Lingual angioedema, ACE inhibitors, and tPA

Hill et al. identified an increased risk of hemi-prolingual angioedema after tissue plasminogen activator treatment of acute ischemic stroke associated with angiotensin-converting enzyme inhibitor use and infarction of the frontal and insular cortex. The reaction was usually clinically mild.

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Commentary by Patrick Lyden, MD

Thrombolysis—a therapy of proven benefit for stroke—has defined risks, notably a 6% cerebral hemorrhage rate.¹ Allergic reactions are rare, but an intriguing syndrome of hemi-oro-lingual angioedema can occasionally occur contralateral to the treated stroke.² In the largest case series to date, the Calgary stroke team collected nine patients who experienced hemi-oro-lingual angioedema after receiving tissue plasminogen activator (t-PA) for stroke for >5 years.³ The team carefully examined 176 consecutively treated stroke patients to find these nine cases.

The 5% incidence of hemi-oro-lingual angioedema in this study is remarkable and is hard to explain; other stroke programs with equal or larger numbers have not seen angioedema as often. Indeed, after *many hundreds* of t-PA doses administered personally, I have seen it only once, despite looking for it. The mechanism proposed in the article, involving bradykinin metabolism, is plausible and suggests a way to treat the complication.

The statistical analysis of Hill et al. provides credence that early ischemic changes (EIC) seen on acute CT brain scans may have related to the incidence of the hemi-oro-lingual angioedema, although their patient numbers are not sufficient to make this conclusion secure. Moreover,

subtle EIC does not define risk after thrombolysis.^{4,5} As the authors note, a larger prospective confirmation of this relationship is called for. So, for the time being, patients should be selected for recombinant t-PA (rt-PA) using the same imaging criteria used in the original trial.¹

Also of interest, the Calgary stroke group has published data showing the hazard of not treating mild or rapidly improving stroke patients with t-PA: Thirty-two percent were dead or disabled at hospital discharge.⁴ It would be imprudent to offer yet one more potential exclusion rule that is not well supported by large numbers: Patients with EIC that are “mild” or fluctuating should be treated per protocol.⁶

This article clearly illustrates the relationship between angiotensin-converting enzyme (ACE) inhibitors, t-PA, and angioedema. The strength of the report is that the authors carefully followed consecutive patients for angioedema, but such a careful look would bias the study to finding transient or minimal findings. A blinded study is needed to confirm these associations with certainty. However, ACE inhibitors are widely used in the population most at risk for stroke. If the relationship is confirmed with other studies, then we

will all see more patients with hemi-oro-lingual angioedema after rt-PA treatment for stroke. It remains unclear whether this side effect will ever prove sufficiently dangerous to patients that preventive measures will be indicated.

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Idiopathic intracranial hypertension: diagnosis with MR venography

MR venography demonstrates compressive stenoses.

Farb et al. applied auto-triggered elliptic-centric-ordered three-dimensional gadolinium-enhanced MR venography to 29 patients with idiopathic intracranial hypertension (IIH) and 59 control patients. Characteristic narrowings were seen in the transverse sinuses in >95% of IIH patients. With use of a newly developed grading system, IIH patients were discriminated from normal control subjects with 93% sensitivity and specificity.

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The accompanying editorial by Silberstein and McKinstry asks whether this demonstration of venous outflow obstruction in nearly all patients with idiopathic intracranial hypertension (IIH) answers the question of the syndrome's etiology. They note that obstruction may well be the result rather than the cause of IIH. What is needed is to see if the MRI evidence of obstruction resolves with measures that lower pressure.

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Neck manipulation is causal in vertebral dissection

Smith et al., using a nested case-control design, compared patients with and without cervical arterial dissection and found that recent spinal manipulative therapy was an independent risk factor for stroke or TIA from vertebral dissection.

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The accompanying editorial by Williams and Biller considers this possible risk of chiropractic. They note that Smith et al. addressed the "chicken-egg" issue of chiropractic manipulation for neck pain: Could the symptoms of dissection have prompted the visit to the chiropractor? The study carefully pursued this possibility with interviews of all subjects. Whereas recall bias as well as age differences in the control vs dissection patients are concerns, the sixfold increase of dissection/stroke suggests that the risk of chiropractic neck manipulation for patients with acute neck pain outweighs its benefits.

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TIA prevalence and knowledge in the US

Johnston et al. surveyed 10,112 US adults. Only 8.2% correctly related the definition of TIA and 8.6% could identify a typical symptom. They estimate that 4.9 million in the US report a history of a physician diagnosis of TIA.

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Mass effect and seizures after intracerebral hemorrhage

Vespa et al. monitored EEG continuously after ischemic (n = 46) and hemorrhagic (n = 63) stroke and considered whether seizures influenced outcome. They found that 28% of patients with intracerebral hemorrhage have seizures within the first week and that seizures were related to worsening mass effect and clinical deterioration.

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Cortical dysfunction in hysterical anesthesia

Mailis-Gagnon et al. studied four patients with chronic pain and clinically documented hysterical anesthesia. Functional MRI revealed an association between diminished perception and altered sensory-evoked responses within somatosensory and frontal/cingulate cortical areas. The data suggest a neurobiological component for some symptoms in patients with hysterical anesthesia.

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The accompanying editorial by Richard Gracely reflects on the subjectivity of the assessment of all afferent input to the CNS. He notes that nondermatomal sensory loss has often suggested a psychological cause for symptoms. However, a new somatotopic map is formed once afferents reach the CNS. The Mailis-Gagnon et al. fMRI study of hysterical anesthesia shows distinctive patterns of cerebral activity and suggests strategies for dissecting the neuroanatomy of altered pain perception.

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Lamotrigine for painful HIV-associated neuropathy

Simpson et al., in a placebo-controlled trial of 227 subjects with painful HIV-associated polyneuropathy, showed that lamotrigine reduced pain in subjects receiving neurotoxic antiretroviral therapy but not in those with HIV neuropathy.

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Epilepsy in China: prevalence and treatment

Wang et al. report a door-to-door survey for epilepsy in 55,000 people in China. They found a lifetime prevalence of 7.0 of 1,000 and a treatment gap of 62.6% in the patients with active epilepsy.

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The accompanying editorial by Jerome Engel notes that this study from China is the first of several such demonstration projects supported by the Global Campaign Against Epilepsy—a joint effort of the World Health Organization, International League Against Epilepsy, and International Bureau for Epilepsy. It shows that the number of untreated patients with epilepsy is much higher than anticipated. Preventing disability from epilepsy must be a target for international efforts.

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Voter participation by cognitively impaired elders

Ott et al. surveyed 100 outpatients with dementia following the 2000 US election. Sixty percent of demented subjects voted. The more severely demented, as expected, knew less about the election and voted less.

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