

**Conclusion.** In young patients without stroke risk factors in which either ischemia or hemorrhage affects the basal ganglia, an isolated vasculopathy within the lenticulostriate arteries requires consideration. Immunosuppressive treatment may be beneficial in such patients.

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## Serum substance P concentrations and silent aspiration in elderly patients with stroke

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Substance P (SP) is released from sensory nerve terminals and degraded by angiotensin-converting enzyme (ACE),<sup>1</sup> and its action is potentiated by ACE inhibitors.<sup>2</sup> SP levels in the sputum are reportedly low in patients with aspiration pneumonia,<sup>3</sup> and silent aspiration disappears by treatment with ACE inhibitors in association with an increase in serum concentrations of SP in hypertensive patients with stroke.<sup>4</sup> However, the relation between serum SP concentrations and improvement in silent aspiration has not been investigated yet in elderly patients with stroke. Therefore, we administered various doses of an ACE inhibitor to elderly patients with stroke to determine the effective concentration of serum SP that correlates best with improvement of the silent aspiration in such patients.

**Methods.** The eligible patients had a history of stroke but were not bedridden. We enrolled 60 patients (29 men and 31 women) with normotension and silent aspiration detected by the method described below. Randomization was done by a random-numbers table, and the list was held independently of the investigators. The patients were randomly given imidapril hydrochloride 1.25 mg/day (13 patients, 80 ± 4 years), 0.625 mg/day (14 patients, 79 ± 5 years), 0.5 mg/day (12 patients, 79 ± 5 years), OR 0.25 mg/day (9 patients, 80 ± 4 years) or no active treatment (Control Group; 12 patients, 79 ± 5 years).

To determine the occurrence of silent aspiration, we administered 1 mL of technetium tin colloid (<sup>99m</sup>Tc) to the patients during sleep via a nasal catheter. At 0900 hours the next morning, we checked for silent aspiration by imaging.<sup>5</sup> We measured serum SP concentrations before and at 12 weeks after oral administration of the ACE inhibitor. Because the given doses of the ACE inhibitor were lower than the standard dose, no reduction in the systemic blood pressure due to administration of the ACE inhibitor was observed in any of these patients.

The values are expressed as means ± SD. Statistical analysis was performed by the Kruskal-Wallis test followed by the Mann-Whitney *U* test. For the development of silent aspiration, the difference was analyzed by the  $\chi^2$  test. The level of significance was set at *p* < 0.05.

We excluded six patients receiving the ACE inhibitor because three patients had pneumonia and three patients had excessive cough during the study period.

**Table Doses of the angiotensin-converting enzyme inhibitor**

Group	Imidapril hydrochloride, mg			
	1.25	0.625	0.5	0.25
A, n = 31	10	10	8	3
B, n = 11	2	3	3	3

## References

- Newman W, Wolf A. Non-infectious granulomatous angitis involving the central nervous system. *Trans Am Neurol Assoc* 1952;77:114-117.
- Cupps TR, Moore PM, Fauci AS. Isolated angitis of the central nervous system: prospective diagnostic and therapeutic experience. *Am J Med* 1983;74:97-105.
- Sakaki T, Morimoto T, Utsumi S. Cerebral transmural angitis and ruptured cerebral aneurysms in patients with systemic lupus erythematosus. *Neurochirurgia* 1990;33:132-135.
- Moore PM. Diagnosis and management of isolated angitis of the central nervous system. *Neurology* 1989;39:167-173.
- Nishikawa M, Sakamoto H, Katsuyama J, Hakuba A, Nishimura S. Multiple appearing and vanishing aneurysms: primary angitis of the central nervous system. Case report. *J Neurosurg* 1998;88:133-137.
- Alrawi A, Trobe JD, Blaiva M, Musch DC. Brain biopsy in primary angitis of the central nervous system. *Neurology* 1999;53:858-860.
- Alhalabi M, Moore PM. Serial angiography in isolated angitis of the central nervous system. *Neurology* 1994;44:1221-1226.

**Results.** Silent aspiration was detected in all patients before treatment. Among the remaining 42 patients receiving the ACE inhibitor, the silent aspiration disappeared in 31 patients (73.8%) (Group A), but it did not change in 11 patients (26.2%) (Group B). In contrast, silent aspiration disappeared in only 1 (8.3%) of the 12 patients in the Control Group. There were differences in improvement of silent aspiration between Groups A and B (*p* < 0.01) and between Group B and the control patients (*p* < 0.01).

The doses of the ACE inhibitor in each group are listed in the table. Stroke severity assessed by the NIH Stroke Scale<sup>6</sup> was 6 ± 1 in Group A, 6 ± 2 in Group B, and 6 ± 2 in the Control Group. Poststroke durations were 2.0 ± 0.2 years in Group A, 2.0 ± 0.3 years in Group B, and 2.0 ± 0.3 in the Control Group. There were no differences in the stroke severity, poststroke interval, or baseline values of serum SP concentrations among the three groups.

The mean serum SP increased from 26.0 ± 1.7 to 68.8 ± 6.0 pg/mL in Group A (*p* < 0.001) and from 26.4 ± 1.1 to 45.4 ± 8.6 pg/mL in Group B (*p* < 0.01). However, the mean serum SP level did not change in the Control Group (26.4 ± 1.0 pg/mL before study vs 25.3 ± 1.1 pg/mL at the study end). Differences in the serum SP levels at the study end were observed between Groups A and B (*p* < 0.01) and between Group B and the Control Group (*p* < 0.01).

**Discussion.** These findings suggest that ACE inhibitors improve silent aspiration via increasing the serum SP in elderly patients with stroke. The pharyngeal, laryngeal, and tracheal epithelium (i.e., the sites most important for initiation of the swallowing and cough reflexes) have extensive plexuses of nerves that contain SP.<sup>7</sup> Capsaicin desensitization that abolishes SP from the airway and upper digestive tract markedly attenuates the cough response to tussive stimuli<sup>7</sup> and distilled water-induced swallowing reflex<sup>7</sup> in guinea pigs, suggesting an important role of SP-containing nerves in the initiation of protective reflexes. The optimal concentration of serum SP was around 70 pg/mL. The current study suggests that the serum SP may be a useful marker for monitoring the control of silent aspiration in elderly patients with stroke.

In conclusion, ACE inhibitors have a beneficial role in not only blood pressure reduction but also prevention of aspiration in elderly patients with stroke.

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## References

- Skidgel RA, Erdos EG. Cleavage of peptide bonds by angiotensin I converting enzyme. *Agents Actions* 1987;22:289S-296S.
- Shore SA, Stimler-Gerard NP, Coats SR, Drazen JM. Substance P-induced bronchoconstriction in guinea pig: enhancement by inhibitors

- of neutral endopeptidase and angiotensin-converting enzyme. *Am Rev Respir Dis* 1988;137:331-336.
- Nakagawa T, Ohru T, Sekizawa K, Sasaki H. Sputum substance P in aspiration pneumonia. *Lancet* 1995;345:1447.
  - Arai T, Yasuda Y, Takaya T, et al. ACE inhibitors and symptomless dysphagia. *Lancet* 1998;352:115-116.

- Arai T, Yasuda Y, Takaya T, et al. Technetium tin colloid test detecting symptomless dysphagia and ACE inhibitor prevented occurrence of aspiration pneumonia. *Int J Mol Med* 2000;5:609-610.
- Goldstein LB, Bertels C, Davis JN. Interrater reliability of the NIH Stroke Scale. *Arch Neurol* 1989;46:660-662.
- Sekizawa K. Mechanisms and prevention of pneumonia in the elderly. *Tohoku J Exp Med* 1998;184:73-84.

## Proteomic applications for differential diagnosis of histologically identical tumors

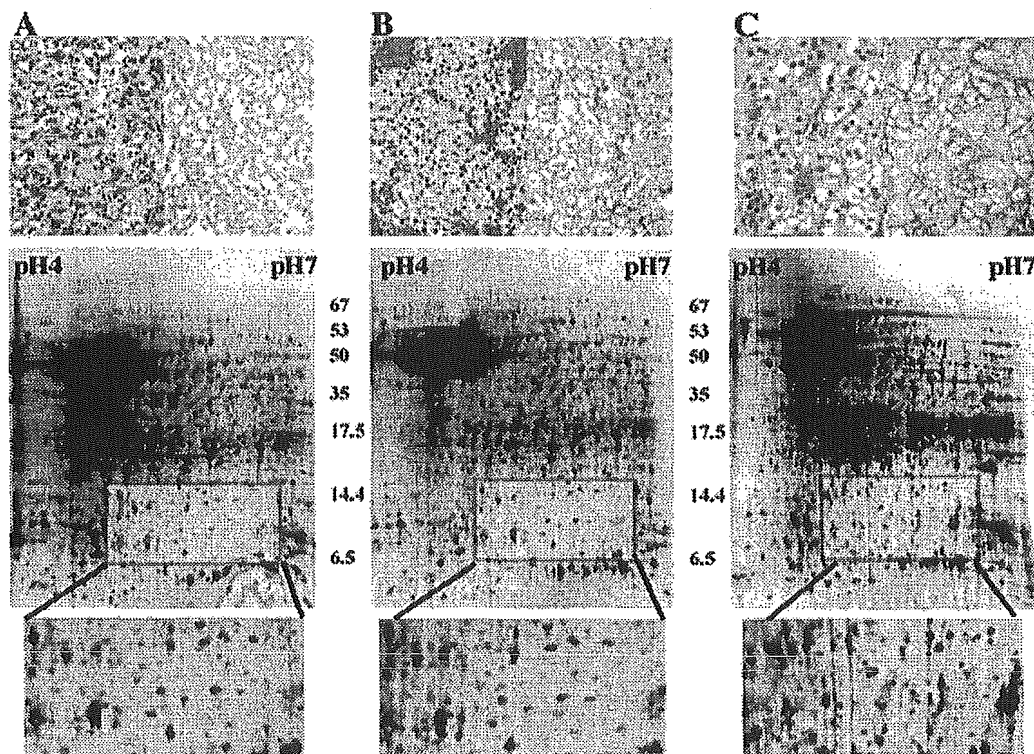
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As many as 5 to 10% of cases presented for pathologic review pose a significant diagnostic dilemma. Among the most challenging of these are different lesions with similar clinicopathologic features.<sup>1</sup> Whereas modern methods such as immunohistochemistry and molecular tools such as the PCR can help distinguish some conditions, there remain lesions, such as tumors, that share the same genetic alterations but for which differentiation remains imperative for prognostic and therapeutic reasons. A setting in which this may be especially true is in familial, multiple neoplastic syndromes, in which tumors may share histologic features and also have an identical pathogenesis.

von Hippel-Lindau (vHL) disease is a hereditary cancer syn-

drome characterized by multiple tumors of the CNS and retina, kidney, adrenal medulla, and pancreas. Although CNS hemangioblastomas (Hb) are considered benign, renal clear cell carcinomas (RCCC) frequently metastasize and are the cause of death in up to 30% of vHL patients.<sup>2,3</sup> Given the morphologic resemblance of Hb and RCCC, distinguishing them is difficult but has important consequences for prognosis and therapy.<sup>2,3</sup> In addition, a predisposition of RCCC to metastasize to CNS Hb has been noted recently.<sup>4,5</sup>

Differential pathologic diagnosis of Hb and RCC relies on immunohistochemistry, where RCCC express epithelial markers, including epithelial membrane antigen (EMA); in contrast, Hb are not known to express EMA.<sup>3,6,7</sup> In an unselected, consecutive series of 30 vHL-associated Hb, none expressed EMA (data not shown). Recently, however, a solid cerebellar tumor in a 46-year-old woman with vHL, who had had nephrectomy for RCCC and five previous surgeries for typical cerebellar and brainstem Hb, presented a significant diagnostic challenge: The cerebellar tumor



**Figure.** Microscopic and immunohistochemical pathology and proteomic differentiation of a patient's hemangioblastoma and renal cell carcinoma. (A, top) Hemangioblastoma tissue with reticular architecture, composed of numerous neoplastic "stromal" cells and vascular cells (left); corresponding areas are negative for epithelial membrane antigen (EMA) by immunohistochemistry (right). (A, middle and bottom) Representative two-dimensional gel electrophoresis panels showing specific proteins; the bottom panel is an enlargement of the area noted on the middle panel. The pH range for all two-dimensional gels is from pH 4 on the left to pH 7 on the right. Molecular weights on the y axis range from 67 to 6.5 kD, as indicated. (B, top) Other areas within the hemangioblastoma reveal epithelioid stromal cell clusters with extensive positive membranous staining for EMA (left); see brown staining on the cell membranes (right). (B, middle and bottom) Identical two-dimensional gel electrophoresis protein expression pattern, when compared with A. C (top) Typical histologic features of renal cell carcinoma (left); characteristic EMA staining (in brown) of the renal cell tumor (right). (C, middle and bottom) Strikingly different patterns of protein expression at low (middle) and high (bottom) magnification from the same regions of the two-dimensional gels.  $\times 200$  (histologic images in A and B);  $\times 400$  (C).