al. (Mas-Serrano et al., 2022). In line with the reported risk factors, we also observed a higher incidence in females (3:1); and
hypertension in three out of four patients. Further, one patient included in our study was diagnosed with diabetes, and one patient was taking ACE-I medication.

t-PA is known to convert plasminogen into plasmin, which facilitates the cleavage of kininogen into bradykinin and leads to increased vascular permeability and oedema (Molinaro et al., 2002). This can potentially explain the 3 - 4 fold increased risk in patients on ACE-I, whom have already higher serum bradykinin levels (Lin et al., 2014; Mazzoli et al., 2021). Further, the complement system is also known to be activated by plasmin, resulting in mast cell degranulation and release of histamine, causing submucosal swelling (Molinaro et al., 2002). Oral angioedema is not as frequent in t-PA treated myocardial infarction patients as in cerebral ischaemia, consequently a cerebral lesion site hypothesis can be a further potential explanation. For instance, in a recent study right insular ischaemic lesion was associated with autonomic dysfunction, sympathetic hyperactivity, and in turn cytokine production and increased vascular permeability (Fröhlich et al., 2019). In our cases acute insular cortical ischaemia signs were detectable on admission CT-s for Patients 2 and 3 and on a control CT for Patient 1 (data not shown). Most probably both histamine- and bradykinin-, as well as lesion site related mechanisms are involved in alteplase related oral angioedema, and even unrecognized hereditary conditions cannot be ruled out.

To improve patient safety, a compromise must be reached which not only ensures the protection of patient’s airways from a potential exposure to the novel coronavirus, but also guarantees that life-threatening physical sign will not be missed upon physical examination. We assumed that inspection of the face, was a reasonable part of the physical examination even in the setting of the pandemic. Unfortunately, our cases reveal that omitting it is not an isolated phenomenon, and most probably similar complications are encountered in other medical emergency situations as well. We suggest, first of all, the evaluation of incidence of such events, risk determination, and the education of healthcare workers. Currently, most evaluations focus on acceptability, adherence, effectiveness of face masks, their effect on patients with pulmonary diseases, and socio-economic aspects. Secondly,
management guidelines should emphasize the quality and thoroughness of physical examination and must include scheduled unmasking of patients, with higher frequency for patients prone to allergies.

**Acknowledgments:** We are grateful for the healthcare teams who contributed to the management of the patients.

**Sources of funding:** None.

**Disclosures:** No conflict of interest.
References


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Available at: https://covid19.who.int/table.

Table and figure legends

**Table 1. Summary of clinical data** for the four patients developing oral angioedema as a reaction to intravenous thrombolysis with alteplase. (Abbreviations: NIHSS: National Institutes of Health Stroke Scale; ACE-I: angiotensin-converting-enzyme inhibitor; MCA: medial cerebral artery; ICA: internal carotid artery; i.v.: intravenous; i.m.: intramuscular.)

**Figure 1. Alteplase induced angioedema.**

(A) Patient 1: Oedematous oropharynx and angioedema shown on a CT image. The circumferential thickening of the oropharyngeal mucosa and airway narrowing (arrow) was described in the report of the neuroradiologist. The CT was performed immediately after administration of methylprednisolone and norepinephrine.

(B) Patient 2: Resolving angioedema of the lower lip and tongue. Images taken five hours after administration of chloropyramine and methylprednisolone.

(C) Patient 3: Moderately severe angioedema of the lip and tongue. Both images taken immediately after administration of chloropyramine and methylprednisolone.

(D) Patient 4: Mild angioedema of the upper lip. Top image photographed upon admission; lower image approximately 14 hours after treatment.
<table>
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<th>Patient number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<td><strong>Age</strong></td>
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<td>77</td>
<td>78</td>
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<tr>
<td><strong>Medical history of allergies</strong></td>
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<td>balsamum peruvianum, rubber acethylene, metal hypersensitivity</td>
<td>no known allergies</td>
</tr>
<tr>
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<td>2020 August</td>
<td>2020 September</td>
<td>2021 July</td>
<td>2021 July</td>
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<td><strong>Covid-19 wave</strong></td>
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<td>no wave</td>
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<tr>
<td><strong>Daily covid cases (3-day moving average)</strong></td>
<td>37</td>
<td>778</td>
<td>33</td>
<td>38</td>
</tr>
<tr>
<td><strong>Covid-19 vaccination status</strong></td>
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<td>no vaccine available</td>
<td>2 doses of Sinopharm vaccine</td>
<td>2 doses of Comirnaty vaccine</td>
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<td>desorientation, confusion, mild dysarthria, suspicion of dysphagia, central facial paresis</td>
<td>global aphasia, central facial paresis</td>
<td>severe dysarthria, central facial paresis</td>
<td>mild central facial paresis</td>
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<td><strong>NIHSS</strong></td>
<td>15</td>
<td>15</td>
<td>22</td>
<td>9 at symptom onset and 3 at arrival (after thrombolysis)</td>
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<td><strong>Large vessel occlusion</strong></td>
<td>right MCA M2 segment occlusion</td>
<td>left MCA M2 segment occlusion</td>
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<td>tandem occlusion of right ICA (previous stenosis) and right MCA M3 segment</td>
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<td>hypertonia</td>
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<td><strong>Angioedema severity</strong></td>
<td>severe angioedema which started compromising patient’s airways minimum 30 minutes-1 hour</td>
<td>moderate severity: lip and tongue swelling minimum 1-1.5 hours</td>
<td>moderate severity: lip and tongue swelling minimum 30 minutes-1 hour</td>
<td>relatively mild: upper lip swelling minimum 1-1.5 hours</td>
</tr>
<tr>
<td><strong>Temporal connection between start of alteplase treatment and symptom onset</strong></td>
<td>methylprednisolone (125mg i.v.), norepinephrine (0.5mg i.m.), oxygen therapy (5l/min via O2 mask),</td>
<td>chloropyramine (20mg i.v.), methylprednisolone (125mg i.v.)</td>
<td>chloropyramine (10mg i.v.), methylprednisolone (125mg i.v.)</td>
<td>prednisolone (100mg i.v.)</td>
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<tr>
<td><strong>Angioedema treatment</strong></td>
<td>methylprednisolone (125mg i.v.), norepinephrine (0.5mg i.m.), oxygen therapy (5l/min via O2 mask),</td>
<td>chloropyramine (20mg i.v.), methylprednisolone (125mg i.v.)</td>
<td>chloropyramine (10mg i.v.), methylprednisolone (125mg i.v.)</td>
<td>prednisolone (100mg i.v.)</td>
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Figure 1