



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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Neurological emergencies, such as acute stroke, are especially challenging during the current Coronavirus disease-2019 (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 centers. 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

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Introduction

Over the last two years more than 440 million Coronavirus disease-2019 (COVID-19) cases have been documented globally, which has claimed the lives of 6 million people (Zhu et al. 2020; World Health Organization 2022). Alongside respiratory symptoms, a wide spectrum of neurological manifestations have been described in the severe acute respiratory syndrome-coronavirus-2 (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 ischemic stroke, seizures, Guillain-Barré syndrome or acute disseminated encephalomyelitis (Abdi et al. 2020; Helms et al. 2020; Khosravani et al. 2020; Korálnik 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).

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We report four cases of oral angioedema, related to administration of the thrombolytic agent alteplase, that has 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 sum-

marized in Table 1. Fig. 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 centers. 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 center for endovascular recanalization therapy (mechanical thrombectomy). 50% of the patients claimed a history of mild allergies, while

Table 1. Summary of clinical data for the four patients developing oral angioedema as a reaction to intravenous thrombolysis with alteplase.

Patient number	1	2	3	4
Age (years)	79	59	77	78
Sex	Female	Male	Female	Female
Medical history of allergies	No known allergies	Ragweed allergy	Balsamum peruvianum, rubber acethylene and metal hypersensitivity	No known allergies
Date	August 2020	September 2020	July 2021	July 2021
COVID-19 wave	No wave	Beginning of 2nd wave	No wave	No wave
Daily COVID-19 cases (3-day moving average of the cases/9.6 million population)	37	778	33	38
COVID-19 risk assessment	Non-cooperating patient, no COVID-19 symptoms	Not communicating, no COVID-19 symptoms	Communicating, no COVID-19 symptoms, rapid antigen test negative	Communicating, no COVID-19 symptoms, rapid antigen test negative
COVID-19 vaccination status	No vaccine available	No vaccine available	2 doses of Sinopharm vaccine	2 doses of Comirnaty vaccine
Neurological symptoms of importance for COVID-19 risk assessment	Disorientation, confusion, mild dysarthria, suspicion of dysphagia, central facial paresis	Global aphasia, central facial paresis	Severe dysarthria, central facial paresis	Mild central facial paresis
NIHSS	15	15	22	9 at symptom onset and 3 at arrival (after thrombolysis)
Large vessel occlusion	Right MCA M2 segment occlusion	Left MCA M2 segment occlusion	Tandem occlusion of right ICA (previous stenosis) and right MCA M2 segment	Tandem occlusion of right ICA (previous stenosis) and right MCA M3 segment
Previous ACE-I treatment	No	Yes (perindopril)	No	No
Involvement of insular cortex	Not upon arrival, but present on later control CTs	Yes	Yes	No
Comorbidities that are risk factors	Diabetes	Hypertonia	Hypertonia	Hypertonia
Angioedema severity	Severe angioedema which started compromising patient's airways	Moderate severity: lip and tongue swelling	Moderate severity: lip and tongue swelling	Relatively mild: upper lip swelling
Temporal connection between start of alteplase treatment and symptom onset	A minimum of 30 minutes-1 hour	A minimum of 1-1.5 hours	A minimum of 30 minutes-1 hour	A minimum of 1-1.5 hours
Angioedema treatment	Methylprednisolone (125 mg i.v.), norepinephrine (0.5 mg i.m.), oxygen therapy (5 L/min via O2 mask)	Chloropyramine (20 mg i.v.), methylprednisolone (125 mg i.v.)	Chloropyramine (10 mg i.v.), methylprednisolone (125 mg i.v.)	Prednisolone (100mg i.v.)
Images	Figure 1A	Figure 1B	Figure 1C	Figure 1D

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.

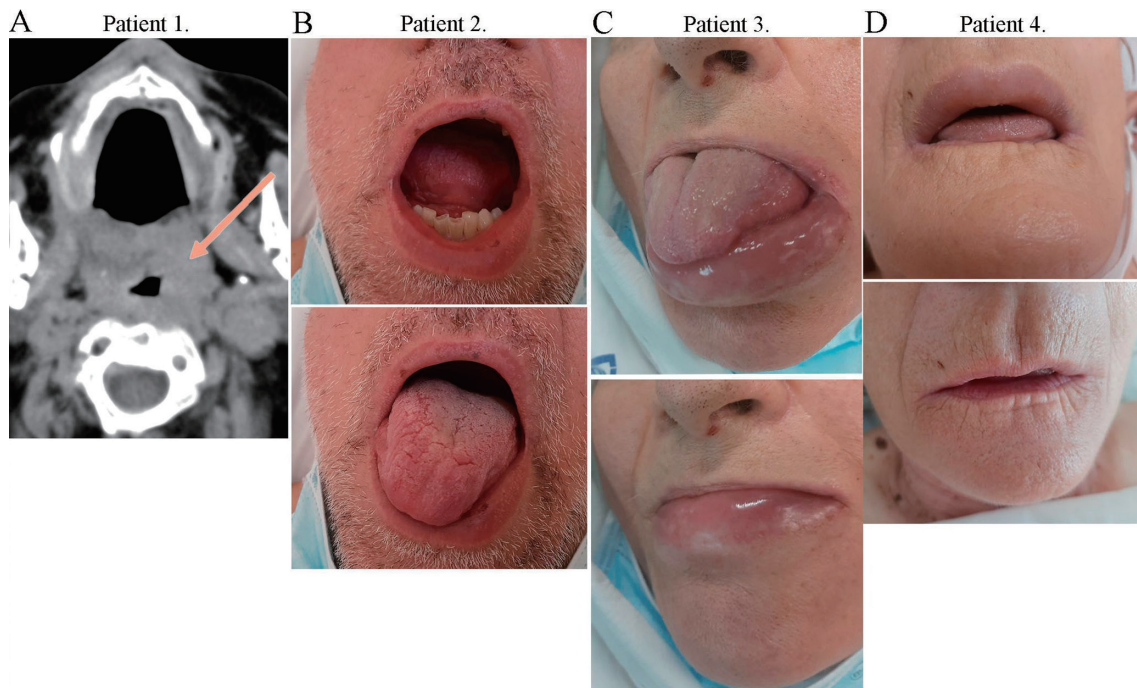


Fig. 1. Alteplase induced angioedema.

(A) Patient 1: Edematous 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 chlorpyramine and methylprednisolone. (C) Patient 3: Moderately severe angioedema of the lip and tongue. Both images taken immediately after administration of chlorpyramine and methylprednisolone. (D) Patient 4: Mild angioedema of the upper lip. The top image was photographed upon admission and the lower image approximately 14 hours after treatment.

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 second wave (in Hungary, third globally) (778 new cases/9.6 million population). At the time of care of the first two patients, no vaccines were authorized yet 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 questionnaires; however, they did not present any of the main COVID-19 symptoms (coughing and 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 Patient 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 a minimum of 30 minutes-1 hour for Patient 1 and 3, and a minimum of 1-1.5 hours for Patient 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, and 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, and 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 chlorpyramine 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 (methylpred-

nisolone 125 mg i.v.) was initiated immediately. The patient's condition worsened despite the steroid therapy. Furthermore, signs of congestive heart failure (lower limb edema) 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 edematous 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 chlorpyramine 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 administered prednisolone (100 mg 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 the 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, and previous angiotensin-converting-enzyme inhibitor (ACE-I) treatment were identified as risk factors in a metaanalysis by 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 edema (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 ischemia, consequently a cerebral lesion site hypothesis can be a further potential explanation. For instance, in a recent study right insular ischemic 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 ischemia signs were detectable on admission CTs for Patient 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.

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Conflict of Interest

The authors declare no conflict of interest.

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