References


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Raising Awareness of Orolingual Angioedema as a Complication of Thrombolysis in Acute Stroke Patients

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Background
Orolingual angioedema (OA) has been increasingly acknowledged as a hitherto underestimated and potentially life-threatening complication of alteplase treatment [1–3] with unilateral painless swelling of the lips, tongue and face 30–120 min after intravenous alteplase application, often contralateral to the ischemic lesion. Usually mild and reversible within 24 h [1], in severe cases OA might extend bilaterally to the oropharynx.

Methods
Between January 2006 and June 2008, 2,287 patients with acute ischemic stroke were treated at the Comprehensive Stroke Center Mannheim. We reviewed all cases undergoing recombinant tissue plasminogen activator (rt-PA) thrombolysis, and identified patients presenting symptoms of OA.

Results
Of the 312 receiving intravenous thrombolysis, 8 (2.6%) suffered OA. Six of 8 patients were on angiotensin-converting-enzyme inhibitor (ACEi) medication. In 5 of 8 cases, OA was lateralized, with 2 cases being ipsilateral to the stroke. Bilateral swelling occurred in 3 cases (table 1). Ischemic stroke lesions were distributed as follows: 5 right middle cerebral artery, 1 left territorial middle cerebral artery, 1 bithalamic and 1 scattered in the posterior circulation. All but 2 cases (1 intubation, 1 death of unrelated pulmonary complications 3 weeks after onset) resolved over 2–36 h, without further complications.

Discussion
According to the few recent systematic reports, the risk of OA is estimated to be between 1–2 [1] and 5% [2], depending on the quality of monitoring for typical symptoms. A considerably higher relative risk of 13.6 is described for patients with premorbid ACEi medication [2]. A well-established hypothesis, concerning the pathomechanisms of OA, suggests a simultaneous activation of complement system and kinin cascades by plasmin, produced by alteplase-induced cleavage of plasminogen [3]. Activation of the complement cascade is considered to be direct, causing mast cell degranulation and histamine release with consequent vaso-dilatation [4]. As alteplase has low antigenicity in humans, IgE-mediated allergic reactions or activation of the complement system through antigen–antibody complexes are considered unlikely (found in only 1 case with unusually severe systemic signs of anaphylaxis [5]). Initiation of the kinin cascades results in raised levels of bradykinin which also leads to vasodilatation [6]. The higher occurrence in patients with ACEIs might be explained by inhibition of plasma kininases, which are responsible for degrading bradykinin [3]. The lateralization is possibly triggered through acute changes in the vasomotor tone of the hemiparetic side caused by central dysfunction of the autonomic nervous system [1, 3]. In particular, lesions involving the insular cortex, but also the postcentral cortex, basal ganglia and the internal capsule, have been shown to be associated with contralateral autonomic imbalance [7].

Acute therapy of OA is still empirical. Most propose the intravenous use of antihistaminic drugs (H1 and H2 blockers) as well as corticosteroids [1, 3], although there is no data on the efficacy of this regime. The rapid progression of edema to the oropharynx may require immediate intubation or even cricothyroidotomy, making early consultation for anesthesia and monitoring in an ICU setting for at least 24 h necessary. In conclusion, a routine inspection of lips and oral cavity of stroke patients during and after thrombolysis is necessary, with special focus on those patients taking ACEi.
Table 1. Review of published cases (in English) including findings at the Comprehensive Stroke Center Mannheim

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Journal</th>
<th>Year</th>
<th>Cases (total)</th>
<th>Cases (OA)</th>
<th>Rate of occurrence, %</th>
<th>Ipsilateral OA</th>
<th>Bilateral OA</th>
<th>Non-ACEi cases with OA</th>
<th>Intubation/CTD</th>
<th>OA-related deaths</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancioli et al. [8]</td>
<td>Ann Emerg Med</td>
<td>1997</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>first case report published</td>
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<tr>
<td>Rudolf et al. [9]</td>
<td>Neurology</td>
<td>2000</td>
<td>2</td>
<td>0</td>
<td>0</td>
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<td>Papamitsakas et al. [10]</td>
<td>Stroke Cerebrovasc Dis</td>
<td>2000</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<td>Hill et al. [3]</td>
<td>CMAJ</td>
<td>2000</td>
<td>105</td>
<td>2</td>
<td>1.9</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1 case with suspected c1 esterase inhibitor deficiency, died of cardiac complications</td>
</tr>
<tr>
<td>Hill et al. [3]</td>
<td>CMAJ</td>
<td>2000</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>addendum to publication above</td>
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<tr>
<td>Hill et al. [2]</td>
<td>Neurology</td>
<td>2003</td>
<td>176</td>
<td>9</td>
<td>5.1</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>prospective study, 1 death of cardiac complications</td>
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<tr>
<td>Jahnke et al. [11]</td>
<td>J Emerg Nurs</td>
<td>2003</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 CTD</td>
<td>emergency CTD</td>
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<tr>
<td>Hill et al. [12]</td>
<td>CMAJ</td>
<td>2005</td>
<td>1,135</td>
<td>15</td>
<td>1.3</td>
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<td>no data</td>
<td>no data</td>
<td>2</td>
<td>0</td>
<td>national prospective cohort study: effectiveness of alteplase therapy</td>
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<td>Rafii et al. [13]</td>
<td>Neurology</td>
<td>2005</td>
<td>1</td>
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<td>0</td>
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<tr>
<td>Engelst et al. [1]</td>
<td>J Neurol</td>
<td>2005</td>
<td>120</td>
<td>2</td>
<td>1.7</td>
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<td>1</td>
<td>0</td>
<td>retrospective analysis</td>
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<td>Schwammenthal et al. [14]</td>
<td>Isr Med Assoc J</td>
<td>2006</td>
<td>46</td>
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<td>no data</td>
<td>0</td>
<td>thrombolysis safety study</td>
</tr>
<tr>
<td>Krmpotic et al. [15]</td>
<td>Eur J Emerg Med</td>
<td>2007</td>
<td>312</td>
<td>8</td>
<td>2.6</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>severe systemic reaction</td>
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<tr>
<td>Comprehensive Stroke Center Mannheim</td>
<td>Cerebrovasc Dis</td>
<td>2008</td>
<td>312</td>
<td>8</td>
<td>2.6</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>retrospective analysis</td>
</tr>
</tbody>
</table>

Summary: 1,894 total cases, 1,894 with OA, 37 with OA-related deaths, 12 with OA-related deaths due to cardiac complications.

<table>
<thead>
<tr>
<th>Rate of occurrence, %</th>
<th>1,894</th>
<th>37/1894</th>
<th>3/300</th>
<th>12/300</th>
<th>9/300</th>
<th>7/452</th>
<th>0/46</th>
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</thead>
<tbody>
<tr>
<td>CTD</td>
<td>1,120</td>
<td>10.0</td>
<td>40.0</td>
<td>30.0</td>
<td>15.6</td>
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</tbody>
</table>

CTD = Cricothyroidotomy. 1 Only patient collectives considered. 2 Only cases and studies providing this detail considered.

References


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