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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 intra-

venous 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 vasodilatation [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 ACEi 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 (H_1 and H_2 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

Author	Journal	Year	Cases (total)	Cases (OA)	Rate of occurrence, %	Ipsilateral OA	Bilateral OA	Non-ACEi cases with OA	Intubation/CTD	OA-related deaths	Comments
Pancioli et al. [8]	Ann Emerg Med	1997	–	1	–	0	1	0	0	0	first case report published
Rudolf et al. [9]	Neurology	2000	–	2	–	0	1	2	0	0	
Papamitsakis et al. [10]	Stroke Cerebrov Dis	2000	–	1	–	0	1	1	0	0	
Hill et al. [3]	CMAJ	2000	105	2	1.9	0	1	1	1	0	1 case with suspected c1 esterase inhibitor deficiency, died of cardiac complications
Hill et al. [3]	CMAJ	2000	–	2	–	0	0	0	0	0	addendum to publication above
Hill et al. [2]	Neurology	2003	176	9	5.1	1	1	2	0	0	prospective study, 1 death of cardiac complications
Jahnke et al. [11]	J Emerg Nurs	2003	–	1	–	0	0	0	1 CTD	0	emergency CTD
Hill et al. [12]	CMAJ	2005	1,135	15	1.3	no data	no data	no data	2	0	national prospective cohort study: effectiveness of alteplase therapy
Rafii et al. [13]	Neurology	2005	–	1	–	0	1	0	0	0	
Engelter et al. [1]	J Neurol	2005	120	2	1.7	0	2	1	1	0	retrospective analysis
Schwammenthal et al. [14]	Isr Med Assoc J	2006	46	1	2.7	no data	no data	no data	no data	0	thrombolysis safety study
Krmpotic et al. [15]	Eur J Emerg Med	2007	–	1	–	0	1	0	1	0	severe systemic reaction
Comprehensive Stroke Center Mannheim	Cerebrovasc Dis	2008	312	8	2.6	2	3	2	1	0	retrospective analysis
Summary			1,894 ¹		37/1894 ¹	3/30 ²	12/30 ²	9/30 ²	7/45 ²	0/46	
Rate of occurrence, %					2.0	10.0	40.0	30.0	15.6	0.0	

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

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